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A Special Connection between γδ T Cells and Natural Antibodies?

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Abstract

Natural antibodies (NAbs) play an important role in early host defense, autophagy and tissue remodeling, and in immune regulation. They arise spontaneously (without specific immunization), and are already present at birth. NAbs are produced by B1 B cells, MZ B cells and other B cell types. They include all major Ig subclasses but IgM antibodies are prevalent, especially early in development. NAbs may be poly-specific, recognize particular auto-antigens, or detect neo-determinants such as those exposed during apoptosis or generated by oxidation. NAbs do not require cognate T cell help but depend on soluble mediators produced by T cells. Our recent studies suggest that γδ T cells may have a special relationship with NAbs, and play a prominent role in their regulation, in part through the fine-tuning of IL-4-levels. The spontaneously activated state of these cells likely enables their cytokine production and other functions in the absence of external stimulation. Ontogenetically, the earlier arising γδ T cells are better positioned than αβ T cells to shape the developing repertoire of NAbs. Intriguingly, ligand specificities of NAbs and γδ T cell receptors appear to be overlapping, perhaps allowing γδ cognate help for certain NAb specificities. Via NAbs, γδ T cells could exert a regulatory influence on numerous processes in health and disease.

Introduction

Prior to any immunization, circulating antibodies already exist in normal healthy humans and mice (Avrameas, 1991; Lutz et al., 2008). They are present at birth, and in mice have been shown to arise under germ-free conditions. These natural antibodies (NAbs) include all Ig subclasses. Natural IgM is prevalent particularly early in ontogeny and has been studied most extensively. B1 B cells appear to be the primary source of NAbs in mice (Savage and

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Baumgarth, 2015), but other B cell-types, most notably marginal zone B cells (Durand et al., 2009), contribute as well (Avrameas and Selmi, 2013; Avrameas, 2016). Although sometimes referred to as “non-specific”, NAbs in fact may be mono- or poly-specific, and recognize auto-antigens, neo-antigens and certain foreign antigens. Importantly, recent studies revealed that NAbs play a critical role in the early host defense against pathogens, protection against malignancy, tissue homeostasis and immune regulation. Available information about NAbs and treatment opportunities with intravenous immunoglobulin (IVIG) has been expertly reviewed by others (Ehrenstein and Notley, 2010; Gronwall and Silvermann, 2014; Madi et al., 2012; McCoy et al., 2006; Panda and Ding, 2015; Rahyab et al., 2011; Schwartz-Albiez et al., 2009; Vas et al., 2013). It is only summarized here, followed by a discussion of new data suggesting that γδ T cells become involved in regulating NAbs and their functional activity.

Specificity and function of natural antibodies

The primary B cell repertoire is not random (Perlmutter et al., 1985). Evidence for recurrent VH gene rearrangements in mice, humans and other vertebrates, at a time when the repertoire is not yet affected by antigenic selection, has been reported (reviewed in (Vas et al., 2013)). Use of microarray chips allowing the simultaneous detection of antibodies specific for up to 300 defined self antigens revealed that IgM repertoires in cord blood were very similar between individuals indicating that different humans are born with the same autoantibodies produced in utero regardless of variances in IgG autoantibodies found in their mothers (Madi et al., 2009). The mechanisms responsible for this consistency are not yet fully understood.

The early IgM antibodies in mice and humans are mostly germline-encoded and are produced by CD5+ B1a B cells (Savage and Baumgarth, 2015). They carry specificities for common bacterial Ags, auto-antigens, certain phospholipids, DNA and several cell membrane proteins. Table 1 lists some of the specificities of these NAbs (Air, 2015; Basnet et al., 2010; Bohn et al., 1994; Bovin, 2013; Buneva et al., 2013; Chen et al., 2009; Chikazawa et al., 2013; Chou et al., 2009; Durrbach et al., 2007; Fukuda et al., 2004; Hamanova et al., 2014; Hardy and Hayakawa, 2005; Kalyanaraman et al., 1982; Kulik et al., 2009; Lebon et al., 2011; Li et al., 2009; Llorente et al., 1999; Morales-Buenrostro et al., 2008; Posner et al., 1981; Robert-Guroff et al., 1982; Sauerborn et al., 2011; Shilova et al., 2011; Silvermann, 2015; Skurnik et al., 2012; Toth et al., 1984; Tsiantoulas et al., 2013; Tuominen et al., 2006; Turunen et al., 2012; Wang et al., 2013; Xu et al., 2013). Other important targets of NAbs include the Thomsen-Friedenreich tumor antigen (CD176) (Ulsemer et al., 2013), neural gangliosides relevant in Guillain-Barre syndrome (Boffey et al., 2004) and amyloid in Alzheimer’s disease (Kayed et al., 2011). Intriguingly, many of the autoreactive specificities are similarly found throughout evolution (Flajnik and Rumfelt, 2000; Gonzalez et al., 1988; Marchalonis et al., 1993). The non-random nature of the natural repertoire suggests that these early antibodies might be programmed to enable normal development, ensure essential functions and protect against common pathogens. Indeed, natural IgM has been characterized as protective in infections with Influenza virus, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* (reviewed in (Ehrenstein and Notley, 2010)). Natural IgM also affects B cell development. Mice genetically deficient in

surface (s) IgM exhibit changes in B cell subsets including B1a B cells and MZ B cells along with increased splenic and impaired peritoneal B cell survival (Baker and Ehrenstein, 2002; Notley et al., 2010). Deficiency in sIgM has also been linked to increases in autoimmunity and atherosclerosis in both humans and mouse models. Self-reactive IgE exacerbates interferon responses in autoimmunity (Henault et al., 2016). Figure 1 lists some of the known functions of NAbs (Benatuil et al., 2005; Chen et al., 2009; Elluru et al., 2014; Matter and Ochsenbein, 2008; Panda et al., 2013; Pires et al., 2010; Rapaka et al., 2010; Stager et al., 2003; Veljkovic et al., 2010; Xu et al., 2008; Zabel et al., 2013), (McCoy et al., 2006), (Britschgi et al., 2009; Dimayuga et al., 2009; Elvington et al., 2012; Frostegard, 2010; Galkina and Ley, 2009; Gounopoulos et al., 2007; Gronwall et al., 2012; Shimomura et al., 2008; Sjoberg et al., 2009; Warrington and Rodrigues, 2010), (Aksentijevich et al., 1991; Lobo et al., 2014; Nogueira-Martins and Mariano, 2010; Warrington and Lewis, 2011).

Influence of T cells and cytokines

B cells are quite capable of producing antibodies in the absence of any T cell help, including isotypes that require class switch recombination. However, in our mouse facility, mice lacking all T cells (B6.TCR-$\beta^{-/-}/\delta^{-/-}$) had serum total Ig levels that reached only about ¼ of those in wt mice. Levels of IgM and surprisingly, IgE antibodies were nearly normal, whereas IgA and IgG antibodies were significantly reduced, especially IgG1 (Huang et al., 2015). Cytokines produced by non-B cells can determine development and steady state levels of NAbs. For example, IL-18 can boost production of protective natural IgM (reviewed in (Ehrenstein and Notley, 2010)). Natural IgE is also produced in the absence of MHCII cognate help but its production depends on IL-4 (McCoy et al., 2006). Their cytokine dependence subjects NAbs to the non-specific regulatory influence of other cell types.

A connection between γδ T cells and IgE production in non-immunized mice

Lymphocytes expressing γδ TCRs (γδ T cells) represent a lineage whose biological role remains poorly defined. Functionally, they resemble αβ T cells (Bonneville et al., 2010) but in terms of specificity and mechanism of TCR-ligand-recognition, they share properties with B cells (Chien et al., 1996; Zeng et al., 2012). In several studies with mice carrying distinct mutations affecting TCR-signaling, increased non-immune IgE levels could be correlated with increases in γδ T cells (Nunez-Cruz et al., 2003). In particular, this was observed in mice deficient in the Tec family tyrosine kinase Itk, which are unable to mount conventional IL-4- or IL-4 plus IL-13 producing T helper 2 (Th2) responses (Felices et al., 2009; Qi et al., 2009). Nevertheless, such mice had elevated levels of serum IgE and increased numbers of germinal center B cells, a phenotype found to be dependent on the presence of γδ T cells. γδ T cells in $Itk^{-/-}$ mice produced more Th2 cytokines and expressed at elevated levels co-stimulatory molecules important for B cell help, which suggested that they directly promote B cell activation and Ig class switching. In the same year, data generated in our lab with TCR-signaling competent mice revealed that IgE levels (both pre- and post-immunization)

are determined by the composition of γδ T cells. Although mice deficient in all γδ T cells had slightly reduced levels of serum IgE, others lacking only Vγ4$^+$ and Vγ6$^+$ subsets had vastly increased background IgE levels as well as exacerbated IgE responses following immunization (Huang et al., 2009). In these mice, Vγ1$^+$ and especially the NKT-like IL-4-producing Vγ1/Vδ6.3$^+$ γδ T cells (Gerber et al., 1999) were much increased, and so were serum levels of IL-4 (Huang et al., 2015). In fact, the genetically γδ-deficient mice (B6.TCR-Vγ4/6$^{-/-}$) closely resembled Itk$^{-/-}$ mice. Together, these observations implied that the composition of γδ T cells can play a critical role in setting steady state levels of IgE antibodies in non-immunized mice.

Effect of γδ T cells on serum Ig levels in non-immunized mice

After these findings, we extended the analysis to other Ig classes (Huang et al., 2015). Our data suggest that the net effect of γδ T cells on total serum Ig in normal non-immunized C57BL/6 mice is slightly enhancing as adult animals genetically deficient in all γδ T cells (B6.TCR-δ $^{-/-}$) had approximately 2-fold lower Ig levels. Net total Ig levels in these mice are lower mainly due to significantly reduced levels of IgG1 and IgG2b. Further insight came from the analysis of partially γδ T cell-deficient mouse strains. Thus, mice lacking Vγ1$^+$ γδ T cells exhibit total Ig levels that are even further diminished than those in B6.TCR-δ$^{-/-}$ mice, and show much reduced levels of IgM, IgG3, IgG1 and IgG2b. IgG2c and IgA were diminished also but to a lesser degree. Hence, Vγ1$^+$ γδ T cells appear to enhance the production of several Ig subclasses in non-immunized mice. On the other hand, mice deficient in Vγ4$^+$ and Vγ6$^+$ γδ T cells exhibit much increased total Ig levels, mainly due to increases in IgM, IgG1, IgG2b and IgG2c. IgE antibodies are even more elevated but, due to their low concentration, contribute only little to overall increases in Ig levels. IgG3 and IgA are not affected. Hence, Vγ4$^+$ and perhaps Vγ6$^+$ γδ T cells, two subsets in mice distinguished by their ability to produce IL-17 (O'Brien et al., 2009), appear to exert an inhibitory effect on most Ig production under steady state conditions. Our data suggest that this inhibition in non-immunized mice is mediated in large part through regulating Vγ1$^+$ γδ T cells, their IL-4 production, and IL-4-dependent IL-4 production by αβ T cells (Huang et al., 2015). Consistently, for some Ig subclasses, most obviously IgM, but also IgG2b and IgG2c, this regulation is still evident even in the absence of αβ T cells. Finally, it has been shown that Vγ1$^+$ γδ T cells kill tissue macrophages and thus resolve inflammatory immune responses (Carding and Egan, 2000; Dalton et al., 2003). As macrophages can be a source of IL-18, this cytotoxic activity might enable indirect control of IL-18-dependent antibody-types, at least in inflammation.

Comparing serum Ig levels in non-immunized adult wt C57BL/6 mice with mice lacking all γδ T cells (B6.TCR-δ $^{-/-}$) or all αβ T cells (B6.TCR-β$^{-/-}$) initially showed that the absence of αβ T cells affects levels of total serum Ig and most Ig subclasses more than does the absence of γδ T cells. IgE antibodies in non-immunized mice were a notable exception: They were diminished in the absence of all γδ T cells but not in the absence of all αβ T cells (Huang et al., 2015). However, mice lacking only subsets of γδ T cells revealed far greater changes in Ig levels, suggestive of potent enhancing and suppressive regulation by these cells (Huang et al., 2015). This powerful regulation is all the more noteworthy

considering that γδ T cells in circulation and in the lymphoid tissues represent a much smaller cell population than αβ T cells.

γδ T cells affect the repertoire of antibodies in non-immunized mice

The observation that changes in γδ T cells differentially affect levels of Ig subclasses in non-immunized mice suggests an influence on the repertoire and specificities of NAbs. To explore this possibility, we examined antibodies specific for chromatin, DNA and nuclear antigens in non-immunized mice (Huang et al., 2015). We found that the same change in γδ T cells that increased all Ig subclasses except IgG3 and IgA - a genetic deficiency in Vγ4+ and Vγ6+ γδ T cells, also led to substantial increases in anti chromatin antibodies. However, the anti chromatin antibodies were still further increased relative to the elevated total Ig levels, indicating a change in the composition of the elevated antibodies, and in their specificity. We also found a clear increase in antibodies detecting dsDNA/histone complexes and smaller increases in antibodies specific for ssDNA, and anti-nuclear autoantibodies. Finally, cell transfer and depletion experiments showed the change in antibody composition/specificity to be driven by the dys-regulated Vγ1+ γδ T cells derived from non-immunized B6.TCR-Vγ4/6−/− mice. Hence, γδ T cells affect the antibody repertoire in non-immunized mice (Huang et al., 2015).

Do γδ T cells have a special connection with natural antibodies?

The above-mentioned observations clearly implicate γδ T cells in the regulation of antibodies independently of immunization, and thus establish their involvement with NAbs. However, it remains to be determined if γδ T cells have a unique functional connection with NAbs. Do they play a role distinct from that of other T cells, in the development and maintenance of these antibodies? Such a role might even help to explain the evolutionary conservation of γδ T cells. We suggest that such a special connection is probable, for the following reasons: Firstly, unlike the majority of unstimulated αβ T cells, which are antigenically naïve and metabolically inactive, many peripheral γδ T cells in non-immunized mice already exist in a state of moderate activation (Tough and Sprent, 1998). This activated/memory phenotype could support background levels of cytokine production capable of sustaining some B cell differentiation and spontaneous antibody production. Secondly, in mouse ontogeny, γδ T cells develop roughly at the same time as the earliest B cells, and for a short period of time, the fetal liver gives rise to precursors of both cell-types (Havran and Allison, 1988; Whitlock et al., 1985). αβ T helper cells, on the other hand, arise several days later (Marrack et al., 1988). Moreover, γδ thymus-emigrants are functionally more mature than αβ thymus-emigrants (Jin et al., 2009; Narayan et al., 2012). In particular, γδ thymocytes are already sufficiently differentiated to produce polarized cytokines including IL-4 and IL-13 (Jin et al., 2009). Thus, γδ T cells are enabled to support and modulate B cell development and antibody production from the start, by supplying cytokines prior to any immunization. In addition, γδ T cells might interact with B cells via ligands expressed on B cells such as members of the CD1 family of molecules (Delia et al., 1988; Duan et al., 2008; Sonoda and Stein-Streilein, 2002), which are recognized by γδ T cells (Dieude et al., 2011; Porcelli et al., 1992; Russano et al., 2006). Lastly, one might consider the early idea that B1 B cells and γδ T cells occupy equivalent positions in a

"layered immune system" (Herzenberg and Herzenberg, 1989). We actually suspect that there is resemblance or overlap between antigen specificities of NAbs and γδ T cells. Thus, both recognize poly-anionic ligands including certain synthetic polypeptides (Cady et al., 2000) but also DNA/protein (unpublished data) and phospholipid/protein complexes (Born et al., 2003; Dieude et al., 2011; Lafer et al., 1981), and recent studies suggest a shared specificity for insulin (Aydintug et al., 2014; Liu et al., 2002; Zhang et al., 2010). Thus, in addition to non-specific cytokine support, at least some γδ T cells conceivably could provide help to B cells via cognate interactions between γδ TCR, antigen and BCR. Hence, he extent to which antigen specificities of γδ TCRs and NAbs might be related in non-immunized mice would be revealing with regard to the biological role of γδ T cells.

Modulating NAbs and their contribution to immune responsiveness via γδ T cells?

Although B cells can spontaneously produce antibodies in the absence of all T cells, T cells affect antibody production when they are present. The assumption that γδ T cells modulate levels and repertoire of NAbs invites additional points: First, γδ T cells in humans undergo large changes in population size and composition during ontogeny (Parker et al., 1990), due to genetic variation, in the course of hematopoietic transplantation (Airoldi et al., 2015), and as a consequence of diseases (Bank and Marcu-Malina, 2013; Pauza et al., 2015). Thus, one might expect based on the findings in mice that such changes in human γδ T cells have an effect on human B cells and their natural production of immunoglobulins: Large variation of NAbs might occur as a consequence of the changes in human γδ T cells. Furthermore, similar to the mice, specific targeting of the relevant human γδ T cells, directly or through their regulators, might effectively change human NAbs, complement IVIG in certain cases, and at times might be preferable over targeting all B cells (e.g. using antibody drugs against CD19) or entire antibody classes (e.g. antibody drugs against IgE).

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Abbreviations

NAb	natural antibody
TCR	T cell receptor
IL-4	interleukin 4

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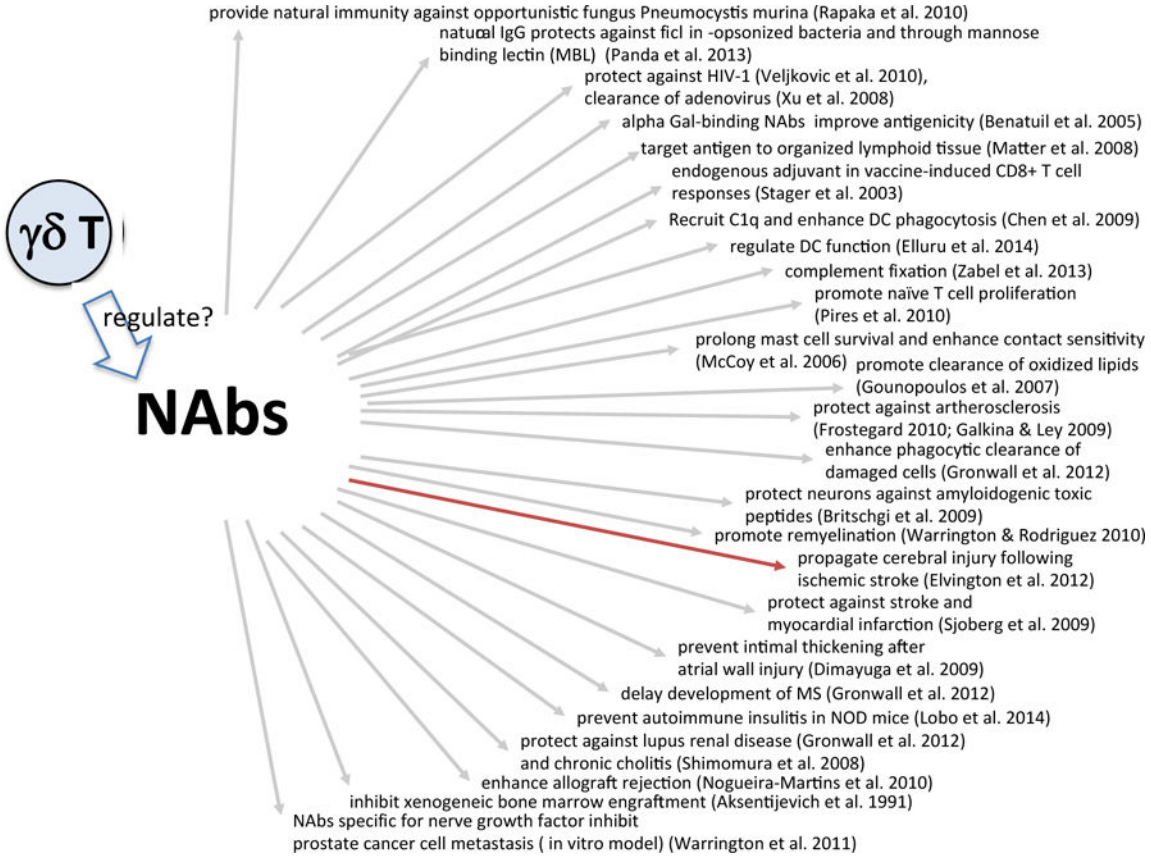

Figure 1. Diverse functions of natural antibodies

Marked in red: NAbs with pathogenic effect.

Table 1
Broad Target Range of Natural Antibodies

Reference numbers in the table refer to list of references following the main body of the text. Marked in red: NAbs with pathogenic effect.

Category	Antigens recognized	species	References
Pathogen-derived	Poly-N-acetyl glucosamine (Staph. aureus capsule)	human	Skurnik et al. 2012
	Porphyromonas gingivalis gingipain		Turunen et al. 2012
	Pneumococcal virulence proteins		Lebon et al. 2011
	Adenovirus type 5	mouse	Xu et al. 2013
	HIV	human	Llorente et al. 1999
	HTLV, simian type C virus p24 structural core protein p19		Toth et al. 1984 Kalyanaraman et al. 1982 Robert-Guroff et al. 1982 Posner et al. 1981
	Influenza		Air 2015
	Measles virus		Durrbach et al. 2007
autologous	Apoptotic cells including thymocytes and senescent eythrocytes and their antigens phosphorylcholine	mouse, human	Chou et al. 2009 Silverman et al. 2015 Chikazawa et al. 2013 Hardy et al. 2005 Chen et al. 2009
	Tumor cells, activated T cells	human	Bohn et al. 1994
	Proliferation-related self peptides		Fukuda et al. 2004
	Annexin IV	mouse, human	Kulik et al. 2009
	Nucleic acids	human	Buneva et al. 2013 Henault et al. 2016
	Glycans, sialoglycans	chicken, human	Shilova et al. 2011 Bovin et al. 2013
	Bone morphogenic protein	human	Sauerborn et al. 2011
	IFN-β, IFN-γ		Sauerborn et al. 2011
	α(1,3)-galactosyl		Hamanova et al. 2014
	CD40		Elluru et al. 2014
allogeneic	HLA		Morales-Buenrostro et al. 2008
xenogenic	αGal		Li et al. 2009
	N-glycolylneuraminic acid	mouse	Basnet et al. 2010
Oxidation-induced	Apoptotic cells	mouse, human	Chou et al. 2009
	Oxidized lipids, cardiolipin	mouse	Tsiantoulas et al. 2013 Tuominen et al. 2006
	Malondialdehyde acetaldehyde adducts	human	Wang et al. 2013