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# Innate and adaptive immune abnormalities underlying autoimmune diseases: the genetic connections

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With the exception of an extremely small number of cases caused by single gene mutations, most autoimmune diseases result from the complex interplay between environmental and genetic factors. In a nutshell, etiology of the common autoimmune disorders is unknown in spite of progress elucidating certain effector cells and molecules responsible for pathologies associated with inflammatory and tissue damage. In recent years, population genetics approaches have greatly enriched our knowledge regarding genetic susceptibility of autoimmunity, providing us with a window of opportunities to comprehensively re-examine autoimmunity-associated genes and possible pathways. In this review, we aim to discuss etiology and pathogenesis of common autoimmune disorders from the perspective of human genetics. An overview of the genetic basis of autoimmunity is followed by 3 chapters detailing susceptibility genes involved in innate immunity, adaptive immunity and inflammatory cell death processes respectively. With such attempts, we hope to expand the scope of thinking and bring attention to lesser appreciated molecules and pathways as important contributors of autoimmunity beyond the 'usual suspects' of a limited subset of validated therapeutic targets.

**autoimmune diseases, etiology, pathogenesis, innate immunity, adaptive immunity**

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## Introduction

Autoimmunity refers to a wide array of collective conditions in which broken self tolerance leads to manifestations of pathological alterations and clinical symptoms resulted from immune responses against self targets. One of the major challenges of treating autoimmune conditions is the almost impossible mission of reversal of break of tolerance. When patients walk into rheumatology clinics, they often complain about swollen joints or morning stiffness whereas few would state emergence of anti-nuclear antibodies or high levels of rheumatoid factors as the main reason for their doctor visits. Consequently, rheumatologists face the challenges of treating illnesses whose etiology stems from uncharacterized events that may be traced back for an extended period of time, sometimes decades ago. The current therapeutic strategies for autoimmune diseases are analogous to the solutions practiced by firefighters, i.e., putting forward best attempts to extinguish the fire regardless of the cause that

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originally ignited the flammables.

Information that may shed light on etiology of autoimmunity is in part provided by the fact that certain individuals are more susceptible to given diseases than the rest of the general populations. Analyses of genetic predispositions using population genetics approaches such as genome-wide association studies (GWAS) have yielded rich information regarding etiology and pathogenesis of autoimmunity. Albeit many susceptibility loci are located in the non-coding segments of the genome with unclear functional implications, a substantial proportion of the described loci fall into protein-coding regions that encode products involved in a wide varieties of biological processes. While a subset of autoimmune susceptibility genes presents themselves with clear ties to immune phenotypes given the well-established roles in innate and/or adaptive immune responses, connections of other genes such as those whose functions are predominantly implicated in developmental processes and metabolic activities to autoimmunity are more cryptic. In this extensive review, we discuss what we have learned from the recent studies aiming to elucidate the underlying genetic components of autoimmunity and how such knowledge may educate us towards better understanding of autoimmunity-associated immune abnormalities. In combination with progressively deepened knowledge of contributing environmental factors, the ultimate goal is to provide insights into development of novel therapeutic approaches against autoimmunity and to alleviate symptoms or even achieve disease-free status for autoimmune patients.

## The genetic basis of autoimmune diseases

### *Genetic epidemiology of autoimmune disease*

Autoimmune diseases are one of the most common diseases worldwide and have significant public impact because of their high morbidity and mortality (Rioux and Abbas, 2005). The general prevalence of autoimmune diseases ranged from less than 5 per 100,000 (e.g., uveitis (Miserocchi et al., 2013), wegener granulomatosis (Cotch et al., 1996)) to more than 500 per 100,000, such as rheumatoid arthritis (RA) (Almutairi et al., 2021) and ankylosing spondylitis (AS) (Dean et al., 2014). Although most autoimmune disease can occur at any age, the peaks of onset differ by illness (Amador-Patarroyo et al., 2012). For instance, type 1 diabetes (T1D) (Maahs et al., 2010) primarily occur in childhood and adolescence, but multiple sclerosis (MS) (Schwehr et al., 2019) and systemic lupus erythematosus (SLE) (Mina and Brunner, 2013) mostly appear during the mid-adult years, and RA (Symmons, 2002) mainly among older people. In addition, autoimmune diseases present gender disparities with a greater prevalence amongst women in a 2:1 ratio (Angum et al., 2020). Furthermore, the genetic epidemiology of autoimmune diseases becomes more complicated when variations in ethnicity, geographical regions and susceptibility genes are considered (Wang et al., 2015). Coeliac disease is a typical example, which is less prevalent in Asia. This may be due to the genetic factor that carriers of the HLA-DQ2 antigens linked to celiac disease occur in 5%–10% of Chinese and sub-Saharan Africans when compared to 5%–20% in Western Europe. In contrast, HLA-DQ8 occurs in 5%–10% of English, Tunisians and Iranians, but less than 5% in Eastern Europeans, Americans and Asians (Kang et al., 2013). Collectively, autoimmune diseases are the common diseases with genetic heritability and exhibit gender and age disparities with ethnic and geographic differences (Cooper and Stroehla, 2003).

The genetic heritability of autoimmune disease varies greatly (Ramos et al., 2015), for instance, from very high in AS (>90%) (Brown et al., 2016) to relatively low in inflammatory bowel disease (IBD, 12%) and MS (15%) (Kuusisto et al., 2008), whereas RA and SLE have a mid-average genetic heritability of roughly 60% (Guerra et al., 2012). The explanation for these differences is mainly due to the heritability and the interaction result of epigenetic factors and environmental factors (Baranzini and Oksenberg, 2017). Furthermore, the hereditary bias between familial cases and the general population for prevalent complicated diseases should be taken into account (Momozawa et al., 2018). Mounting evidence indicates a tendency toward familial aggregation of autoimmune disease (Cárdenas-Roldán et al., 2013). Many family studies have indicated that first-degree relatives (FDRs) of individuals with diagnosed autoimmune disease (e.g., RA, MS, AS) had increased familial risk of acquiring certain other autoimmune disease versus control probands (Cooper et al., 2009), which is even higher in monozygotic twins (Bogdanos et al., 2012). Furthermore, researchers also observed that not only FDRs but also spouses of individuals with autoimmune disease are at increased risk (Emilsson et al., 2015).

### *Genetic factors of autoimmune diseases*

*The GWAS revolution has accelerated the identification of autoimmune disease-associated variants*

Detecting the exact disease-causal variants and susceptibility loci may help us to better understand the mapping between genotype and phenotype of complex traits in disease mechanisms (Hirschhorn et al., 2002). However, the traditional linkage analysis methods are not enough to map genomic loci accurately due to the great variability and extensive linkage disequilibrium (LD) of the majority of autoimmune disease (Fernando et al., 2008). The GWAS revolution in the early 2000s, which is a powerful tool for unbiasedly identifying regions of the genome related to human variation and disease, opened up new avenues for global research into the

inheritance patterns of autoimmune disease (Visscher et al., 2012).

The joint Genome-wide association study coordinated by the Wellcome Trust Case Control Consortium (WTCCC) in 2007 that was the first real advance step forward in discovering new genetic correlations of autoimmune disease susceptibility through GWAS (Wellcome Trust Case Control Consortium, 2007). Notably, this WTCCC study revealed several novel genes that are highly linked to RA, T1D, and celiac disease (a type of IBD). For the first time, researchers have uncovered a gene called *PTPN2* that links these three autoimmune diseases. In the same year, WTCCC published another large-scale genetic studies in AS and MS, reporting two new AS loci: *ARTS1* and *IL23R* and highlighting the *IL23R* may as a shared susceptibility factor for the major 'seronegative' diseases like AS and Crohn's disease (CD) and psoriasis (Wellcome Trust Case Control Consortium and The Australo-Anglo-American Spondylitis Consortium (TASC), 2007).

Growing international collaboration across different ethnic cohorts expands the sample size of GWAS studies, yielding in more compelling autoimmune disease findings. As an example, the International Genetics of Ankylosing Spondylitis Consortium (IGAS) consortium conducted a dense SNP genotyping study in 10,619 cases and 15,145 controls of European, East Asian and Latin American ancestry in 2013, which increased the number of AS-associated loci to 31 (including 13 new loci) and 12 additional AS-associated haplotypes at 11 loci, revealed the critical role of aberrant peptide processing before major histocompatibility complex (MHC) class I presentation and alterations of the IL-23 proinflammatory cytokine pathway in the pathogenesis of AS (International Genetics of Ankylosing Spondylitis Consortium et al., 2013).

In addition, meta-analysis of GWAS is becoming increasingly prominent, which can improve the ability to identify association signals by combining samples from multiple cohorts to detect more variations and cover more genomic areas than a single dataset (Zeggini and Ioannidis, 2009). In 2014, A three-stage trans-ethnic meta-analysis (Okada et al., 2014) conducted for 100,000 subjects of European and Asian ancestries (29,880 RA cases and 73,758 controls) have discovered 42 novel RA risk loci and identify 98 biological candidate genes at in total 101 risk loci. Particularly, they devised an *in silico* pipeline which developed by well-established bioinformatics methodologies and based on functional annotation to identify 98 biological candidate genes at these 101 risk loci, and first conducted functional annotation of RA risk SNPs which aim to provides empirical evidence for drug discovery. Furthermore, employing the cross-disease meta GWAS methodology can improve the power to identify common susceptibility loci across several autoimmune disease, even if the association signals differ between diseases. As early as 2011, Zhernakova et al. (Zhernakova et al., 2011) discovered fourteen non-HLA common loci associated with the mechanism of antigen presentation and T-cell activation in a meta-analysis of two published GWAS on celiac disease and RA of European ancestry cohorts. Similarly, cross-disease meta GWAS analysis for five published data of psoriasis and Crohn's disease performed by Ellinghaus et al. (Ellinghaus et al., 2012) identified 20 shared disease association loci and tested cross-disease associations in additional cohorts in 2012. Then in early 2019, the first cross-disease genome-wide meta-analysis in systemic seropositive rheumatic illnesses (including systemic sclerosis, SLE, RA and idiopathic inflammatory myopathies) (Acosta-Herrera et al., 2019) was published, which revealing five new shared genome-wide significant independent loci from a cohort of 11,678 patients and 19,704 non-affected controls from European ancestry groups.

*Post-GWAS era: the functional genomics of autoimmune disease*

However, while GWAS has successfully led to the discovery of thousands of loci that have been statistically related to disease and trait risk, a number of challenges and limits have emerged. Including biological relevance to disease and clinical utility for prognosis or treatment lag far behind, could not explain the vast majority of genetic heredity for diseases, as well as the research constraint at the cell level (Visscher et al., 2017). Naturally, the Post-GWAS era has arrived, which is primarily arguing for causation and risk gene identification (Pierce et al., 2020), as well as encouraging the transition from association to function (Gallagher and Chen-Plotkin, 2018).

During this period, numerous remarkable studies with newly-rising so called post-GWAS methods were published. One of the most effective techniques is "fine mapping", for identifying trait-relevant genetic elements in a genomic locus that has already been restricted, which has proven useful in translating GWAS findings into possible therapies (Schaid et al., 2018). A new method known as CC-GWAS (case-case genome-wide association study) (Peyrot and Price, 2021) has recently gained traction. Peyrot W.J. et al. using summary statistics from the respective case-control GWAS to test for variations in allele frequency between cases of two disorders, which transcends conventional approaches that require individual-level information. They have effectively identified loci with varying allele frequencies among patients of eight psychiatric diseases via CC-GWAS, and validated the CC-GWAS method using three publicly available autoimmune disease GWAS datasets, which including CD, ulcerative colitis (UC), and RA. Demonstrate the ability to use this strategy to improve clinical diagnoses and treatment of other autoimmune diseases.

Furthermore, population cohort studies also play a critical

role in proving causality and promoting medication development (Wijmenga and Zhernakova, 2018). Recently, a large-scale meta-analysis across East Asian and European populations on RA via various post-GWAS approaches performed by Eunji Ha et al. (Ha et al., 2021) they integration of accumulated knowledge of RA variants with emerging high-throughput omics data which led to the identification of 11 new RA susceptibility loci. So far, enormous success of wide-scale genetic studies in identifying genetic variants of autoimmune disease. The question of how to make effective use of these data remains a challenge.

### *The shared genetic mechanisms between autoimmune diseases*

The previously epidemiological studies have demonstrated that the human autoimmune diseases are complex disorders that result from the interaction between genic susceptibility and environmental factors (Wang et al., 2015). Despite the fact that autoimmune diseases are heterogeneous conditions in clinical and therapeutic features with the involvement of multiple organ systems (Ramos et al., 2015), it is the general consensus that autoimmune diseases share complicated and similar genetic background. Meanwhile, genetic research also supports the existence of distinct pathogenesis pathways for various autoimmune diseases (Richard-Miceli and Criswell, 2012). A decade ago, researchers already found almost half of the 107 immune disease-risk SNPs across seven immune-mediated inflammatory and autoimmune diseases (including CD, MS, psoriasis, RA, SLE, and T1D) are shared, which as is the case with alleles in the major histocompatibility locus (Cotsapas et al., 2011).

Lately, Caliskan M. et al. (Caliskan et al., 2021) developed a catalog of 85 fine mapping studies on autoimmune GWAS locus by combining text mining with a systematic review. They compiled 230 GWAS loci which consist of 455 combinations of locus-by-disease association signals with 15 autoimmune diseases. In order to refine the genes shared by the main autoimmune diseases in this study, we chose five major autoimmune disorders (CD, RA, T1D, IBD, MS) to display the overlapping genes within these diseases with the information of disease association loci (Figure 1A). The 74 GWAS loci spanning more than two primary autoimmune diseases from this catalog were then visualized using a chord diagram based on the causative gene confidence scores of these GWAS loci and their associated autoimmune disorders (Figure 1B). Notably, we can clearly see that *IL2* and *TAGAP* are both found shared in four autoimmune diseases (*IL2* in CD, IBD, RA, and T1D, and *TAGAP* in IBD, MS, RA, and T1D, respectively), which is consistent with earlier mice studies and clinical experiment results (Chen et al., 2020; Clough et al., 2020; Pérol et al., 2016). Insight gained from these analyses underlined the crucial function of regulatory T cells in immunological homeostasis, will contribute to the development of regulatory T-cell treatments for these autoimmune diseases.

Many common variations have been discovered in autoimmune diseases and other human disorders, so called "pleiotropy" (Inshaw et al., 2018). It is widely established that the immune system dysfunction is linked to an increased risk of Parkinson's disease (PD) (Tan et al., 2020). For example, in a comprehensive epidemiological study of 310,000 people in Sweden with 33 different autoimmune diseases, the prevalence of increased risk of Parkinson's disease was as high as 33% (Li et al., 2012). In contrast, findings from a large GWAS involving 47,580 instances of RA and 482,703 cases of PD suggest that Rheumatoid arthritis lowers the risk of Parkinson's disease (Li et al., 2021a). The association between autoimmune diseases and Parkinson's disease appears to be inconclusive, which could be related to sample size constraints. Nevertheless, the study of pleiotropy between autoimmune diseases and other comorbidities could aid to the discovery of novel loci not previously associated with disease. Witoelar et al. reported 17 novel loci were identified overlap between PD and autoimmune diseases including the 4 known PD loci (*GAK*, *HLA-DRB5*, *LRRK2*, and *MAPT*) which presented in RA, UC, and CD, and highlight the involvement of Human leukocyte antigen (HLA) (Witoelar et al., 2017).

### *Gene-environment interaction effect on autoimmune disease*

It is consensus that environmental factors and ascertainment bias may play a role in disease risk in addition to genetic factors. With the development industrial civilization advances and science and technology advances, including new industries, new chemicals and pharmaceuticals. The prevalence of autoimmune diseases caused by environmental factors has increased. Improve the understanding of "environmental triggers" to autoimmune diseases may help people avoid dangers and determine treatment alternatives (Gioia et al., 2020; Vojdani, 2014). In recent years, an increasing number of studies have demonstrated that smoking (Ishikawa and Terao, 2020), red meat (Pattison et al., 2004), and the high-sodium diet (Salgado et al., 2015) have negative consequences on disease development, whereas a vegetarian diet (Kjeldsen-Kragh et al., 1991), polyunsaturated fatty acids (Fetterman Jr. and Zdanowicz, 2009), vitamin D (Jeffery et al., 2016), and probiotics (Bungau et al., 2021) contribute to improved health assessment. Consequently, dietary patterns and supplements were encouraged as future adjuvant therapy in the treatment of autoimmune disease, such as the Mediterranean Diet (MD), which consists primarily of vegetables, fruit, fish, olive oil, and dairy products (Pocovi-Gerardino et al., 2021).

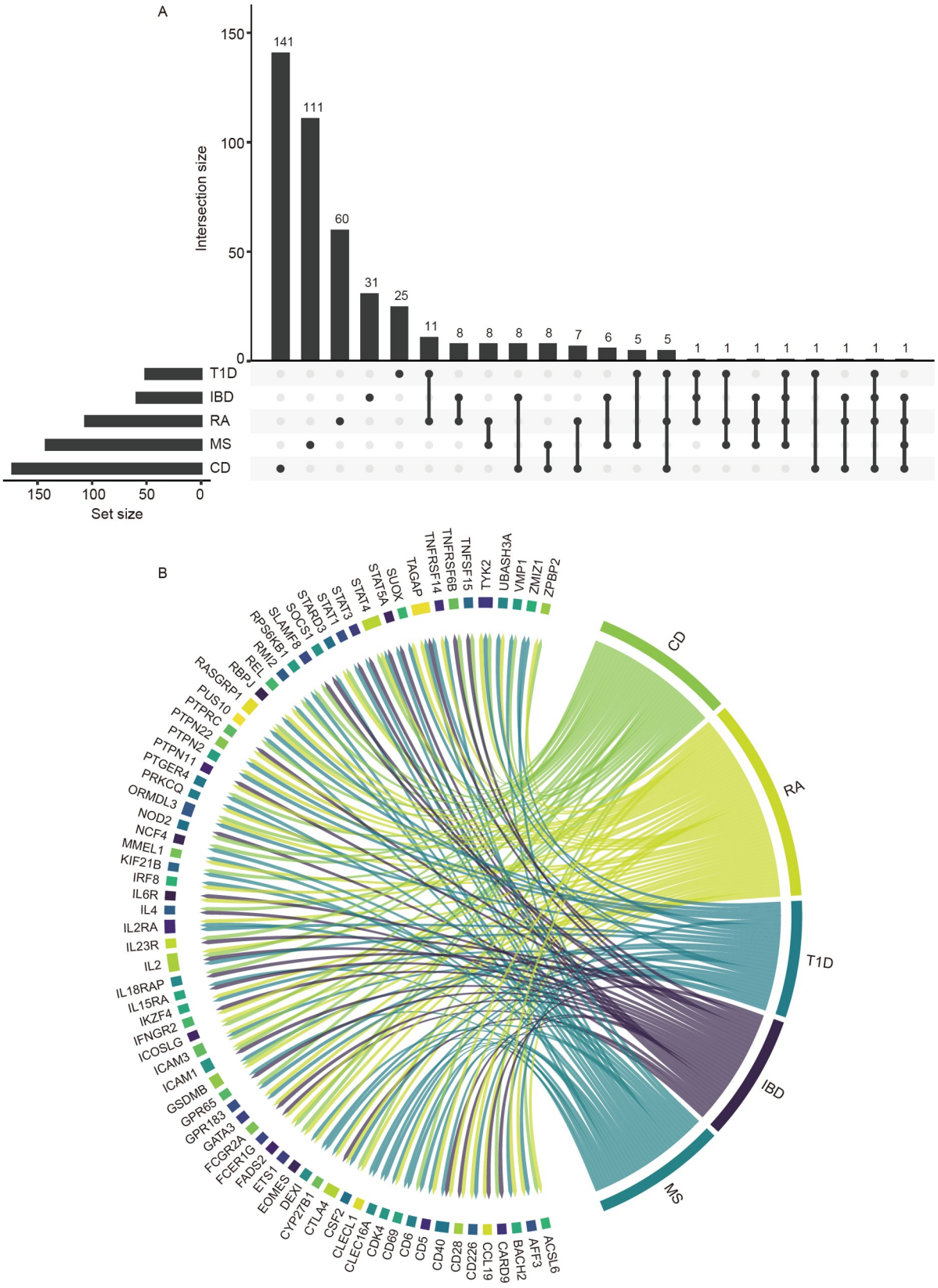


**Figure 1** Overlapping genes (GWAS loci) association between main autoimmune diseases. A, The UpSet graphic generated by UpSetR (Conway et al., 2017) shows the number of GWAS loci that overlap for each of the five common autoimmune diseases (CD, Crohn disease; RA, rheumatoid arthritis; T1D, and type 1 diabetes; IBD, inflammatory bowel disease; MS, multiple sclerosis), which is based on the comprehensive catalog of autoimmune disease GWAS fine-mapping research. B, The chord diagram created with the R package "circlize" (Gu et al., 2014) , presenting the relationship between 74 GWAS loci (left) that overlap in more than two major autoimmune diseases and the diseases with which they are associated (right).

Modulation of gut microbiota-derived metabolites is one of the most important indirect mechanisms of how dietary habits and nutrition influence disease progression (Han et al., 2021). Altered microbiota composition has been linked to reduced intestinal barrier function and mucosal immune system dysregulation (Khan and Wang, 2019), one of the well-known hypotheses is and "the gut-joint axis" (Zaiss et al., 2021). However, it is uncertain if gut dysbiosis is a cause or an effect of autoimmune disease. A result from the general population cohort of the all babies in Southeast Sweden project indicated that genetic risk for T1D autoimmunity is related with unique alterations in the gut microbiota (Russell et al., 2019). Evidence from animal and human studies indicated that HLA alleles influence the process of the gut microbiota interacting with host immunity (Xu and Yin, 2019). Besides, an emerging study using shotgun metagenomics on AS patients indicates an enrichment of potentially cross-reactive bacterial epitopes, and the TNFi therapy has an effect on microbiome composition (Yin et al., 2020).

### *Advanced genetic study and perspective of autoimmune disease*

The GWAS successfully applied to the identification of a large numbers of genetic variants (mainly SNPs) of the disease and the association with many complex traits. However, it had limited predictive ability in diseases. Polygenic risk score (PRS) profiling method, which can aggregate the effects of variants across the genome, is able to be use in the estimation of an individual's genetic liability to a trait or disease by calculating based on disease genotype profile and relevant GWAS data. Li Z. et al. (Li et al., 2021b) highlighted the significant diagnostic capacity of PRS in AS patients compared to traditional diagnostic test methods including C-reactive protein (CRP), HLA-B27 and sacroiliac MRI. For reality clinical application, more study of PRS applied in autoimmune disease within specific ethnic groups is required. In 2020, Choi et al. (Choi et al., 2020) published a tutorial on performing polygenic risk score analyses in nature protocols calculated according to their genotype profile and relevant GWAS data, which may help in the interpretation of PRS-trait associations.

Another challenge of GWAS is that it is difficult to confirm causal genes or disease distal regulatory areas that relate cell-type specific behaviors. Single-cell RNA sequencing (scRNA-Seq) is a powerful method for collecting gene expression in individual cells from living tissues using high-throughput sequencing analysis across the entire transcriptome. It has already shown promising results in MS, AS, and RA. For example, recent research by Simone D. et al. (Simone et al., 2021) applied single-cell transcriptome analysis by using peripheral blood and synovial fluid samples from patients with AS and psoriatic arthritis (PsA), with results showing detailed characterization of Tregs cell and demonstrate LAG-3 directly inhibits IL-12/23 and TNF secretion by patient-derived monocytes, which could be a potential mechanism for SpA.

The majority of current autoimmune disease treatments rely on systemic immunosuppression, which makes patients prone to infections. Precision medicine is regard as the cornerstone of future cancer therapies (Shin et al., 2017), involving the development of novel diagnostics and customized drugs to a patient's individual needs based on genetic, biomarker, phenotypic, or psychological characteristics. In mid 2016, Ellebrecht C. T. et al. (Ellebrecht et al., 2016) shown that chimeric antigen receptor T cells (CAR-T cells) can be modified to seek out and kill self-reactive B cells, which may provide specific targeting of autoreactive B cells in antibody-mediated autoimmune disease and eventually help identify potential therapies.

Nowadays, the intersection of precision medicine and artificial intelligence (especially machine learning and deep learning algorithms) is a popular area in autoimmune disease medical research. The goal is to better capture individual variation in genes, function, and environment in order to build and optimize diagnostic, therapeutic, and prognostic pathways (Jameson and Longo, 2015). This could lead to a new chance to personalize therapies specifically for autoimmune disease patients, particularly those with rare autoimmune disease, in order to achieve effective treatment (Subramanian et al., 2020). Meanwhile, the ethical and legal issues surrounding artificial intelligence-driven healthcare are gaining traction in society and provoke discussion (Amann et al., 2020).

## Genetic components underlying innate immune abnormalities in autoimmune diseases

Autoreactive immune responses are the major pathogenic driving force in autoimmune diseases. Although different autoimmune diseases manifest themselves with drastically distinct symptoms, certain common genetic risk factors broadly underlie autoimmunity-associated immune abnormalities (Cho and Feldman, 2015). In the following three chapters, based on the knowledge obtained from human genetics studies such as GWAS, we discuss the plausible factors and pathways that might be involved in aberrant activation of immune system. The first part in this chapter briefly discusses risk genes with apparent connections to innate immune functions while the next two chapters are focusing on T cell-related immune abnormalities and pathogenic factors in TNF signaling. In addition, in the second and third parts of this chapter, we expand the discussion of the risk genes whose connections to autoimmunity may not appear as obvious at the first glance, exemplified by those

genes and pathways best known for their roles in developmental and metabolic processes.

### *Autoimmune disease susceptibility genes with well characterized functions in innate immunity*

*Risk genes in the antigen presentation process*

In homeostasis, DCs are the major inducer of peripheral tolerance for humoral immunity, in which tolerogenic DCs induce depletion or anergy in auto-reactive T cells and also polarize the T cells into regulatory T cells (Iberg et al., 2017). While, in autoimmunity activation, bypassed peripheral tolerance could be resulted from the genetic risk variants in antigen presentation pathways and/or hyper-activation of T cells (Theofilopoulos et al., 2017). With extensive investigations, HLA risk variants in autoimmune diseases are related to the abnormal antigen presenting by DCs, and non-HLA risk factors could also be involved. The autoimmune disease-related polymorphisms in *ERAP1* and *ERAP2* loci have been linked to impropriate antigen presentation, resulted from the disturbed antigen peptide trimming by *ERAP1*/*2* encoded enzymes for MHC-I presentation. Additionally, the T cells hyper-proliferation and inflammatory polarization could be genetically influenced by autoimmune disease-causative risk alleles, such as *PTPN22* for TCR signaling, *IL12A* and *STAT4* for Th1 polarization by IL-12, and *IL23R* for IL-23 mediated Th17 polarization.

*Pathogenic interaction between plasmacytoid DCs (pDCs) and neutrophils*

One characteristic of a subset of autoimmune diseases represented by SLE is the increase of pDCs in circulation and in disease-affected tissues, such as kidney (Coutant and Miossec, 2016). pDCs are the professional type I interferon (IFN) producing cells, which play an essential role in antiviral innate immune response. In SLE-related conditions, accumulated pDCs in circulation and local lesion tissues promote inflammation and autoantibody production, largely dependent on type I IFNs (Soni and Reizis, 2019). In SLE pathogenesis, a devastating forward loop is mediated by neutrophils, pDCs and B cells. In inflammatory environments, such as SLE patients' renal tissues, neutrophils are recruited and activated by inflammatory cytokines, such as IL-8 and IL-17 (Fresneda Alarcon et al., 2021). Upon activation, neutrophils could undergo a suicidal cell death, NETosis, which releases DNA contents form the neutrophil extracellular trap (NET). NET structure contains nuclear DNA and oxidated mitochondrial DNA, both of which are potent TLR9 agonists and auto-antigens for type I IFN production in pDCs and autoantibody production in B cells, respectively (Soni and Reizis, 2019). In such pDC-mediated interferonopathy, multiple signaling components are genetically pre-deposited to disease-prone conditions (Mohan and Putterman, 2015). Firstly, the polymorphism in genes related to TLR signaling pathway components have been identified in autoimmune diseases, such as *IRAK1* and *IRF5*. For predisposed TLR signaling in SLE pathogenesis, resulted type I IFN production in pDC has been considered as a major player, and crosstalk between TLR7/9 signaling and B cell activation has also been implied in promotion of autoantibody-producing plasma cells (Suthers and Sarantopoulos, 2017). Some gene loci for signaling regulators are also identified as risk alleles, such as *TNFAIP3* and *TNIP3* for NF-κB signaling that contributes to the inflammatory phenotypes in myeloid cells. Secondly, the abnormal type I IFN signaling could also be genetically imprinted in autoimmune disease patients, where the genes encoding type I IFN receptor and downstream signaling cascade kinase, *IFNAR1* and *TYK2*, have been identified with autoimmune disease-related polymorphism. In contrast to SLE, pDCs function in other autoimmune diseases are less characterized, and the less commonly shared pDC-mediated pathogenesis has been implied among different diseases. Similarly to SLE, in mouse model for type I diabetes, pDC has been shown to promote disease progression by producing type I IFN (Reizis, 2019). While, tolerogenic pDC phenotypes in synovium and periphery of RA patients have been described (Cooles et al., 2018; Kavousanaki et al., 2010; Takakubo et al., 2008), and such protective role is supported by the worsened disease conditions with pDC depletion in arthritis mouse model (Jongbloed et al., 2009).

*Monocyte and macrophage-mediated inflammation*

A central role of macrophages and monocytes in autoimmune disease-related tissue inflammation is underpinned by the success of therapeutic interventions targeting inflammatory cytokines produced by monocytes and macrophages (Conigliaro et al., 2019). In general, inflammatory macrophages and monocytes are considered as effector cells for disease-related tissue inflammation (Navegantes et al., 2017). With functional dissection for commonly presented risk alleles across different autoimmune diseases, the genetically pre-deposited pathogenic pathways in macrophages and monocytes have been unraveled. In such inflammatory responses, myeloid cells, specifically the monocyte-derived macrophages, are the central node to sense the pro-inflammatory environments resulting inflammatory mediator production and further to bridge the local adaptive immune activation by favoring the differentiation of pathogenic $CD4^+$ T cells and autoantibody-secreting plasma cells (Tsokos, 2020; Weyand and Goronzy, 2021).

Immune complex induced inflammatory response in inflamed tissues are universally manifested by Fc receptor signaling activation and complement pathway activation in myeloid cells, and the anti-complement therapy and blockade of Fc receptor exhibit promising clinical efficacy in RA

and SLE patients (Galindo-Izquierdo and Pablos Alvarez, 2021; Zuercher et al., 2019). Genetic variants in both complement and Fc receptor pathways are also associated with autoimmune diseases (Theofilopoulos et al., 2017). In particular, polymorphisms in *ITGAM* and *FCGR2B* loci have been correlated with impaired negative regulation of immune complex induced inflammation. *ITGAM* encodes CD11b, also known as complement receptor CR3, to mediates complement-dependent phagocytosis for immune complex and apoptotic cells, and C3b activates CR3 to induce production of anti-inflammatory cytokines in macrophages. For polymorphism in the *FCGR2B* locus, the impaired function of FcγRIIB-mediated repression on Fc receptor signaling could result in excessive inflammatory activation of myeloid cells by immune complex. Thus, the accumulation of immune complex and cell debris and downstream hyper-inflammatory activation of macrophages in local lesion tissues are genetically pre-deposited in autoimmune diseases to promote the pathogenesis. Given the genericity of immune complex accumulation presented in autoimmune disease settings, such abnormally activated Fc receptor signaling and complement pathway are considered to be therapeutically targeted with broad effects in different diseases.

Although the shared genetic risk factors and inflammatory myeloid cells could be observed under various autoimmune diseases, the responsiveness of different autoimmune disease patients to myeloid-targeting therapy could be totally different. For anti-GM-CSF therapy, RA patients receive prominent disease control from therapy, but disease conditions were worsened by anti-GM-CSF intervention in SLE patients (Lotfi et al., 2019). The mechanism underlying such difference is still unclear, but it suggests that myeloid cells receiving GM-CSF signaling in SLE patients could be protective. This practical issue suggests that acknowledging of the heterogeneity of inflammatory conditions helps the development of anti-inflammatory therapy by targeting the critical inflammatory mediators in specific disease setting.

Macrophages and monocytes could be over-activated by a plethora of inflammatory stimuli in autoimmune diseases, which further results in systemic inflammation termed as macrophage activation syndrome (Crayne et al., 2019). Such systemic inflammation mediated by macrophages and monocytes could be developed to the global symptoms and even to be life-threatening. Macrophage activation syndrome could be observed in systemic juvenile idiophatic arthritis (sJIA), where the pro-inflammatory phenotypes are presented in the periphery, as blood monocytes of patients produce an array of inflammatory cytokines, such as TNF, IL-6, IL-1β. In such hyper-inflammatory macrophage activation, the dysregulated inflammatory pathways in innate immunity could be resulted from genetic variants, such as *IRF5* for type I IFN signaling, *NLRC4* for IL-1β-producing inflammasome pathway and *TNFAIP3* for NF-κB signaling (Schulert and Cron, 2020).

### *Notch signaling is genetically associated with autoimmune diseases*

As previously mentioned, genetic risk factors associated with self-tolerance and inflammatory pathways contribute to the autoimmune diseases. Meanwhile, genetic variants that could not be directly aligned to abnormalities of immune responses are being functionally annotated with accumulating knowledge (Figure 2), within which we will discuss the pathological processes participated by Notch signaling and mitochondria-centric metabolism, two pathways with genetic relevance to autoimmune diseases.

Notch signaling is one of the essential pathways for embryonic tissue and organ development, after which Notch signaling also maintains local homeostasis in various tissues. In mammals, four Notch signaling receptors (Notch1–4) and five Notch ligands have been identified. Upon activation by

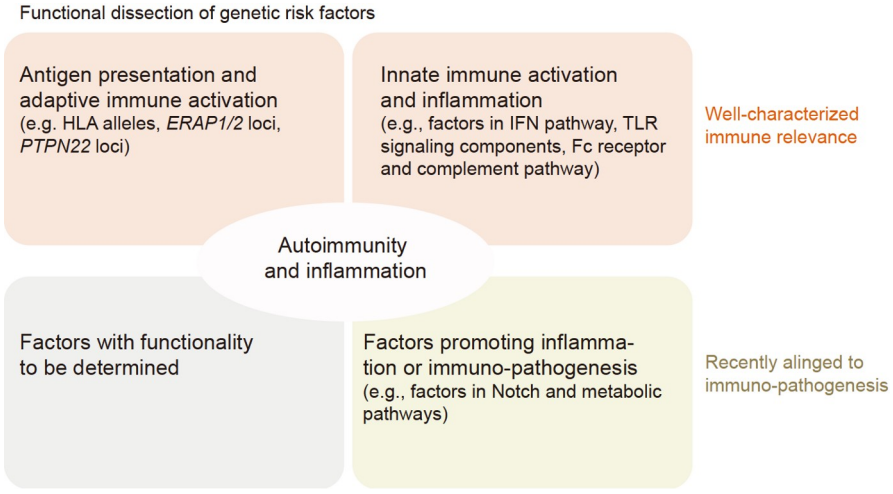


**Figure 2** Functional category of genetic components underlying autoimmune diseases.

Notch ligands, receptor proteolytically releases Notch intracellular domain (NICD) and regulates gene expression via interaction with RBPJ which is the central nuclear transcription regulator in canonical Notch signaling pathway. Notch signaling is broadly related to the immune system, where Notch signaling participates in the development of immune cells in both lymphoid and myeloid lineages and also regulates the function of terminally differentiated immune cells to fine-tune the immune responses in homeostasis and disease conditions (Vanderbeck and Maillard, 2021). In recent studies, accumulating evidences on Notch signaling involved pathogenesis in multiple autoimmune diseases suggest targeting Notch-related pathway would be a promising therapeutic intervention. Therefore, summary of current knowledge on regulation of pathogenesis, especially the inflammatory responses, in autoimmune diseases by Notch pathway is informative and insightful for the design of therapy.

Three out of four Notch receptor gene loci have been identified as risk alleles in autoimmune diseases (Table 1). In addition, the gene locus of *RBPJ* has been identified as RA risk allele, and loci of *DLL1* and *DLL4* have been identified as risk alleles in SLE, multiple sclerosis and type I diabetes (Table 1). Thus, the dysregulated Notch signaling is genetically implied in autoimmune diseases. Herein, we will discuss the Notch related regulation during the pathogenesis of RA and SLE, two autoimmune diseases associated to risk variants in Notch receptors, ligands and RBPJ loci with high prevalence and broad attentions.

*Upregulated Notch signaling contributes to RA pathogenesis*

In RA patients, Notch receptor activation has been identified in both immune and non-immune cells. In lymphoid lineage, activation of Notch1 has been identified in synovial T cells (Yabe et al., 2005), and the peripheral T cells of active RA patients show upregulated Notch2, 3, 4 expression and Notch signaling activation (Jiao et al., 2010). In collagen II-immunized mice, Notch signal is activated in synovium, and RA-like manifestations are alleviated upon Notch signaling inhibition by γ-secretase inhibitors (Choi et al., 2018; Jiao et al., 2014; Jiao et al., 2011; Park et al., 2015). In most of these studies, the altered Th1/Th17 to Treg ratio by Notch signaling pathway was suggested for progressive disease outcome in mouse model (Choi et al., 2018; Jiao et al., 2014; Jiao et al., 2011), where Notch3 and DLL1 promote both Th1 and Th17 expansion (Jiao et al., 2011), DLL3 promotes Th17 expansion (Jiao et al., 2014), and Notch1 suppresses Treg population (Choi et al., 2018). However, the context-dependent Notch signaling function presented by different studies could be the results of variations among different experiment systems. Albeit promotion of Th17 expansion by DLL1 was shown by Jiao et al. via DLL1 treatment of *in vitro* splenic mononuclear cells (Jiao et al., 2011), in another study, DLL1 failed to promote Th17 expansion (Jiao et al., 2014). Therefore, whereas the beneficial effects of blocking Notch signaling were consistent in RA disease mouse models, the detailed mechanism, especially the specific contributions from each Notch receptor and ligand remain to be clarified. Lineage specific knockout mice for Notch receptors and ligands should be useful to specifically evaluate Notch signaling function in T cell-mediated RA pathogenesis.

Notch signaling activation is also observed in myeloid cells in both RA patients and RA disease mouse model (Sekine et al., 2012; Sun et al., 2017). As mentioned in RA pathogenesis, myeloid cells, specifically monocytes and monocyte-derived cells, could function either as macrophages or osteoclast to promote inflammation and bone erosion. While, Notch signaling, indeed, participates the both parts, modulating the polarization of macrophages and differentiation of osteoclasts. Notch signaling promotes inflammatory polarization of macrophages under various conditions (Shang et al., 2016). However, the proinflammatory function of Notch signaling in macrophages is much less characterized in RA-related inflammation. Indeed, global inhibition of notch signaling results in the reversed hyper-inflammatory phenotype in macrophages in RA disease mouse model (Sun et al., 2017). As discussed in Notch function in RA T cells, it is also important to investigate the specific contribution of Notch receptor-ligand pairs in macrophages to the inflammatory response in RA pathogenesis. For osteoclastogenesis, Notch signaling has been shown to both positively and negatively regulate the osteoclast differentiation (Shang et al., 2016), which could be the result of either different receptor-ligand Notch signaling activation or the variations in different experimental systems. Actually, the regulation by different Notch receptor-ligand pairs in RA-related osteoclastogenesis could be hypothesized, as a previous study showing that Notch2/DLL1 promote, but Notch1/Jagged1 suppress osteoclast development under a unified experimental system (Sekine et al., 2012).

Notch signaling also plays an important role in synovial fibroblast-mediated RA pathogenesis. The pathogenesis contributed by Notch-mediated pathogenic fibroblasts is relatively well documented, as most findings are derived from patient samples, and were solidified by well-controlled *in vitro* system. Firstly, the Notch activation in synovial fibroblast were identified in RA patients' synovium (Ando et al., 2003; Ishii et al., 2001; Nakazawa et al., 2001a; Nakazawa et al., 2001b; Wei et al., 2020; Yabe et al., 2005). In addition, activated Notch signaling is induced by inflammatory environment, such as excessive TNF and hypoxia (Ando et al., 2003; Gao et al., 2015; Gao et al., 2012; Jiao et al., 2012; Nakazawa et al., 2001a; Nakazawa et al., 2001b). Inhibition of Notch activation by γ-secretase inhibitor not only alle-

**Table 1** Summary of Notch receptors, ligands and RBPJ related risk alleles identified by GWAS studies in autoimmune diseases

| Genes | SNPs | Associated diseases | Population |
|---|---|---|---|
| *NOTCH1* | rs3124998 (3′UTR variant) | Ankylosing spondylitis, psoriasis, ulcerative colitis, Crohn's disease, sclerosing cholangitis (Ellinghaus et al., 2016) | European |
| *NOTCH2* | rs835573 (intronic variant) | Systemic lupus erythematosus (Langefeld et al., 2017) | European, African-American, Hispanic |
| | rs2453042 (intronic variant) | Systemic lupus erythematosus (Langefeld et al., 2017) | European, African-American, Hispanic |
| | rs1493696 (intronic variant) | Type I diabetes (Chiou et al., 2021) | European |
| *NOTCH4* | rs549182 (intergenic variant) | Ulcerative colitis (Juyal et al., 2015) | Indian |
| | rs9267972 (intergenic variant) | Systemic lupus erythematosus (Chung et al., 2014) | European |
| | rs6927022 (intronic variant) | Inflammatory bowel disease (de Lange et al., 2017) | European |
| | rs422951 (missense variant) | Systemic lupus erythematosus (Tangtanatakul et al., 2020) | Thai |
| | rs9267911 (intergenic variant) | Crohn's disease (Yamazaki et al., 2013) | Japanese |
| | rs3130320 (intronic variant) | Systemic lupus erythematosus (Chung et al., 2011a) | European |
| | rs3134938 (intergenic variant) | Type I diabetes (age at diagnosis) (Syreeni et al., 2021) | European |
| | rs1270942 (intronic variant) | Autoimmune thyroid disease, type I diabetes (Tomer et al., 2015) | European |
| | rs9296015 (intergenic variant) | Systemic scleroderma (Gorlova et al., 2011) | European |
| | rs443198 (synonymous variant) | Systemic scleroderma (Gorlova et al., 2011) | European |
| *RBPJ* | rs12506688 (intronic variant) | Rheumatoid arthritis (Eyre et al., 2012; Kim et al., 2015) | Korean, European |
| | rs6448432 (intronic variant) | Rheumatoid arthritis (Orozco et al., 2014) | European |
| | rs874040 (intergenic variant) | Rheumatoid arthritis (Stahl et al., 2010) | European |
| | rs17630466 (intronic variant) | Rheumatoid arthritis (Eyre et al., 2012) | European |
| | rs16878091 (intronic variant) | Rheumatoid arthritis, type I diabetes (Marquez et al., 2018) | European |
| *DLL1* | rs1028488 (intergenic variant) | Interferon-α level in systemic lupus erythematosus (Kariuki et al., 2015) | European, African-American |
| | rs924043 (intergenic variant) | Type I diabetes (Bradfield et al., 2011) | European |
| *DLL4* | rs6492971 (intergenic variant) | Multiple sclerosis (International Multiple Sclerosis Genetics, 2019) | European |

viated inflammation-induced fibroblast proliferation but also decreased inflammatory cytokine production, such as IL-6 (Jiao et al., 2012; Nakazawa et al., 2001a). For specific mechanisms, Notch1 signaling has been functionally implicated in inflammatory RA fibroblasts (Gao et al., 2015; Nakazawa et al., 2001a; Nakazawa et al., 2001b), and Notch3 signaling has been recently identified to mediates the pathogenic expansion of *THY1*-expressing RA fibroblasts (Wei et al., 2020).

Given the successful attempts in experimental animal models, the Notch signaling pathway may represent a promising therapeutic target of RA. While the detailed mechanism, especially the Notch signaling regulated Th1/Th17 response in RA pathogenesis, still needs to be further investigated. Moreover, for a better therapy design, the evaluation of RA pathogenesis that is mediated by different

Notch receptors or ligands should be performed comprehensively, as evident by only moderate disease alleviation by blocking Notch1 comparing to Notch3 blockade in K/BxN mice serum transferring RA mouse model (Wei et al., 2020).

*Dysregulated Notch signaling is associated with SLE pathologies*

In SLE patients, upregulation of Notch signaling has been observed in local damaged renal tissues. Specifically, Notch3 expression is upregulated in kidney tissues of patients with lupus nephritis comparing to healthy individuals (Breitkopf et al., 2020). Moreover, the activation of Notch signaling in renal tissues with lupus nephritis is evidenced by the cleavage of Notch1 and Notch2 and the nuclear localization of Notch1 and Notch3 in podocytes (Lasagni et al., 2010; Murea et al., 2010). In addition to patients, the experimental mouse model showing lupus-like syndromes also exhibits altered Notch signaling in renal tissues (Breitkopf et al., 2020; Lemos et al., 2019; Zhang et al., 2010).

Although the global Notch signaling inhibition alleviates the damage of renal tissues and autoantibody production in lupus mouse model (Teachey et al., 2008; Zhang et al., 2010), the contributions from Notch signaling in specific cell types to the SLE pathogenesis are still under evaluation.

On one hand, Notch signaling is required for mounting adequate Th1 response during T cell activation, and Th17 differentiation has also been substantially proved to be dependent on Notch signaling (Tindemans et al., 2017). On the other hand, Treg cells could be negatively regulated by Notch signaling in mouse models for autoimmune diseases (Tindemans et al., 2017). As mentioned in RA disease setting, the pro-inflammatory role of Notch signaling in T cell response could be extrapolated from the current knowledge that elevation of Notch signaling in RA T cells accounts for the enhanced Th1 and Th17 but downregulated Treg response. In SLE patients, Notch signaling in T cells is dysregulated to the opposite directions between local damaged tissues and peripheral blood. In contrast to the upregulation of Notch signaling in damaged renal tissues (Breitkopf et al., 2020), the evidence showing decreased Notch signaling in peripheral T cells were collected as, first, the deceased Notch1 expression in SLE patients' T cells is mediated by cAMP-responsive element modulator α (CREMα) associated suppressive epigenetic regulation (Rauen et al., 2012); second, the Notch signaling activation could also be downregulated in SLE patients' T cells via soluble CD46 interfered interaction between Jagged1 and Notch receptor (Ellinghaus et al., 2017). Although inhibition of Notch signaling with γ-secretase inhibitor in lupus-prone mice significantly alleviates lupus-related autoantibody production, nephritis and local inflammation, the Notch signaling mediated T cell response seems to play a protective role in SLE disease progression. In SLE patients and *lpr* mice, disease-associated guanidinylated YB-1 functions as ligand for Notch3 to potently mediate Notch activation in kidney tissues and promote IL-10 production in T cells via Notch3 (Breitkopf et al., 2020). Similarly, in SLE peripheral blood, interfered Notch activation by soluble CD46 impedes the switching of IFN-$\gamma^+$ Th1 cells to IL-10 producing IFN-$\gamma^+$ Th1 cells (Ellinghaus et al., 2017), which have been named as Tr1 cells and play the role in peripheral immune tolerance (Pot et al., 2011). Meanwhile, the effector T cells in SLE patients is resistant to the suppressive regulation by Treg (Vargas-Rojas et al., 2008; Venigalla et al., 2008). Mechanistically, Notch activation in effector T cells potentiates receiving TGF-β signaling from Treg to mediate immune tolerance (Grazioli et al., 2017). Thus, bypass of suppression by Treg in SLE T cells is highly possible to be attributed to decreased Notch-coopted TGF-β signaling.

Given the crucial role of Treg in immune tolerance, the quantitative and qualitative defects in Treg have also been identified in SLE patients (Valencia et al., 2007; Vargas-Rojas et al., 2008). Then, could decreased Notch activity in T cells contribute to dysfunctional Treg response in SLE patients as well? Currently, the studies by specific manipulation of Notch signaling in mouse Treg cells suggest the suppressive function of Notch signaling in Treg maintenance or function in autoimmune disease-related settings (Charbonnier et al., 2015; Rong et al., 2016). However, the Notch related regulation in Treg development and function is rather complex, exemplified as the inconsistent conclusions on Notch-mediated *FOXP3* expression drawn by studies with various experimental systems, and the outcome of Notch activation during Treg development and maintenance depends on the contexts, the different combinations of Notch receptor-ligand pairs, different types of Treg cells, and specific tissue environments, which has been comprehensively reviewed by Paola G. et al. (Grazioli et al., 2017). For Treg in SLE patients, low CD25 expression is another disease-related Treg defect which could be related to Notch signaling (Horwitz, 2010). Although the *IL2RA* (CD25) gene locus has been identified as one of the risk alleles for SLE, such genetic mutation could barely explain the low CD25 expression in resting SLE T cells (Costa et al., 2017). Interestingly, Notch signaling could maintain CD25 expression in T cells (Adler et al., 2003), making it possible that downregulation of Notch signaling might lead to the defect of CD25 expression in SLE patients' T cells. Therefore, the decreased Notch activity in SLE patients' T cells could be hypothesized as one of the reasons for defects in Treg, and the further dissection of Notch signaling in SLE Treg cells would be informative to elaborate the Notch regulated Treg response during SLE pathogenesis.

According to the direct characterization of Notch signaling in kidney tissues of SLE patients, Notch signaling activation has been evidenced by increased cleavage of Notch1 and

Notch2 and increased expression of Jagged1 in glomerulus (Murea et al., 2010), and increased nuclear Notch1 and Notch3 in $PDX^+$ podocytes and increased nuclear Notch3 in $CD24^+$ renal podocyte progenitor cells in renal tissues of SLE patients (Lasagni et al., 2010). Moreover, the severity of glomerulosclerosis is closely correlated to increase of cleaved Notch1 in podocytes (Murea et al., 2010). Podocytes are the major structural component of glomerulus, and lupus nephritis manifests the loss of podocytes. Pathologically, the Notch signaling contributes to the loss of podocytes during pathogenic conversion in renal tissues by regulating the podocyte regeneration. For detailed mechanisms, human podocyte progenitor cells were isolated and cultured to differentiate into podocytes *in vitro*, and the downregulation of Notch signaling is related to $G_2$/M cell cycle arrest during differentiation (Lasagni et al., 2010). Although enforcing the Notch signaling activation by overexpressing Notch3-NICD in podocyte progenitor cells promotes the expression of podocyte marker genes, the progenitor cells were pushed through the cell cycle checkpoint by activated Notch signaling, which further resulted in cell death of podocytes by defected mitosis (Lasagni et al., 2010). In addition to lupus nephritis, other nephropathic models in mice also show that Notch signaling activation, specifically Notch1 and Notch3, in podocytes results in loss of podocytes, renal tissue damage and impaired kidney function (Asanuma et al., 2017). However, Notch2 activation in podocytes seems to function as the protective feedback loop to constrain cell death (Asanuma et al., 2017). Given the increased Notch2 activation in podocytes of SLE patients (Murea et al., 2010), the global inhibition of Notch signaling by γ-secretase inhibitor might undesirably lead to the dysfunction of such intrinsic protective pathway.

Unlike the overall pathogenic effect of upregulated Notch signaling in RA-related disease conditions, the disturbances of Notch signaling in SLE patients mediate different regulations to disease progression in context-dependent manners. Therefore, targeting Notch signaling for therapeutic purpose with global inhibition for activation is undesirable (Grosveld, 2009), and intervention with specificity for Notch signaling in SLE therapy is anticipated. Of note, DLL4 expression in DCs is upregulated under inflammatory conditions in both human and mice, and DLL4 in DCs could activate Notch signaling in T cells to induce Th1 and Th17 responses, which suggests the potential therapeutic strategy by targeting DLL4 to reverse the Th1/Th17 dominant inflammatory response (Meng et al., 2016). Moreover, the expansion of thymic DCs by DLL4 blockade promotes Treg differentiation (Billiard et al., 2012), and inactivation of DLL4-mediated Notch signaling in autoimmune disease mouse models results in disease remission and less inflammatory T cell response (Billiard et al., 2012; Reynolds et al., 2011). As above, not only the genetic association, dysregulation of Notch signaling in autoimmune diseases leads to the disease progression in autoimmune diseases. Given receptors, ligands and even critical enzymes in Notch signaling are promising druggable targets, further translational investigations that target the context-dependent regulation by Notch, especially for T cells in autoimmune diseases, require a detailed evaluation for the specific Notch receptor-ligand pairs that contribute to the imbalanced Th1/Th17 autoimmune response. Last but not the least, the actual genetic effects on Notch signaling are still largely unknown in autoimmune diseases. The majority of identified genetic variants aligned to Notch signaling are distributed in non-coding regions (Table 1), which suggests that these genetic variants mediate transcriptional regulation via DNA regulatory elements, but not interfering the translation. Therefore, the actual positive or negative regulation to the Notch signaling should be further evaluated with advanced methodologies, such as CRISPR-Cas system implemented genome editing, and the cell-type specific regulation should also be considered during the evaluation (Stewart et al., 2020).

### *Mitochondria-centric metabolism associated genes in autoimmunity*

Among hundreds of risk loci identified in autoimmune diseases, there are genes related to mitochondrial function and cellular metabolism. For example, *C4orf52* in RA and *CMC1* in AS encode the components of the mitochondrial translation regulation assembly intermediate of cytochrome *c* oxidase (MITRAC) (Ellinghaus et al., 2016; Okada et al., 2014; Timón-Gómez et al., 2018). Such SNPs suggest the dysregulated electron transport in inner membrane of mitochondria, and subsequent mitochondrial hyperpolarization and impaired ATP synthesis could lead to ROS production, metabolic program switching and vulnerability to inflammation induced cell death (McGarry et al., 2018). To discuss the pathogenic role of mitochondria malfunction in autoimmune diseases, we will focus on the mitochondria-centric ROS production and metabolic disturbance during disease progression and metabolic-related regulation of inflammatory response in autoimmunity, such as RA and SLE associated pathological processes.

In many inflammatory conditions, accumulation of ROS leads to oxidative stress. Generally, ROS is considered as pro-inflammatory mediator, which exacerbates inflammation via multiple parallel mechanisms. Firstly, ROS could promote the activation of inflammatory signaling pathways, such as TNF-induced NF-κB activation (Blaser et al., 2016). Secondly, ROS could actively mediate oxidation of cellular contents, including neutrophilic mitochondrial DNA which makes the major contribution to type I IFN production in SLE pDCs (Caielli et al., 2016; Lood et al., 2016). Thirdly, dysfunctional mitochondria under oxidative stress are asso-

ciated with reprogramed metabolic profile of immune cells in disease settings, which closely interact with local inflammatory environments and modulate the inflammatory phenotypes of immune cells (Huang and Perl, 2018). Given the accumulating evidence on metabolic pathway regulated inflammation in autoimmune diseases, targeting reprogramed metabolic profile has been considered as one of the promising therapeutic strategies for autoimmune disease treatment.

*Glycolysis, oxidative phosphorylation and ROS in RA and SLE T cells*

Although the glucose metabolism is one of the major energy sources during the immune response, the following metabolic processes are diverse, referring to glycolysis, oxidative phosphorylation and pentose phosphate pathway. Glycolysis (or aerobic glycolysis) and oxidative phosphorylation produce ATP to fuel the immune response, but two pathways are polarized into two directions to govern the different inflammatory phenotypes of immune cells (O'Neill et al., 2016). In most cases, increased glycolysis associates with inflammatory immune cells, and increased oxidative phosphorylation associates with anti-inflammatory or non-inflammatory phenotypes. In T cells, the associations between metabolic status and T cell function in different subsets or different activation states have been extensively studied (Saravia et al., 2020). In shorts, glycolysis-featured Th1 and Th17 cells also require glycolytic pathway for differentiation, and *FOXP3* expression in Treg cells coordinates programming of high mitochondrial oxidation and low glycolysis metabolism.

In SLE patients, T cells exhibit elevated glucose metabolism compared with the T cells from healthy individuals (Doherty et al., 2014; Yin et al., 2015). Glucose uptake is mediated by glucose transporters, and the most well-studied glucose transporter, GLUT1, is highly expressed in SLE T cells (Koga et al., 2019). Interestingly, the mice overexpressing GLUT1 develop lupus-like phenotypes (Jacobs et al., 2008), such as autoantibody production and immune complex deposition in kidney tissues, which suggest the pathogenic role of enhanced glucose metabolism. Meanwhile, both the increased oxidative phosphorylation and increased glycolysis rate have been observed in SLE T cells (Doherty et al., 2014; Yin et al., 2015), but such increased glucose metabolism fails to generate ATP and leads to an ATP-depriving condition in SLE T cells, which is part of the prominent oxidative stress in SLE pathogenesis that mitochondria hyperpolarization accounts for failure of ATP generation and promotes production of ROS (Perl, 2013). Moreover, the accumulation of ROS could also be resulted from impaired ROS-neutralizing system, antioxidant-glutathione and NADPH from pentose phosphate pathway, in SLE patients (Gergely et al., 2002; Perl et al., 2015). Thus, increased glycolysis could promote Th1 or Th17 differentiation in SLE patients based on previous findings. Additionally, the oxidative stress manifested by accumulation of ROS could also contribute to altered T cell responses, where increased oxidative stress associates with enhanced Th1/Th17 response and SLE disease progression (Scavuzzi et al., 2018). The topic on promotion of Th17 differentiation by ROS in various autoimmunity conditions has been previously summarized (Peng et al., 2021). Thus, with such upregulated glycolysis and redox signaling in SLE T cells, a Th1/Th17 dominant T cell response could be derived from these rewired metabolic pathways.

T cells in RA patients also suffer the ATP shortage, which could be resulted from defected mitochondrial biogenesis that is caused by deficiency of nuclease MRE11A in RA T cells (Li et al., 2016b; Li et al., 2019b). While, another mechanism for ATP deprivation is rewired glucose metabolism in RA T cells. In contrast to enhanced glycolysis in SLE T cells, RA T cells show low glycolytic metabolism profile (Yang et al., 2013; Yang et al., 2016). Actually, glucose metabolism is still utilized by RA T cells, but glycolysis is switched to pentose phosphate pathway by insufficient expression of glycolytic enzyme 6-phosphofructo-2-kinase (*PFKFB3*) and upregulation of glucose-6-phosphate dehydrogenase (*G6PD*) (Yang et al., 2013). Consequently, hyperproduction of NADPH from the pentose phosphate pathway neutralizes ROS in RA T cells, and the redox-sensitive kinase, ataxia telangiectasia mutated (ATM), remains inactive during T cell proliferation, which allows the RA T cells to hyper-proliferate by bypassing the $G_2$/M cell cycle checkpoint and further differentiate into Th1 and Th17 cells (Yang et al., 2016). Thus, the glucose metabolism promotes the RA pathogenesis via pentose phosphate pathway-mediated inflammatory T cell response.

*Metabolic abnormality in other immune cells in autoimmunity*

In both RA and SLE-related disease conditions, besides T cells, the metabolic signatures of macrophages and other immune cells are largely unknown. Under inflammatory environments, activated macrophages adapt to the dysfunctional mitochondria and promote glycolysis to measure up to sufficient ATP production (Kelly and O'Neill, 2015). Meanwhile, the reduced rate of oxidative phosphorylation will make metabolites in tricarboxylic acid (TCA) cycle accumulate, which could modulate inflammatory genes expression, such as succinate-stabilized HIF1α for *Il1b* expression (Murphy and O'Neill, 2018). Macrophages or monocytes could undergo similar metabolic reprogramming in autoimmune diseases. For example, in RA synovium, not only enriched lactate suggests the high level of glycolysis in tissues (Fujii et al., 2015; Haas et al., 2015; Kim et al., 2014), but accumulation of intermediate metabolites in TCA cycle

is also evident in RA synovial fluids (Kim et al., 2014). Despite of the to-be-determined macrophage-specific metabolic profile in RA synovium, autocrine or paracrine of succinate has been implied to mediate pathogenic IL-1β production in RA synovial macrophages via macrophage-expressed succinate receptor, GRP91 (Littlewood-Evans et al., 2016). Therefore, metabolic reprogramming in inflammatory tissues profoundly influences the pathogenic role of macrophages in autoimmune diseases, caused by the intrinsic or extrinsic metabolic signals (Liang et al., 2020). Further metabolic characterization of macrophages and other immune cells in autoimmune diseases would be informative to deepen our understanding of the immunometabolism-related pathogenic mechanisms.

### *Future perspective: understanding autoimmunity at the single cell level*

Single cell sequencing of mRNA expression levels for each individual cell in inflammatory conditions provides unique opportunities to dissect the inflammatory phenotypes in autoimmune diseases at an unprecedented resolution. Single cell expression profiles may aid in identification of disease-specific cell subsets in lesion tissues and circulation as well as extrapolation of the complex intercellular communication networks. One of the successful examples for investigation of autoimmune disease pathogenesis with scRNA-seq is in RA synovial tissues. In 2019, Accelerating Medicines Partnership Rheumatoid Arthritis and Systemic Lupus Erythematosus (AMP RA/SLE) Consortium published their multi-center investigations on the inflammatory characteristics of cellular components in RA synovial tissues (Zhang et al., 2019a). This study revealed the unexpected inflammatory phenotypes of local immune cells and fibroblasts, where *HLA-DRA*$^{hi}$ sublining fibroblasts, but not monocytes, are one of the major *IL6* expressing cell types in RA synovial tissues, and CD8$^+$ T cells, but not CD4$^+$ T cells, are the major contributors for *IFNG* expressing cells in RA synovial tissues. Meanwhile, the expanded *THY1* (CD90)$^+$ *HLA-DRA*$^{hi}$ sublining fibroblasts, *IL1B*$^+$ pro-inflammatory monocytes, *ITGAX*$^+$*TBX21*$^+$ autoimmune-associated B cells and *PDCD1*$^+$ peripheral helper T cells and follicular helper T cells were identified by scRNA-seq as RA-associated cell subsets comparing to osteoarthritis patients' synovial tissues (Zhang et al., 2019a). The insightful findings on RA-associated cell subsets not only solidified the previously identified pathogenic role of peripheral helper T cells in RA synovium (Rao et al., 2017), but also guided the following studies pursuing the RA pathogenesis mediated by Notch-induced sublining fibroblasts and pathogenic *HBEGF*$^+$ monocyte subset (Kuo et al., 2019; Wei et al., 2020). In this regard, the successful experience of scRNA-seq analysis for RA synovial tissues could be broadly applied to inflammatory tissues in autoimmune diseases, and advanced bioinformatics tools could be used to identify the prominent signaling pathways that are potentially involved in formation and functionality of disease-associated cell subsets (Armingol et al., 2021).

In the past few years, a subset of autoimmune diseases have been analyzed by the approach of single cell expression profiling (Baglaenko et al., 2021). Studies of individual disease types have achieved certain success such as identification of disease-associated immune cell subsets. Nevertheless, illustrating generic versus disease-specific inflammatory phenotypes across various autoimmune diseases remains challenging given the difficulty of integrating distinct data sets from different sources (Stuart and Satija, 2019). Another promising direction for single cell sequencing data analysis is the single cell immunometabolism (Artyomov and Van den Bossche, 2020). In conventional metabolism profiling for immune cells, the metabolites are measured in bulk cell populations, which demands a large quantify of purified immune cells in certain types. However, the limited size and amount of tissue samples demand the alternative experimental strategies to characterize the metabolic features of immune cells in inflammatory tissues from autoimmune disease patients. With the successful compiling of metabolic features from transcriptome data in immune cells, the current methodologies for transcriptome-based metabolic analysis are developed based on either pathway-based analyses or flux balance analysis (FBA)-based methods, which are conducted for evaluation of specific metabolic pathways or global characterization of interactively connected metabolic networks, respectively (Artyomov and Van den Bossche, 2020). Excitingly, both pathway-based analysis and flux balance analysis have been successfully applied for scRNA-seq-based investigations in disease-related immunometabolism (Miragaia et al., 2019; Wagner et al., 2021). Therefore, combining single cell expression profile and advanced bioinformatics tools could be the powerful approach to dissect metabolic status of immune cells in autoimmune diseases.

Genetic risk factors have been identified in various autoimmune diseases, among which some gene loci encode components of multiple pathways with specified functionality in immune system. The abnormalities in these pathway associate with break of self-tolerance and excessive inflammation, contributing to the pathogenesis, such as HLA alleles and *ERAP1*/*2*-related antigen presentation and *IFNAR1*-related type I IFN pathway. Meanwhile, some genetic variants could not be directly aligned to autoimmunity and inflammation. The pathways behind these variants are being functionally associated to autoimmune diseases with accumulating knowledge, such as Notch signaling and metabolic pathway related immuno-pathogenesis. In future, annotating the variants with unknown functionality into the pathological

processes will provide in-depth dissection of predisposed disease-prone conditions with therapeutic insights.

## T cell and autoimmune diseases

The expansion of self-reactive T cells is a biomarker in many autoimmune diseases, which is essential in orchestrating both innate and adaptive immune responses and inducing tissue damage. Among which, $CD4^+$ T cell is the major contributor by secreting several cytokines, chemokines and cell-cell interaction. As we discussed above, GWASs have been widely used to identify susceptibility genes in autoimmune diseases, and a number of related mutations in the T cells have been identified, including SNPs in *IL23R*, *IL17A*/*F*, *IL21*, *JAK2*, *STAT2*, *CARD9*, *CCR6* and etc. (Kochi, 2016). When activated by antigen presenting cells (APCs), $CD4^+$ T cells differentiate into distinct lineages in a context-dependent manner with unique functions, including T helper (Th) 1, Th2, Th17, Th9, T follicular helper (Tfh) and regulatory T (Treg) cells.

### *T cell subsets and autoimmune diseases*

*Th1/Th2 cells*

Three decades ago, Mosmann and Coffman divided T helper cells into two groups: Th1 and Th2 T cells. Th1 cells express IFN-γ and are important in cellular immunity and autoimmune diseases, whereas Th2 cells express IL-4, IL-5, and IL-13, and are related to humoral immunity and allergic diseases (Mosmann and Coffman, 1989). The Th1/Th2 binary paradigm had been prevailing for almost two decades until further new mechanisms have been revealed in mouse models of autoimmune diseases early this century.

Th1 cells are important pathogenic players in autoimmune diseases. The development of Th1 cells is induced by IL-12 and IFN-γ, and is tightly regulated by the master transcription factor T-bet. One of the major functions of Th1 cells is secreting IFN-γ, an important pro-inflammatory cytokine that activates macrophage and upregulates MHC-II expression on APCs. Elevated IFN-γ expression has been found in several autoimmune diseases, including IBD, MS, RA, SLE patients and etc. T cells infiltrated in central nervous system during experimental autoimmune encephalomyelitis (EAE), the mouse model of MS, showed increased IFN-γ and lymphotoxin secretion, but not IL-4, indicating that Th1 instead of Th2 cells are essential in this model (Ando et al., 1989). However, mice with IFN-γ deficiency are still susceptible to EAE. Later studied revealed that IL-23, instead of IL-12 which shares the common chain p40 with IL-23, is necessary for EAE pathogenicity (Cua et al., 2003), leading to the identification of autoimmune-mediated Th17 cells and the query of Th1 cells function in autoimmune diseases. The following studies revealed that IL-12 and IL-23, as well as modulated Th1 and Th17 cells, induce distinct types of EAE with different pathological phenotypes and diseased lesions (Kroenke et al., 2008). Moreover, Th1 cells facilitate Th17 cells to entry into the central nervous system (O'Connor et al., 2008). Similarly, pathogenic function of Th1 cells, including its effector molecule IFN-γ or the regulatory factors T-bet and STAT4, have been found in other autoimmune diseases, including experimental autoimmune uveitis (EAU), collagen-induced arthritis (CIA) and colitis (Raphael et al., 2015).

Th2 cell development is mainly induced by IL-4 and IL-2, and use GATA3 as the master transcription factor. Compared with Th1 and Th17 cells, the function of Th2 cells in regulating autoimmune diseases is restricted and less well studied. The pathogenic role of Th2 cells in asthma have been widely studied, and several drugs targeting Th2 related cytokines have been approved to be effective in severe asthma patients (Lee et al., 2021; León and Ballesteros-Tato, 2021). Lyn deficient mice, an important Th2 negative regulator, develop strong Th2 response with severe asthma (Beavitt et al., 2005). Interestingly, these mice develop spontaneous autoimmune disease that mimic lupus-like nephritis at late life stage, with increased self-reactive IgE, and deleting *Il4* greatly reduced IgE production and ameliorated disease severity (Charles et al., 2010). Considering the function of IL-4 in inducing B cell immunoglobulin class switching to IgG1 and IgE, Th2 might be important in mediating B cell dependent autoimmune responses.

*Th17 cells*

The discovery of the unique function of IL-23 in inducing IL-17A producing T cells and autoimmune diseases, but not IL-12, the Th1 cell inducer that shares a common p40 subunit with IL-23, strongly suggest the presence of a distinct T cell subset (Cua et al., 2003). In 2005, our group together with others established a new T cell subset, Th17 cells, based on their IL-17A secreting function and independent developmental requirements.

Despite their importance in host protective immune responses and maintaining tissue homeostasis, excessive Th17 cell responses cause various tissue inflammations and multiple autoimmune diseases, indicated by high frequency of Th17 cells in the blood or affected organs. In multiple sclerosis, elevated IL-17A has long been found in lesions of active patients, and Th17 cells migrate efficiently through the blood-brain barrier and kill neurons. In arthritis patients, IL-17A level in synovial fluid significantly increased, which directly induces osteoclastogenesis. Similarly, IL-17A expression also increased in both active CD and UC patients (Korn et al., 2009). Moreover, mucosal IL-23p19, IL-23R and IL-17A expression were elevated in anti-TNF therapy non-responders compared to those in responding patients

(Schmitt et al., 2019). GWAS also has linked a number of gain-of-function mutations in the Th17/ IL-17 axis to many autoimmune diseases, including SNPs in *IL23R*, *CCR6* and *IL17A*/*F* (Kochi, 2016). The essential causative role of Th17 cells have been further confirmed by a large cohort of clinical studies targeting key components in Th17 related pathways, including IL-6, IL-23, IL-17, STAT3 and IL-17RA, which would be discussed later.

The development of Th17 cells is tightly regulated by epigenetic modifications, transcriptional network and multiple cytokines. RORγt and RORα, highly expressed in Th17 cells compared with other lineages, are two essential transcription factors for Th17 cells. The combination of TGF-β and IL-6 is essential for Th17 cell initiation, and IL-1β and IL-23 further enhanced Th17 response. However, in human, IL-21, instead of IL-6, is more important in inducing Th17 cells in combination with TGF-β (Dong, 2021). Th17 cell pathogenicity is specifically regulated. IL-23 is the critical cytokine to induce pathogenic Th17 cells, as well as TGF-β3 and SAAs. The single cell study also revealed several pathogenicity regulators, including *Gpr65*, *Plzp*, *Toso*, and *Cd5l*. Interestingly, recent research found that IL-17A in turn limits Th17 pathogenicity through inducing autocrine secretion of IL-24 (Chong et al., 2020).

Environmental factors are also involved in regulating Th17 cells development and pathogenicity. Microbiota, such as commensal bacteria SFB, is essential to induce intestinal Th17 cells at steady state, while pathogens such as *Citrobacter rodentium* induce transcriptional and metabolic different pathogenic Th17 cells (Omenetti et al., 2019). Ketogenic diets decrease gut Th17 cells through inhibiting bifidobacterial growth (Ang et al., 2020). Moreover, not only gut microbiota, but also oral inflammation related pathobionts induce Th17 cells response and facilitate colitis (Kitamoto et al., 2020). Importantly, Th17 cells with dual-TCR that recognize both SFB and self-antigen provoke lung autoimmunity (Bradley et al., 2017), emphasized the potential importance of microbiota induced Th17 cells in autoimmune responses. We also found that fever, the common symptom in many autoimmune diseases, promotes Th17 cells differentiation and pathogenicity by promoting SMAD4 SUMOylation (Wang et al., 2020). High salt diet also markedly increases Th17 cell differentiation and exacerbates Th17 associated autoimmune diseases, by inducing inflammatory related genes expression such as *Tnf*, *Ccl20*, *Il23r* and *Csf2* (Kleinewietfeld et al., 2013).

Unlike relatively stable Th1 and Th2 cells, Th17 cells are highly heterogenous and plastic in response to various environmental conditions. Using *Il17a*$^{cre}$*Rosa*$^{YFP}$ fate mapping mice, researchers found that Th17 cells may lose IL-17A secreting ability and start to express IFN-γ in EAE model, and almost all the IFN-γ-expressing CD4$^+$ T cells in spinal cord converts from ex-Th17 cells. Th17 cells with *Tbx21* deficiency, which encodes T-bet, cannot induce EAE, further highlighting the importance of Th17 cells plasticity in driven autoimmune diseases (Kamali et al., 2019). In peyer's patch, Th17 cells deviate to Tfh phenotype expressing PD-1 and CXCR5, and is necessary for IgA production by GC B cells (Hirota et al., 2013). Later, Th17 cells expressing IL-10, which convert to Tr1-like cells, was identified both at steady state or under pro-inflammatory condition in gut (Gagliani et al., 2015). The ex-Th17 cells also could convert to IL-4 secreting cells in asthma model (Tortola et al., 2020), and Th17 cells losing RORγt expression spontaneously convert into IL-4-expressing Th2-like cells (Chi et al., 2022). All these findings lead to the potential considerations of therapeutic targeting Th17 cells.

IL-17A, the major Th17 signature cytokine, plays a key role in inducing tissue inflammation and damage in various autoimmune diseases through modulating cellular responses. IL-17A dominantly signals in non-hematopoietic cells through IL-17RA and IL-17RC, such as fibroblast, epithelial cells and endothelial cells (Korn et al., 2009). IL-17A induces cascade inflammatory response by promoting these cells secreting a large cohort of inflammatory cytokines, chemokines, matrix metalloproteinases and antimicrobial proteins. CXCL1, CXCL2 and CXCL8 further recruit myeloid cells such as neutrophils to the inflamed tissues. IL-17A also participates in humoral immunity through regulating germinal center reaction and antibody production. In pSS patients, the increased IL-17A is correlated GC formation and autoantibodies levels (Verstappen et al., 2018). IL-17A directly promotes Tfh cell localization to the light zones, B cells proliferation/isotype class switching, and T and B cell interactions through activating stromal cells to support follicular organization (Subbarayal et al., 2016). In addition to Th17 cells, IL-17A is also expressed by several innate immune cell subsets, including ILC3, γδ T, NK, NKT and neutrophils, which play similar or redundant roles but function as the first line responders in response to various immune challenges or host requirements (Dong, 2021).

*Tfh cells*

One of the fundamental functions of CD4$^+$ T cells is helping B cells and antibody response. Tfh cell is a specialized subset that helps geminal center (GC) formation, a unique structure in the follicles of secondary lymphoid organs, and helps B cells undergo immunoglobulin somatic hypermutation, antibody isotype class switch and differentiation into plasma or memory B cells. They were initially described in human tonsils, where several groups identified a distinct CD4$^+$ population highly expressing surface marker CXCR5, as well as co-stimulatory molecules ICOS and PD-1, cytokine IL-21 and specific transcription factor BCL-6. The surface molecules ICOS, PD-1 and CD40L directly bind with their receptors expressed on B cells and thus induce B cell

proliferation, maturation and differentiation, which is also promoted by Tfh secreted cytokines such as IL-21 (Crotty, 2011). The T-B interaction and cytokine production support GC B cells producing high-affinity antibodies upon antigen stimulation.

Tfh cells are important in driving autoimmune response, especially in autoantibody mediated or associated diseases. In active SLE patients, autoreactive GC B cells and increased circulating Tfh cells (cTfh) in blood have long been observed, with increased cTfh2 but decreased cTfh1 response. The altered cTfh cells is correlated with disease severity, plasma cell abundance and autoantibody titers. Moreover, functional Tfh cells and T-B aggregates have been observed in lupus nephritis (Blanco et al., 2016). Similarly, increased cTfh cells expressing high levels of ICOS and PD-1 also have been found in several other autoimmune diseases such as T1D, RA, MS, and pSS (Ueno et al., 2015). Tfh involved ectopic lymphoid-like structure (ELS), which supports autoantibody response by B cells in peripheral tissues, also have been found in synovial tissue in RA patients, meninges in MS patients and salivary glands in SS patients (Pitzalis et al., 2014). The pathogenic role of Tfh cells in autoimmune diseases have been further confirmed in mouse models. Sanroque (*Roquin*$^{san}$) mice, with uncontrolled systemic autoantibody production and increased Tfh cell number in B cell follicles, have lupus-like autoimmune phenotypes. Depleting *Bcl6* is sufficient to ameliorate the lupus phenotype with dramatically reduces spontaneous GC formation and Tfh cell number, which directly established the causative role of Tfh cells in driving autoimmune response (Linterman et al., 2009). Consistently, the pathogenic function of BCL-6, ICOS, OX40, CXCR5, SAP and IL-21 signaling in lupus models, experimental Sjögren syndrome (ESS) model or RA models also have been established (Gensous et al., 2018). Meanwhile, the essential role of IFN-γ or IL-4/IL-13 expressing Tfh cells has been identified in response to virus infection and allergy, respectively (Feng et al., 2022; Gowthaman et al., 2019). Whether Tfh plasticity related antibody response is involved in autoimmune diseases remains to be further analyzed.

The multistage differentiation of Tfh cells is tightly regulated, but not yet fully understood. DC activation allowed CD4$^+$ T cells upregulating CXCR5 and downregulating CCR7 expression to migrate to the T-B border. The following T-B interaction through ICOS-ICOSL and MHC-peptide further drives GC-Tfh maturation and promotes GC formation (Crotty, 2011). Our group, together with others, have identified BCL-6 as the master transcription factor for Tfh cells development, while ASCL2, but not BCL-6, directly promotes *Cxcr5* transcription and further promotes Tfh migrating into the follicles. TOX2, induced by BCL-6, also is needed for optimal Tfh differentiation and promotes BCL-6 expression in a feed-forward loop (Dong, 2021). The differentiation of Tfh cells is also regulated by cytokine milliu. Deficiency of both IL-6 and IL-21 signaling, but not either cytokine alone, significantly reduces Tfh numbers, suggesting potential redundant function of these cytokines, while IL-7 and IL-2 suppress Tfh development. In human, different cytokine milieu is required to induce Tfh cells. IL-12 is more important in inducing BCL-6 expression at early stage, together with TGF-β and IL-23, to induce the expression of various Tfh signature genes, including CXCR5, ICOS, IL-21, BATF and BCL-6 (Crotty, 2014). Environmental factors, such as gut microbiota, are also involved in systemic Tfh cell response. In RA patients, SFB induced Tfh cells in peyer's patch enter systemic circulation and boost autoantibody production to exacerbate arthritis (Teng et al., 2016). Treating arthritis mice with antibiotics significantly abrogated disease progress with reduced Tfh cell number, germinal center formation and autoantibody production (Block et al., 2016).

*Treg cells*

A functionally distinct T cell subset that maintains self-tolerance and homeostasis has long been observed, with specific expression of transcription factor FOXP3, determined as Treg cells. The development of Treg cells is induced by several cytokines such as TGF-β, IL-2, TSLP, IL-33, and IL-6, environmental factors, microbiome such as *Clostridia* strains, and metabolisms of gut microbiota and diet such as bile acids, retinoic acid, short chain fatty acid and amino acids (Kanamori et al., 2016).

In human, disrupted *FOXP3*, the master transcription factor for Treg cells, results in immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome, accompanied with various autoimmune diseases, linking the crucial function of Treg cells to autoimmune diseases. People with CD25, STAT5B and CTLA4 deficiency, other Treg related molecules, also develop severe autoimmune syndromes indistinguishable with IPEX. Treg specific variants are common features in autoimmune diseases. Polymorphisms in *FOXP3*, *CTLA4* and *CD25* are highly correlated with disease onset in autoimmune thyroid diseases, T1D and multiple sclerosis patients respectively (Ohkura et al., 2020). Importantly, Treg cells isolated from MS patients are indeed defected in their suppression ability, and Treg cells in RA patients express low levels of CTLA4 compared with healthy control (Mohr et al., 2019). In consistent with human patients, mice with FOXP3, CD25 and CTLA4 deficiency also develop autoimmune pathology in multiple organs, and CD4$^+$CD25$^{hi}$ Treg cell transfer rescued the lymphoproliferative syndromes (Fontenot et al., 2003).

Treg cells restrain immune response through several mechanisms. Treg cells contain TCR repertoires strongly recognize self-antigen/MHC complex in the thymus, and are more sensitive to self-peptides upon activation compared

with conventional T cells in the peripheral, which enabled Treg dependent self-tolerance (Sakaguchi et al., 2008). Treg cells express a broad spectrum of surface molecules including CD25, CTLA4, TIGIT, CD39 and CD73 to compete with effector T cells and further inhibit T cell activation and expansion. Meanwhile, Tregs also secret immunosuppressive cytokines such as IL-10, TGF-β and IL-35. The precise function of these cytokines in modulating autoimmune diseases is not fully understood. IL-10 directly inhibits the antigen presentation ability of APCs and further prevents the development and function of effector/memory T cells such as Th1 cells, or directly inhibit IL-10Ra-expressing Th17 and Th1/Th17 cells pathogenicity (Huber et al., 2011). TGF-β not only limits T cell proliferation and promotes apoptosis by antagonizing antiapoptotic BCL-2 expression, but also modulates DCs and directly regulates Th17/Treg balance (Travis and Sheppard, 2014). Moreover, Treg cells also directly secret Grzm B and perforin to induce targeted cells death, including APCs.

Treg cells are heterogenous. T-bet expressing Treg cells are induced by IFN-γ stimulation, and specifically restrain IFN-γ but not IL-17A and IL-4 expressing $CD4^+$ T cells. GATA3 expressing Treg cells have been found both at steady state and during inflammation. Both T-bet and GATA3 expression is highly dynamic, and deleting both *Tbx21* and *Gata3* in Tregs results in severe autoimmune-like diseases at young age in mice (Yu et al., 2015). Meanwhile, RORγt-expressing Treg cells, mainly resident in intestines at steady state, restrain both Th1/Th17 mediated colitis and Th2 associated helminth infection. Deleting STAT3, another Th17 specific transcription factor, in Treg cells results in fatal intestinal inflammation with increased IL-17A expression but not IFN-γ and IL4, indicating selective dysregulation of Th17 mediated inflammation (Qiu et al., 2020). Our group also identified a population of Treg cells that express both FOXP3 and BCL-6, named Tfr cells. These cells derived from nTregs in the peripheral and suppress germinal center reactions (Chung et al., 2011b). Deficiency of *Bcl6* in Tregs promotes humoral autoimmunity in ESS model (Fu et al., 2018). These transcription factors on the one hand control surface markers expression on Treg cells such as CXCR3, CCR6 and CXCR5, to promote the migration of Treg cells into inflammatory sits. On the other hand, inhibitory function of Tregs was directly regulated since effector molecules expression, such as *Il10* and *Gzmb*, were reduced in Tregs lacking T-bet.

*Others*

$T_{GM\text{-}CSF}$. Using the GM-CSF fate-mapping mice, Becher et al. found that T cells producing GM-CSF is a discrete subset induced by IL-23 and IL-1β (Komuczki et al., 2019). Considering its function in promoting myeloid cells migration, activation and survival, GM-CSF might be important in the cellular immune response dependent autoimmune diseases. So far, GM-CSF is the only cytokine that have been found to completely abolish EAE progress after deletion, but not IL-17A or IFN-γ (Codarri et al., 2011). This finding also reminds us that Th17 cells might not be the only target of IL-23. Blocking GM-CSF also ameliorates disease severity in the CIA model (Cook et al., 2001). In the EAU model, inflammation still happens in the IL-17A and IFN-γ double deficiency mice, indicating the presence of an extra effector pathway. Blocking GM-CSF in these mice further reduced EAU severity, with decreased eosinophil infiltration (Bing et al., 2020). Based on these promising pre-clinical results, drugs anti-GM-CSF has been widely studied in clinical trials treating RA and MS.

*$CD8^+$ T cell*. The function of $CD8^+$ T cells in infection disease and cancers have been widely analyzed (Guo and Dong, 2022; Zhao et al., 2020). Interestingly, increasing evidences indicate that $CD8^+$ T cells are also involved in the pathogenicity and protection in autoimmune diseases. In the central nervous systems of MS patients, infiltrated $CD8^+$ T cells even outnumber of $CD4^+$ T cells. Moreover, $CD8^+$ T cell mediated severe CNS inflammation with similarities to MS patients not found in $CD4^+$ T cell mediated EAE (Huseby et al., 2001). The cytotoxic function of $CD8^+$ T cells, including FASL and granules secretion, potentially induces cell death and promotes self-antigens exposure. Meanwhile, $CD8^+$ T cell secreted cytokines, such as IFN-γ, TNFα and IL-17A, are well-characterized pro-inflammatory in autoimmune responses. Beyond the pathogenic function of $CD8^+$ T cells in MS, SLE, T1D and Grave's disease, regulatory $CD8^+$ T cells also have been characterized in MS, colitis, lupus, RA and T1D. These cells help to control disease development by secreting IL-10, restricting self-reactive $CD4^+$ T cells, rendering APC tolerogenic and cytotoxic activity (Li et al., 2022; Yu et al., 2018).

*Double negative T cells*. The $TCR\alpha\beta^+CD3^+CD4^-CD8^-$ (double negative, DN) T cell is a small fraction of peripheral $CD3^+$ T cells counting 1%–3%, with little understanding about its biology. The expansion of DN T cells is a characteristic phenomenon in autoimmune lymphoproliferative syndrome, and DN T cell number in blood is correlated with autoantibody titertiter (Li et al., 2016a). Similarly, the increased cell number of DN T cell also is correlated with disease severity in SLE patients, and these cells could express IL-4, IL-17A, IFN-γ and TNFα. Meanwhile, DN T cells infiltrated into salivary glands also could produce IL-17A in SS patients (Brandt and Hedrich, 2018). Briefly, DN T cells might participate in the system and local inflammation by producing cytokines and modulating B cell response, and more studies are needed to understand its function in autoimmune diseases.

*Tissue resident memory T cells (Trm)*. Trm cells, including $CD4^+$ and $CD8^+$ Trm cells, are long-lived memory T cells

resident in peripheral tissues, defending against pathogens. The importance of Trm cells in autoimmune diseases has drawn attention in recent years, especially in skin diseases, including psoriasis, mycosis fungoides and fixed drug eruption. Cytotoxic Trm cells expressing IFN-γ or IL-17A have been identified in vitiligo and psoriasis patients. Importantly, targeting CD122, the receptor for IL-15 which promotes the Trm cells development, reversed vitiligo development in mouse model, highlighting the potential clinical application of targeting Trm cells (Ryan et al., 2021). Trm cells accumulated in the gut of IBD patients express a large amount of pro-inflammatory cytokines such as *Il17a*, *Tnf*, *Ifng* and *Il13*. The enrichment of Trm cells, especially $CD4^+$ Trm cells, significantly correlated with the clinical flares of IBD patients (Zundler et al., 2019). Trm cells in intestines also provide perspective of the non-responsiveness of Vedolizumab treatment in some IBD patients, which blocks lymphocytes gut homing. Diverse Trm cells also have been found in human brains, including in MS patients. Interestingly, viral infection at early life promotes the generation of CCL5-producing Trm in brain, which predispose brain autoimmunity later in life in the mouse EAE model (Steinbach et al., 2019). All these observations highlight the importance of autoantigen-specific Trm cells in promoting autoimmune diseases, and the potential of targeting Trm cells for treatment.

### *T cell targeted therapy*

Underlining the importance of T cells in mediating autoimmune diseases and the limited clinical drug choices, targeting T cells has gained extensive attention. Anti-TNF antibodies have achieved huge success in autoimmune diseases. With more targets identified, especially pro-inflammatory cytokines, targeting T cells have achieved great success, and innovation methods also have been widely studied in pre-clinical experiments.

#### *Targeting Th17 cells*

Immediately following their discovery, Th17 cells have been linked to a wide range of autoimmune diseases, and received great attentions from both basic research field and pharmaceutical companies. The essential causative role of Th17 cells also have been further confirmed by a large cohort of clinical studies targeting key components in Th17 related pathways, including IL-6, IL-23, IL-17A, STAT3 and IL-17RA. So far, nine monoclonal antibodies and one small molecular inhibitor targeting Th17 pathway have been approved for treatment of various autoimmune diseases by FDA (Table 2). These include 2 targeting IL-6 receptor (Tocilizumab and Sarilumab), 4 monoclonal antibodies targeting IL-23 (Ustekinumab, Tildrakizumab, Guselkumab and Risankizumab) and 3 targeting IL-17 or IL-17RA (Secukinumab, Ixekizumab, Brodalumab), as well as Tofacitinib, a JAK1/3 inhibitor that inhibits STAT3 activation. Despite all these drugs block Th17 cell responses, they display distinct effects among different autoimmune syndromes, possibly due to their pleiotropic effects in the immune system. For examples, the IL-6→STAT3 pathway is also important in regulating germinal center and humoral responses, which may be one of the reasons that the related drugs exhibit a better efficacy in treatment of joint inflammations with heightened humoral responses, including moderate to severe RA and sJIA (Hunter and Jones, 2015), whereas those target IL-23 or IL-17 are approved mainly for treatment of moderated to severe plaque psoriasis, PsA and AS patients. Ustekinumab, which targets both IL-12 and IL-23 and inhibits both type 1 and type 17 immunity, has been approved for treatment of moderate to severe Cohn's disease (CD) and UC due to its beneficial effect. However, IL-17A related monoclonal antibodies, including Secukinumab and Ixekizumab, can even worse the disease in CD patients, likely due to its protective function in maintaining barrier functions (Hueber et al., 2012). Brodalumab, a monoclonal antibody against IL-17RA, can increase the suicide risk in patients, which is not observed for IL-17A monoclonal antibodies including Secukinumab and Ixekizumab, possibly because IL-17RA is also required for transmitting signals from other cytokines (Greig, 2016). Overall, due to their excellent efficacy in treatment of autoimmune syndromes over traditional TNF-α related biological regents, especially psoriasis-related diseases, Th17-related drug markets are rapidly expanding.

The above drugs all target key cytokine signaling pathways involved in Th17 cell differentiation and effector functions. Recently, RORγt, the master transcription factor in Th17 cells, has also called great attentions from pharmaceutical companies. In 2011, three groups have independently demonstrated the proof-of-concept of targeting

**Table 2** Summary of FDA approved drugs related to Th17 cells

| Target | Drug | Disease |
|---|---|---|
| IL-17A | Secukinumab | Psoriasis, PsA, AS |
| | Ixekizumab | Psoriasis, PsA, AS |
| IL-17RA | Brodalumab | Psoriasis |
| IL-23p40 | Ustekinumab | Psoriasis, PsA, CD |
| IL-23p19 | Tildrakizumab | Psoriasis |
| | Guselkumab | Psoriasis |
| | Risankizumab | Psoriasis |
| IL-6R | Tocilizumab | RA, GCA, pJIA, ssJIA, CRS |
| | Sarilumab | RA |
| JAK1/3 | Tofacitinib | RA, PsA, UC |
| CTLA4 | Abatacept | RA |
| | Belatacept | Renal transplantation |

RORγt in treatment of Th17-related autoimmune diseases in animal models. Since then, more than 10 RORγt small molecular inhibitors have entered phase I or II clinical trials, for treatment of psoriasis, dry eye's disease and MS. It is expected that these RORγt inhibitors can provide an alternative yet costly effective therapy in treatment of Th17-related autoimmune diseases over biological regents.

These findings not only confirm an important role of Th17/IL-17 axis in human autoimmune diseases, but also suggest the complexity of these diseases, and some of them may involve multiple inflammatory axis and risk factors, in which a combinational therapeutic strategy may be required and need to be further investigated in the future.

*Others*

*Targeting cell migration*. Upon priming in the lymphoid organs, T cells re-enter the circulation system and migrate to different peripheral sites dependent on the expressed surface receptors such as integrins and chemokine gradients. Targeting lymphocytes homing molecule α4 significantly ameliorates spontaneous and T-cell transfer induced colitis (Neurath, 2019). These observations lead to the development of drugs targeting lymphocytes trafficking in treating IBD. However, Natalizumab, targeting α4, has a potential severe side effect in inducing progressive multifocal leukoencephalopathy, might due to the affected α4β1 integrins which is protective in brain infection (Van Assche et al., 2005). Later, Vedolizumab targeting α4β7, the specific gut homing receptor, achieved great clinical benefit and has been approved by FDA treating both UC and CD. In addition inhibiting lymphocytes homing into intestines, other strategies also have shown clinical benefits, including antibody targeting αEβ7 which blocked the gut retention of lymphocytes, and S1PR1 agonist which sequesters T cells in the lymphoid organs (Neurath, 2019). Meanwhile, Natalizumab also has been approved for MS treatment with warnings.

*Targeting co-stimulatory molecules*. GWASs revealed several SNPs in associated with co-stimulatory molecules such as *CD28*, *CTLA4*, *ICOS*, *CD40* and *OX40L*, which are important in modulating T cell response. The CTLA4-Ig molecule Abatacept has been approved for RA treatment, and is also efficient in juvenile idiopathic arthritis (JIA) treatment according to a phase 3 clinical trial. Drugs targeting CD40-CD40L, OX40-OX40L and others also are studied in pre-clinical or early clinical trials. Anti-BAFF drug Belimumab have been approved for SLE treatment, and also showed benefits in phase 2 clinical trials treating primary Sjögren syndrome and RA, and anti-OX40 antibody GBR830 in improving moderate to severe atopic dermatitis (Edner et al., 2020). The combination of anti-co-stimulatory molecules and other immunosuppressor is under test.

*Treg cell therapy*. Considering the importance of Treg cells in inhibiting inflammatory response, promising preclinical results have been reported of adoptive Treg transfer in treating autoimmune diseases, such as MS, SLE, T1D and graft-versus-host disease. Antigen specific Treg cells shows better therapeutic effect compared with polyclonal Tregs. The combination of CRISPR based gene editing with Treg cells may advance its function in controlling immune response (Ferreira et al., 2019).

## TNF receptor signaling and auto-inflammatory diseases: NF-κB and Necroptosis

Tumor necrosis factor (TNF) receptor signaling is an intricately regulated and multi-component pathway involved in diverse cellular processes including cell proliferation, cell survival, cell death and inflammation. Dysregulation of TNF receptor signaling by genetic mutations has been involved in multiple human and animal autoimmune diseases including IBD, psoriasis and RA. Thus far, most studied gene variants downstream of TNF receptor in these autoinflammatory diseases are involved in dysregulated NF-κB activation such as OTULIN deficiencies, and haploinsufficiency of A20. However, recent advances have explored a critical role of abnormal TNFR-mediated cell death signaling especially necroptosis in these autoinflammatory diseases. In this review, we will discuss the important role of necroptosis in the pathogenesis of autoimmune diseases caused by mutations of NF-κB pathway-associated genes including NEMO, LUBAC, OTULIN and A20. Also, we summarize recent advances of genetic mutations of necroptosis signaling components in autoinflammatory diseases including RIPK1-associated autoinflammation and other necroptosis-mediated inflammatory disorders. Together, this review expands the insights on the complex interplay between NF-κB and necroptosis downstream of TNF receptor signaling in autoimmune diseases and provides future directions of therapeutic targeting necroptosis in modulation of related human diseases.

### *Current knowledge of TNF receptor signaling*

*TNF-TNFR1 induced NF-κB activation for survival*

Tumor necrosis factor (TNF) is a critical pro-inflammatory cytokine which could bind to cognate receptor TNFR1 and TNFR2 to initiate inflammatory signaling as well as multiple cell death pathways including apoptosis and necroptosis (Apostolaki et al., 2010). Upon TNFα ligation, TNFR1 undergoes trimerization and rapidly forms a multicomponent signaling complex named TNFR1 signaling complex (TNFR1-SC) or complex I (Micheau and Tschopp, 2003). Ligated TNFR1 could further recruit adaptor proteins including receptor interacting protein kinase-1 (RIPK1) and TRADD, which in turn binds to TRAF2 and TRAF5. Then

E3 ubiquitin ligases, cIAP1 and cIAP2, could be recruited to TNF-RSC, and generate K63-linked ubiquitin chains on various regulators such as RIPK1 and cIAP1 itself. This ubiquitination event could further recruit linear ubiquitin chain assembly complex (LUBAC) to generate linear ubiquitin chains (also known as Met1-linked) on various components of complex I including RIPK1 and NEMO. These K63-linked and linear (Met1-linked) ubiquitin chains mediate the recruitment and activation of the TAK1-TAB1-TAB2 and IKK1-IKK2-IKKγ kinase complexes by ubiquitin binding. TAK1 phosphorylates and activates IKK complex, leading to phosphorylation, subsequent ubiquitination, and proteasome-mediated degradation of IκBα, and activation of NF-κB. In addition, TAK1 can also phosphorylate and activate the MAPK signaling, which coordinates with NF-κBmediated inflammatory response to promote cell survival (Yuan et al., 2019) (Figure 3).

*TNF-mediated death signaling: RIPK1-dependent apoptosis, necroptosis and pyroptosis*

In addition to pro-survival gene induction, activation of TNFR1 could also induce programmed cell death by apoptosis, necroptosis and pyroptosis signaling. Similar to other death domain-containing receptor and adaptor proteins such as Fas and FADD, TNFR1 contains an intracellular death domain interacting with RIPK1 and TRADD upon TNFα stimulation, which involve in TNFα-induced apoptosis or necroptosis (Yuan et al., 2019). Thus, RIPK1 acts as an essential regulator of TNF receptor signaling, controlling the balance between cell survival and cell death. RIPK1 consists of N-terminal kinase domain (KD), intermediate domain (ID) and C-terminal Death Domain (DD). The kinase domain is critical for RIPK1 autophosphorylation on S166 and kinase activation-dependent apoptosis and necroptosis induction by TNFα. The intermediate domain of RIPK1 is essential for pro-survival NF-κB and MAPK signaling via various ubiquitination modifications. The intermediate domain also contains a receptor-interacting protein homotypic interaction motif (RHIM) that mediates interactions with other RHIM-containing proteins, such as RIPK3 for necroptosis induction. The death domain of RIPK1 is involved in binding to other death domain family adaptor proteins such as TNFR1, TRADD and FADD for its recruitment into TNF-RSC to promote survival or cell death complexes to induce apoptosis (Yuan et al., 2019).

In the normal situation with TNF stimulation alone, the cell death signaling is suppressed due to NF-κB and MAPK-mediated expression of anti-apoptotic genes such as cIAP1 and c-FLIP. As c-FLIP has a very similar structure with Caspase-8 but lacks enzymatic activity, c-FLIP could heterodimerize with Caspase-8 and inhibit full activation of Caspase-8. When NF-κB activation is inhibited by protein synthesis inhibitor cycloheximide (CHX), the anti-apoptotic c-FLIP expression is blocked and Caspase-8 could then form active homodimers and cell death complex II with TRADD and FADD to trigger apoptosis. However, RIPK1 kinase activity is dispensable for this process as RIPK1 kinase inhibition has no effect on apoptosis induction (Wang et al., 2008). On the other hand, disruption of TNF-RSC formation by either cIAP1/2, LUBAC, TAK1, MK2, TBK1 or NEMO/IKK deficiency, which inhibits the ubiquitination and phosphorylation status of RIPK1, could promote the activation of RIPK1 kinase activity and formation of RIPK1-FADD-Caspase-8 complex to trigger RIPK1-dependent apoptosis (Delanghe et al., 2020; Peltzer et al., 2016).

Nevertheless, when apoptosis is blocked by deficiency or inhibition of Caspase-8, cells are still sensitive to TNF-induced caspase-independent cell death. Instead of apoptosis, this caspase-independent cell death termed necroptosis could trigger cell membrane rupture and inflammation. During necroptosis induction, RIPK1 is auto-phosphorylated and activated to form necrosome with RIPK3, which further promotes oligomerization of phosphorylated MLKL (He et al., 2009). Thus, necroptosis is tightly regulated by caspase-dependent cleavage and kinase activity of RIPK1 and RIPK3. In addition, the formation of RIPK1/Caspsae-8/FADD complex triggers non-inflammatory apoptosis-mediated cell death. However, recent studies found that activation of RIPK1 and Caspase-8 by TNF with TAK1 or IKK inhibitors in macrophages could trigger both apoptosis and pyroptosis, another lytic and pro-inflammatory form of cell death caused by Caspase-8-mediated cleavage of GSDMD (Orning et al., 2018). Thus, RIPK1 and Caspase-8 are key checkpoints in regulation of TNF-induced apoptosis, necroptosis and pyroptosis (Figure 3).

*Posttranslational modifications: checkpoints in cell fate determination*

At present, it is still not very clear what determines the switch that decides whether RIPK1 is kept in complex I to suppress cell death or transit to complex II and necrosome to promote apoptosis and necroptosis. A potential explanation to this could be the post-translational modifications of the checkpoint protein RIPK1 especially ubiquitination, phosphorylation and cleavage (Yuan et al., 2019). There are multiple ubiquitinating and deubiquitinating enzymes involved in the regulation of cell death and pro-survival NF-κB signaling (Peltzer et al., 2016). The widely studied ubiquitin E3 ligases that positively regulate NF-κB activation and downstream gene expression are cIAP1/2 and LUBAC complex (consist of HOIP, HOIL-1 and SHARPIN). Moreover, recent studies have demonstrated that another important function of these E3 ligases is to suppress RIPK1 kinase activity and induction of cell death. Deficiency of cIAP1/cIAP2 or LUBAC complex impairs K63-linked or Met1-linked ubiquitination on RIPK1 and promotes RIPK1

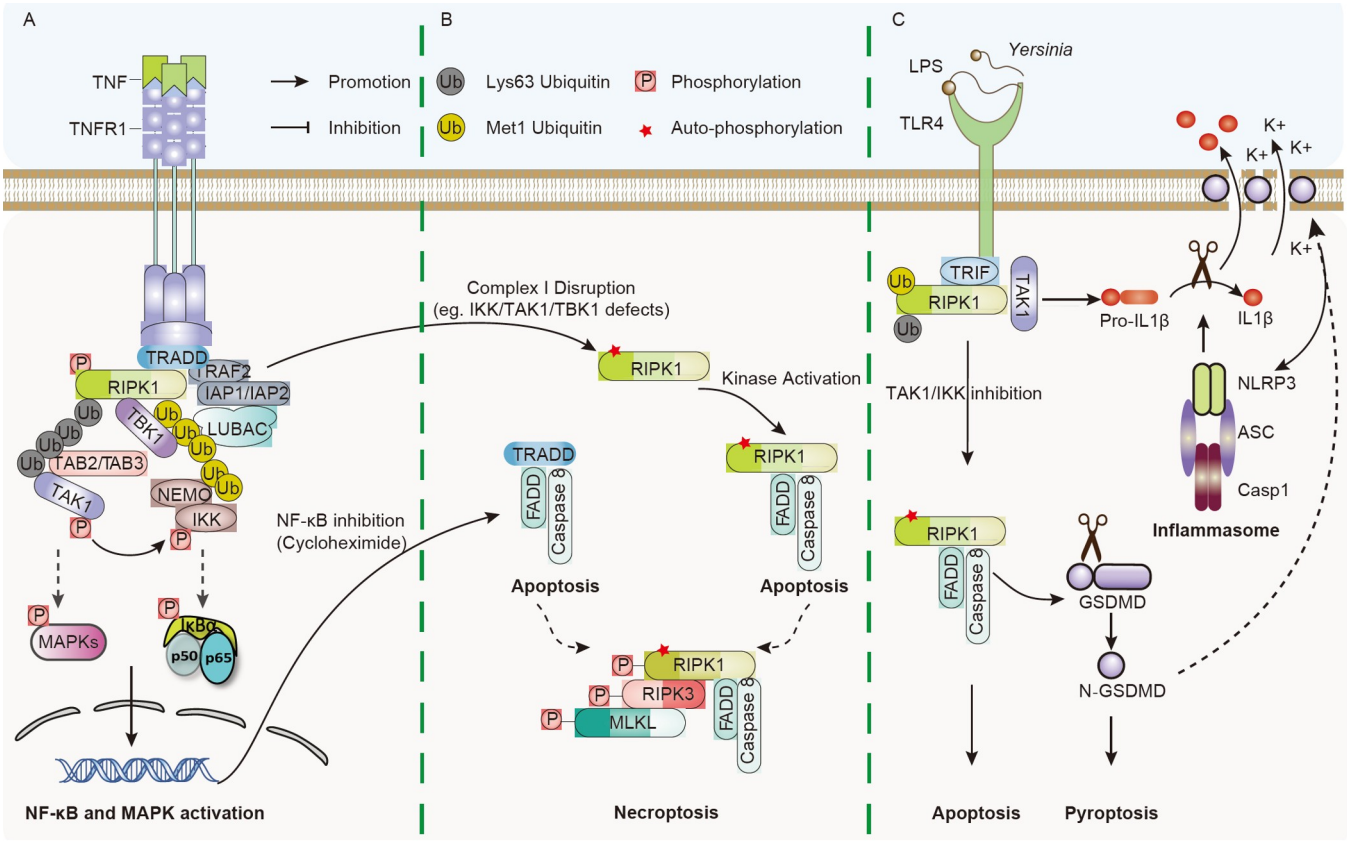


**Figure 3** Overview of gene activation and cell death in TNF receptor signaling. A, Under TNFα stimulation, RIPK1 and other signaling molecules including TRADD, TRAF2/5, E3 ligase cIAP1/2 and linear ubiquitin chain assembly complex (LUBAC, composed of HOIL-1, HOIP and SHARPIN) could be rapidly recruited to form TNFR1 signaling complex (TNF-RSC, also called complex I). The E3 ubiquitin ligases cIAP1/cIAP2 and linear ubiquitin chain assembly complex (LUBAC) could generate K63-linked or Met1-linked ubiquitin chains on various regulators such as RIPK1 and NEMO. These K63-linked and linear Met1-linked ubiquitin chains could mediate the recruitment and activation of the TAK1-TAB1-TAB2 and IKK1-IKK2-IKKγ kinase complexes by ubiquitin binding, which subsequently activates downstream pro-survival MAPK and NF-κB signaling. B, When the formation of TNF-RSC is disrupted (cIAP1/2, LUBAC, TAK1, MK2, TBK1 or NEMO/IKK deficiency) or NF-κB activation is blocked, RIPK1 and/or TRADD could transit from TNF-RSC to form complex II with FADD and Caspase-8 in the cytoplasm, which consequently triggers apoptosis. However, when apoptosis is inhibited by inactivation of Caspase-8, RIPK1 in the cytosolic complex II could also promote RIPK1-RIPK3-MLKL necrosome formation in a kinase-dependent way to trigger necroptosis activation. C, During *Yersinia* infection, TLR and TNF signaling will lead to activation of NF-κB and transcription of proinflammatory genes in macrophages. Secretion of the Yersinia effector protein YopJ leads to inhibition of TAK1 and IKK and triggers the activation of RIPK1 dependent caspase-8 activation and apoptosis. Simultaneously, Caspase-8 also cleaves GSDMD leading to formation of GSDMD pores and NLRP3 inflammasome activation, further inducing pyroptosis.

kinase activation and transition from complex I to complex II to induced apoptosis and necroptosis (Peltzer et al., 2018; Zhang et al., 2019b).

Besides, there are also several deubiquitinating enzymes (DUB) functioning in TNF receptor signaling pathways and negatively regulating the ubiquitination status in complex I to modulate both NF-κB and cell death signaling, most importantly as A20, CYLD, SPATA2 and OTULIN (Lork et al., 2017). A20 is upregulated in response to TNF stimulation and could negatively regulate NF-κB-dependent gene expression through removing K63 ubiquitin on several substrates such as RIPK1 and NEMO. A20 also has a critical function to regulate RIPK1 activity in cell death, as A20 deficiency could dampen Met1 ubiquitination of RIPK1 in response to TNF and promotes RIPK1 kinase-dependent apoptosis and necroptosis (Draber et al., 2015). Moreover, a recent study also showed that loss of ABIN1, essential for recruitment of A20, could impair phosphorylation of A20 and enhance K63 ubiquitination of RIPK1 to promote RIPK1 kinase activation and cell death (Dziedzic et al., 2018). OTULIN is a specific protease to hydrolyze Met1 ubiquitin chains and thought to restrain LUBAC-mediated NF-κB activation. Loss of OTULIN could also prolong the pro-inflammatory cytokine production and cause inflammation (Fiil et al., 2013). Nevertheless, a recent study found that catalytically inactive OTULIN surprisingly enhance LUBAC auto-Met1 ubiquitination with little effect on NF-κB activation and resembles LUBAC deficiency to promote RIPK1 kinase-dependent cell death and inflammation (Heger et al., 2018). Thus, these studies suggest a complex and critical role of K63 and Met1-linked ubiquitination status of complex I in dictating the switch of kinase activation of

RIPK1 to determine cell fate.

However, the underlying mechanism by which cells distinguish different ubiquitination status in complex I to determine the cell fate decision in TNF receptor signaling is still unclear. The current model has been well established that ubiquitin binding proteins such as TAB2/3 and NEMO are key sensors to transit the signal from various ubiquitination events in complex I, since K63 and Met1 ubiquitin chains have a high affinity for TAB2/TAB3 and NEMO binding to fully activate TAK1-TAB2-TAB3 and IKKα/IKKβ/NEMO complex and downstream NF-κB and MAPK signaling (Yuan et al., 2019). In addition, recent studies have revealed multiple kinases including TAK1, IKKα/IKKβ, TBK1 and MK2 could directly or indirectly phosphorylate RIPK1, further inhibiting RIPK1 kinase activity and RIPK1-dependent apoptosis and necroptosis (Delanghe et al., 2020). Thus, the kinase-mediated regulation might serve downstream of various ubiquitination modifications to dictate the signal complexes transition and cell fate determination.

The regulation of TNFR1 complex I to complex II transition has been extensively studied, however, how complex II during apoptosis transits to necrosome by Caspase-8 inhibition-mediated necroptosis remains not very clear. Caspase-8, activated during apoptosis, has been demonstrated to cleave multiple checkpoint proteins in NF-κB and necroptosis signaling such as cFLIP, HOIP, RIPK1, RIPK3 and CYLD (Newton, 2020). Since RIPK1 and RIPK3 are important for necrosome formation, Caspase-8-mediated cleavage of RIPK1 and RIPK3 could be the key regulation of necroptosis. Caspase-8 cleaves RIPK1 at D325 and cleavage-inactive D325A RIPK1 shows early embryonic lethality and causes both enhanced apoptosis and necroptosis (Lalaoui et al., 2020; Newton et al., 2019a; Tao et al., 2020; Zhang et al., 2019c). *In vitro* studies also show that RIPK3 could be cleaved at D328 by Caspase-8 to inhibit necroptosis (Feng et al., 2007). As RIPK3 also has a function in apoptosis and inflammasome, the functional outcome of D328-dependent cleavage of RIPK3 still needs further investigation.

## *Gene mutations in TNF receptor signaling components cause autoinflammatory diseases*

Human genetic diseases caused by the mutations of TNF receptor signaling components are summarized in Table 3.

### *NF-κB-related gene mutations and auto-inflammatory disease: interplay with necroptosis*

The importance of TNFα-induced NF-κB signaling in autoinflammatory diseases has been widely investigated both in human patients and mouse models. Mutations of TNF, *TNFRSF1A* (TNFR superfamily member 1A), A20 and OTULIN which caused constitutive TNFα secretion enhances NF-κB activation, have been associated with different auto-inflammatory diseases in human such as asthma, steatohepatitis and rheumatoid arthritis (Rezaei, 2006; Valenti et al., 2002). Moreover, recent advances have strengthened our understandings on the regulation between NF-κB and proinflammatory necroptosis process. In this part, we will discuss the effects of gene mutations of NF-κB-associated genes including NEMO, LUBAC, OTULIN and A20 on necroptosis in the pathogenesis of autoinflammatory diseases.

(i) NEMO-related diseases. Mutations of *NEMO*/*IKBKG* that is located on the X chromosome have been linked with several distinct X-linked genetic diseases including X-linked recessive ectodermal dysplasia and immunodeficiency (EDA-ID) and incontinentia pigmenti (IP). Patients with EDA-ID showed abnormal development of ectodermal tissues alongside immune deficiency, low antibody levels and NK cell dysfunction, which is dominantly due to loss of NEMO protein and disrupted NF-κB activation (Mancini et al., 2008). However, around 20% of individuals with EDA-ID have disorders involving abnormal inflammation including IBD and SLE (Hanson et al., 2008). Moreover, the incontinentia pigmenti (IP), the first identified NEMO-deficient disease, is characterized with severe skin inflammation including inflammatory rash and hyperproliferation of keratinocytes in the epidermis (Smahi et al., 2000). These observed inflammatory phenotypes of NEMO deficiency in human patients are unlikely due to inflammatory NF-κB activation.

Importantly, numerous genetic mouse studies have given us new insights on the autoinflammatory syndromes of NEMO deficiency. Mice deficient of NEMO caused embryonic lethality in males and inflammatory skin lesions in heterozygous females (Makris et al., 2000). Deficiency of NEMO in skin epithelium caused severe skin inflammation and TNF-mediated apoptosis and necroptosis, which can be delayed by co-deletion of TNFR1 (Nenci et al., 2006). Also, intestinal epithelium-specific NEMO-deficient mice showed severe death of Paneth cells and developed spontaneous colitis, which is prevented when TNFα production is blocked. Importantly, the colitis could be blocked by genetic or pharmacological inhibition of RIPK1 kinase, indicating an essential role of RIPK1-mediated necroptosis in the autoinflammatory diseases caused by NEMO deficiency (Vlantis et al., 2016). Recent studies further demonstrated NEMO mediated IKK complex could phosphorylate RIPK1 at Ser25 and inhibit RIPK1 kinase activity and necroptosis to regulates inflammation and bacterial infection in mice (Dondelinger et al., 2019). These studies suggest that NEMO mutations in human patients are also likely involved in RIPK1-dependent necroptosis signaling to trigger abnormal inflammation.

(ii) A20 haploinsufficiency. A20, a ubiquitin-editing en-

**Table 3** Summary of genetic mutations in TNF receptor signaling and autoinflammatory diseases

| Gene | Specie | Mutation effect | Disease associate | Reference |
|---|---|---|---|---|
| *TNF* | Human | Increased TNF-mediated NF-κB | RA, asthma and AD; | Valenti et al., 2002 |
| *TNFRSF1A* | Human | Enhanced NF-κB activation | TNF receptor associated periodic syndrome (TRAPS) | Rezaei, 2006 |
| *IKBKG* | Human | NEMO-null truncation | Incontinentia pigmenti (IP) | Smahi et al., 2000 |
| | | Missense or partial truncation | X-linked recessive ectodermal dysplasia and immunodeficiency (EDA-ID) | Mancini et al., 2008 |
| | Mouse | Global/conditional knockout | Embryonic lethality; multi-organ inflammation | Makris et al., 2000; Nenci et al., 2006; Vlantis et al., 2016 |
| *TNFAIP3* | Human | Haploinsufficiency | Early-onset systemic inflammation | Zhou et al., 2016a |
| | Mouse | Global/conditional knockout | Spontaneous and systemic inflammation | Lippens et al., 2011; Onizawa et al., 2015 |
| | | C767A Znf7/Znf7 mutant | Spontaneous inflammatory arthritis with activated RIPK1 | Polykratis et al., 2019 |
| *OTULIN* | Human | Biallelic hypomorphic mutations | OTULIPENIA or ORAS mediated inflammation | Damgaard et al., 2016; Zhou et al., 2016b |
| | Mouse | Global knockout | Early embryonic lethality and inflammation | Damgaard et al., 2016 |
| | | Deubiquitinase C129A mutant | Early embryonic lethality and inflammation | Heger et al., 2018 |
| *HOIP* | Human | Hypomorphic | Immunodeficiency and autoinflammation | Boisson et al., 2015 |
| | Mouse | Global knockout | Early embryonic lethality and inflammation | Peltzer et al., 2014 |
| *HOIL-1* | Human | Biallelic LoF | Immunodeficiency and autoinflammation | Boisson et al., 2012 |
| | Mouse | Global knockout | Early embryonic lethality and inflammation | Peltzer et al., 2018 |
| *SHARPIN* | Mouse | Global knockout | Multi-organ inflammation | Seymour et al., 2007 |
| *RIPK1* | Human | Biallelic LoF | Combined immunodeficiency and IBD | Cuchet-Lourenço et al., 2018; Li et al., 2019a |
| | | Autosomal dominant non-cleavable mutants | Autoinflammation, recurrent fevers and lymphadenopathy | Lalaoui et al., 2020; Tao et al., 2020 |
| | Mouse | Global/conditional knockout | Neonatal lethality and autoinflammation | Dillon et al., 2014; O'Donnell et al., 2018; Rickard et al., 2014 |
| | | Non-cleavable D324A mutants | Early embryonic lethality and inflammation | Lalaoui et al., 2020; Newton et al., 2019a; Tao et al., 2020; Zhang et al., 2019c |
| | | K63-Ubi defective K376R mutants | Early embryonic lethality and inflammation | Tang et al., 2019; Zhang et al., 2019d |
| | | Linear-Ubi defective K612R mutants | Systemic inflammation | Tu et al., 2021 |
| | | RHIM motif mutants | Postnatal lethality and inflammation | Lin et al., 2016; Newton et al., 2016 |
| *CASP8* | Human | Haploinsufficiency | Autoimmune lymphoproliferative syndrome | Chun et al., 2002; Niemela et al., 2015 |
| | Mouse | Global/conditional knockout | Early embryonic lethality and inflammation | Kaiser et al., 2011; Varfolomeev et al., 1998 |
| | | Caspase inactive C362S/A mutants | Early embryonic lethality and inflammation | Fritsch et al., 2019; Newton et al., 2019b |
| *RIPK3* | Mouse | Kinase inactive D161N mutant | Early embryonic lethality and inflammation | Newton et al., 2014 |
| *MLKL* | Mouse | Constitutive activate D319V mutant | Lethal perinatal inflammatory syndrome | Hildebrand et al., 2020 |

zyme encoded by the TNFα-induced protein 3 (*TNFAIP3*) gene, is an essential anti-inflammatory regulator of NF-κB activation involved in both Toll-like receptor (TLR) and TNF receptor (TNFR) signaling. *TNFAIP3* gene polymorphisms have been associated with many autoimmune diseases including SLE, RA, psoriasis, type 1 diabetes, coronary artery disease, inflammatory bowel disease, and asthma (Zhou et al., 2016a). In addition to the inhibitory effect on proinflammatory NF-κB activation, A20 has an important role in restraining RIPK1 activity in apoptosis and necroptosis signaling via modulating K63-, K48-, and Met1-linked ubiquitination (Draber et al., 2015; Dziedzic et al., 2018). These studies further suggest a potential role of necroptosis-mediated inflammation in the pathogenesis due to A20 haploinsufficiency.

The importance of A20 in auto-inflammatory diseases was further demonstrated in A20-deficient mice with a range of cell-specific phenotypes. Cell-specific deletion of A20 in keratinocytes results in autoinflammatory symptoms including polyarthritis and enteritis, which resemble human autoimmune diseases (Lippens et al., 2011). Most studies have ascribed the autoimmunity of A20 haploinsufficiency

to loss of inhibition of NF-κB signals. However, these genetic studies in mice provide direct evidence that RIPK1 kinase-dependent necroptosis plays a dominant role in the pathogenesis as either RIPK3 or RIPK1 inhibition could rescue the systemic inflammation in A20-deficient mice (Onizawa et al., 2015). More recently, researchers found mutation of the A20 ZnF7 ubiquitin-binding domain caused spontaneous inflammatory arthritis by activating RIPK1-dependent necroptosis, suggesting that the ubiquitin-regulatory function of A20 is critical for limiting cell death and inflammation (Polykratis et al., 2019). Thus, further studies need to investigate the scaffold, deubiquitinating and K48-ubiquitinatiing enzyme function of A20 in necroptosis, inflammation and related human diseases.

(iii) LUBAC deficiency (HOIP/HOIL/SHARPIN). The LUBAC complex, composed of HOIP, HOIL-1 and SHARPIN, is the only E3 ligase complex which could generate Met1-linked ubiquitination on several substrates to regulate immune signaling (Peltzer et al., 2016). Patients with defects in the LUBAC components develop immunodeficiency and autoimmune diseases characterized by recurrent infections, muscular amylopectinosis and periodic fevers. Loss-of-function mutations of HOIP and HOIL-1 lead to the truncated protein expression and destabilized other LUBAC components, which further impairs downstream NF-κB activation and immunodeficiency (Boisson et al., 2015; Boisson et al., 2012). However, LUBAC could also generate Met-1 ubiquitin chains on RIPK1 and suppress RIPK1 kinase-mediated cell death (Peltzer et al., 2018), which could account for the autoinflammatory phenotypes in the patients with these mutations.

The important function of LUBAC in autoimmune diseases are well-studied by using genetic deficient mouse models. Mice deficient of HOIP- and HOIL-1 lead to early embryonic lethality and display severe TNFR-associated cell death and inflammation. However, deficiency of TNFR1 or TNF could not fully rescue but only delay it, whereas Caspase-8- and MLKL-double deficiency could fully prevent the embryonic lethality (Peltzer et al., 2018; Peltzer et al., 2014). These results suggest a critical role of LUBAC in prevent cell death and inflammation to enable embryogenesis. In addition, SHARPIN deficient mice, also known as chronic proliferative dermatitis mice (*cpdm*), suffer from severe auto-inflammation in skin resembling with atopic dermatitis and psoriasis in humans (Seymour et al., 2007). The skin inflammation of *cpdm* mice can be blocked by deficiency of TNF or inactivation of RIPK1 kinase activity (Berger et al., 2014), further suggesting a critical role of RIPK1 kinase activity and necroptosis in disease pathogenesis caused by LUBAC deficiency.

(iv) Otulipenia/OTULIN-related autoinflammatory syndrome. OTULIN (also called gumby) is the only known deubiquitylating enzyme, regulating TNFR inflammatory signals via the hydrolyzation of Met1-linked Ubiquitin chains formed on LUBAC complex targets, such as NEMO, RIPK1, TNFR1 (Damgaard et al., 2016). Patients with inherited loss-of-function mutations in OTULIN develop a severe autoinflammatory disease, known as OTULIPENIA or OTULIN-related autoinflammatory syndrome (ORAS). These early-onset systemic inflammatory symptoms of OTULIN deficiency includes joint swellings, prolonged fevers, diarrhoea, sterile neutrophilia and lipodystrophy (Damgaard et al., 2016; Zhou et al., 2016b). Unlike patients with the LUBAC deficiency, patients with OTULIN-deficient mutations have no obvious immunodeficiency due to over-activated NF-κB. However, OTULIN-deficient or catalytically inactive C129A mice show early embryonic lethality due to severe RIPK1-dependent cell death and inflammation, which could be delayed by TNF blockage, RIPK1 kinase inhibition, or RIPK3 deficiency (Damgaard et al., 2016; Heger et al., 2018). Importantly, OTULIN deficiency or catalytic inactivation also leads to decreased LUBAC activity which is also negative regulated by self-Met1 ubiquitination. These results suggest the severe sensitivity of RIPK1-dependent cell death during embryogenesis of OTULIN-deficient or catalytically inactive mice could be due to loss of LUBAC activity. In summary, genetic investigations from human patients and mouse models reveal that OTULIN deficiency leads to increased Met1 ubiquitination and promotes proinflammatory NF-κB and necroptosis activation to trigger autoimmune diseases.

*Necroptosis-associated autoinflammation*

Chronic TNFα-induced proinflammatory cell death especially necroptosis has been recently shown to play an essential role in autoimmune diseases such as neurodegenerative diseases, psoriasis and inflammatory bowel disease. TNFα-induced necroptotic cell death could release damage-associated molecular patterns (DAMPs), which promote pathological inflammatory responses. Thus, in this part, we will discuss gene mutations of necroptosis signaling components in the pathogenesis of autoinflammatory diseases.

(i) RIPK1-mediated inflammatory disease. Receptor-interacting protein kinase-1 (RIPK1) is a master regulator of TNF receptor signaling and cell fate determination. As a scaffold protein, RIPK1 could facilitate TNFR complex I formation and promote proinflammatory NF-κB activation for survival. In addition, RIPK1 also has protein kinase activity to promote complex II and necrosome formation to trigger apoptosis and necroptosis (Yuan et al., 2019). Patients with inherited loss-of-function mutations in RIPK1 develop immunodeficiency and autoimmune diseases characterized by intestine inflammation with variable onset and severity and also polyarthritis (Cuchet-Lourenço et al., 2018; Li et al., 2019a). Unlike RIPK1-deficient mice, which die shortly

after birth, patients with RIPK1-deficient mutations could survive for a long time after birth, indicating RIPK1 is not essential for survival in humans (Dillon et al., 2014; Rickard et al., 2014). The loss of RIPK1 in skin fibroblasts in human patients impairs activation of the NF-κB pathway but increases the activation of necroptosis mediated by RIPK3 and MLKL (Cuchet-Lourenço et al., 2018; Li et al., 2019a). The functional transition of RIPK1 in TNFR1 signaling has been reported to be tightly regulated by post-translational modifications, most crucially by phosphorylation, ubiquitination, and Caspase -8-mediated cleavage (Yuan et al., 2019). Caspase-8 cleaves human and mouse RIPK1 after residues D324 and D325 respectively, which could inactivate RIPK1 and suppress RIPK1-mediated necroptosis. Importantly, more recent studies have revealed that human patients with gain of function D234N/Y mutations develop autosomal autoimmune disease characterized with recurrent fevers and lymphadenopathy. Mice with a D325A knock-in mutation show early embryonic lethality and severe inflammation, which could be rescued by inactivating both necroptosis and apoptosis by double deficiency of RIPK3 and FADD, or MLKL and FADD (Lalaoui et al., 2020; Newton et al., 2019a; Tao et al., 2020; Zhang et al., 2019c).

Numerous genetic studies in mice have further revealed the importance of RIPK1 in necroptosis signaling to regulate autoinflammatory diseases. RIPK1 deficiency or cell-specific loss of RIPK1 drives systemic inflammation and emergency hematopoiesis due to enhanced necroptosis activation (O'Donnell et al., 2018; Rickard et al., 2014). In addition, ubiquitination of RIPK1 also plays a crucial role to regulate its scaffold and kinase activity in TNFR1 signaling. We and other groups generate K376R knock-in mice and reveal K63-linked ubiquitination of RIPK1 on K376 is critical for promoting NF-κB activation and limiting RIPK1 kinase-dependent cell death during embryogenesis and inflammation (Tang et al., 2019; Zhang et al., 2019d). Also, we recently found the K612 residue is a dominant site for LUBAC-mediated linear ubiquitination n of RIPK1. By generating K612R knock-in mice, we found Met1 ubiquitination of RIPK1 on K612 is essential for preventing cell death to restrain systemic inflammation (Tu et al., 2021). The ability of RIPK1 to facilitate necrosome activation needs receptor-interacting protein homotypic interaction motif (RHIM)-mediated interaction between RIPK1, RIPK3 and ZBP1. By generating mice bearing mutations in RHIM motif of RIPK1, several groups found RIPK1 RHIM mutant mice show postnatal lethality and severe inflammation due to enhanced necroptosis activation (Lin et al., 2016; Newton et al., 2016). Moreover, recent studies have reported phosphorylation of RIPK1 on Ser25/321/335 mediated by TAK1, p38/MK2, TBK1/IKKε and IKKα/β provide a physiological brake to prevent TNFα-induced RIPK1 kinase-dependent cell death during embryogenesis, infection and neuroinflammation (Delanghe et al., 2020). Thus, the studies of these mutations of post-translational modifications of RIPK1 could further provide mechanistic insight into the inflammatory diseases associated with related human polymorphisms.

(ii) Other inflammatory diseases associated with mutations of necroptosis. Caspase-8, activated during apoptosis, has been demonstrated to cleave checkpoint proteins in necrosome including RIPK1 and RIPK3 to suppress necroptosis activation (Yuan et al., 2019). Patients with inherited genetic loss-of-function mutations of Caspase-8 show ALPS-like disease with lymphadenopathy and splenomegaly. In addition, these patients also have immunodeficiency characterized by recurrent sinopulmonary and herpes simplex virus infections, which is due to impaired antigen-induced activation of T and B lymphocytes (Chun et al., 2002; Niemela et al., 2015). However, unlike the early embryonic lethality of Caspase-8 deficient mice, Caspase-8 loss-of-function patients could survive after birth for a long time which is perhaps due to the redundant function of Caspase-10 in human (Kaiser et al., 2011; Varfolomeev et al., 1998). In addition, Caspase-8 also has been recently demonstrated to cleave GSDMD during apoptotic activation and further trigger pyroptosis to promote host defense against bacterial infection (Orning et al., 2018). More recent studies also shows that Caspase-8 catalytically inactive C326A/S mutant mice show early embryonic lethality and severe inflammation due to enhanced apoptosis, necroptosis and pyroptosis (Fritsch et al., 2019; Newton et al., 2019b), suggesting an essential role of Caspase-8 in modulation of cell death-mediated autoinflammation. GWAS study found two *CASP8* variants, p.K148R and p.I298V as risk alleles in Alzheimer disease (Rehker et al., 2017). However, how K148R mutation of Caspase-8 affects its activity during apoptosis and necroptosis still needs further genetic investigations.

RIPK3 is another important kinase which activates downstream MLKL and necroptosis induction. RIPK3 deficient mice areare viable and have no sign of autoinflammation, and there are no reports of human mutations of RIPK3 associated with autoinflammatory diseases. However, a study by generating RIPK3 kinase-dead D161N mutant mice found that these mice displayed spontaneous apoptosis, inflammation, and early embryonic lethality (Newton et al., 2014). In addition, MLKL, another essential component of necroptosis, has recently been shown to associate with autoinflammatory disease in mice and human studies. A mouse strain with D139V mutation in MLKL, located in the two-helix 'brace', develops lethal inflammation after birth characterized with necroptosis and inflammatory infiltration in salivary glands and pericardium. And these observations in the mouse model offer an important insight into the potential autoinflammatory role of three common human MLKL polymorphisms adjacent to the brace region of MLKL (Hildebrand et al., 2020).

## Concluding remarks and future perspectives

Our understanding of TNFR signaling, including pro-survival NF-κB and pro-death apoptosis and necroptosis signal, has been greatly improved over the last decade. Maintenance of optimal and efficient TNF receptor-mediated immune response is critical for normal immune homeostasis and preventing immunodeficiency or autoinflammatory diseases. Although targeting hyperactivation of NF-κB by TNFα or IKK blockade has been used to treat some human diseases, it still has some side-effects due to further enhanced RIPK1-mediated cytotoxicity. Numerous genetic studies in mice have revealed critical role of cell death especially necroptosis-mediated inflammation in the pathogenesis of autoinflammatory diseases. Thus, further studies are needed to explore and dissect the complex role of NF-κB and cell death signaling during inflammatory diseases pathogenesis caused by these genetic mutations. Notably, mutations of TNF signaling components such as NEMO, LUBAC blocks NF-κB activation and lead to immunodeficiency, but on the other hand it could also trigger severe TNFα-mediated cell death and cause autoimmunity. However, these two-faced characters exactly show the complexity and elegance of our immune system, as the function of these genes in the immune system has high cell-type specificity. Innate immune cells such as macrophages and dendritic cells which always encounter pathogens has a higher sensitivity to TNF-mediated cell death and tendency to autoimmunity. However, the adaptive immune cells such as T cells are more sensitive to Fas-mediated cell death during development and activation. Therefore, genes deficiency in these cells majorly blocks antigen-induced NF-κB activation and causes immunodeficiency. Since deficiency of these genes trigger severe autoimmunity and innate immune responses which causes huge damage to the host, the simultaneous immunodeficiency might provide negative feedback to dampen the inflammatory response. Thus, further studies need to explore the function of these genetic mutations in multiple immune cell types in regulating both innate and adaptive immune responses during inflammatory disease pathogenesis.

A critical question remained in TNFR1 signaling is how cells determine the switch between NF-κB activation-related complex I formation to cell death-related complex II or necrosome formation in response of TNFα stimulation. Previous studies suggest that RIPK1, which participates in NF-κB activation, apoptosis and necroptosis signal, seems to be a key checkpoint since many TNFR complex I components including A20, LUBAC, IKK and TBK1 have all been demonstrated to inhibit RIPK1 activity to suppress cell death. Consistently, recent studies using samples from human patients have revealed essential role of RIPK1 and its cleavage in restricting necroptosis and related autoinflammatory diseases. It will be of great interest to investigate the regulation of necroptosis and the post-translational modifications of RIPK1 by using genetic knock-out and knock-in mice or analyzing samples from human patients. Since RIPK1 kinase activity is critical for apoptosis and necroptosis activation, it raises a question that how the kinase activity of RIPK1 is suppressed in TNFR complex by post-translational modifications. Interestingly, the kinase activity of RIPK1 requires its autophosphorylation in N-terminal kinase domain but the inhibitory phosphorylation of RIPK1 is mostly located in intermediated domain and surrounds the cleavage site of RIPK1. Thus, further biochemical and structural analyses are needed to investigate the potential crosstalk between inhibitory phosphorylation and autophosphorylation or cleavage of RIPK1. Furthermore, development of selective, potent and safe small-molecule inhibitors targeting necroptosis such as RIPK1, RIPK3 and MLKL would facilitate future clinical treatment for related autoinflammatory diseases.

**Compliance and ethics** *The author(s) declare that they have no conflict of interest.*

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