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Historical Review of Cytokines[1]

Charles A. Dinarello
University of Colorado Health Sciences Center, Denver, Colorado

Abstract

Cytokines affect nearly every biological process; these include embryonic development, disease pathogenesis, non-specific response to infection, specific response to antigen, changes in cognitive functions and progression of the degenerative processes of aging. In addition, cytokines are part of stem cell differentiation, vaccine efficacy and allograft rejection. This short review focuses on the milestones in cytokine biology and how the various and often contradictory activities of these small, non-structural proteins affected the fields of inflammation and immunology. Multiple biological properties or pleiotropism is the hallmark of a cytokine. Today, the term “cytokine” encompasses interferons, the interleukins, the chemokine family, mesenchymal growth factors, the tumor necrosis factor family and adipokines. As of this writing, 33 cytokines are called interleukins, but many are part of families of related but distinct gene products. There are certainly over 100 separate genes coding for cytokine-like activities, many with overlapping functions and many still unexplored. Also discussed in this overview are the failures and successes of cytokines as therapeutic targets. A recent advance in the field has been that of differential cytokine production, which can be used to classify human disease as being “auto-immune” or “auto-inflammatory” thus impacting on therapeutic interventions.

Introduction

Cytokines can be divided into functional classes. For example, some cytokines are primarily lymphocyte growth factors, others function as pro-inflammatory or anti-inflammatory molecules whereas other cytokines polarize the immune response to antigen. During the past 25 years, cytokines have become an important frontier in medicine in a vital place as diagnostic, prognostic and therapeutic agents in human disease. Although cytokines are studied today in nearly every biological discipline, cytokine-mediated effects dominate the fields of inflammation, immunology, atherosclerosis and cancer. For instance, chemokines and their receptors have impacted on inflammation, HIV-1 pathogenesis, lymphocyte trafficking and auto-immune disease. Some chronic diseases appear to be driven by “auto-inflammatory” pathways whereas others have classic characteristics of “auto-immune” mechanisms. Mutations in the gene NALP1 are associated with auto-immune diseases [1] whereas mutations in NALP3 are associated with auto-inflammatory diseases [2]. Although there is clinical overlap in this classification, distinct cytokine portfolios have emerged based on the functions of the caspase-1 “inflammasome”. The discovery of the mammalian surface Toll-like receptors (TLR) for recognizing a large and heterogeneous number of microbial products is intrinsic to cytokine biology because the intracellular signaling domains of TLR are nearly identical to those of the interleukin-1 receptor, both mediating host responses to infection and injury.

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University of Colorado Health Sciences Center, 4200 East Ninth Ave. B168, Denver, CO 80262, TEL (303) 315-3558, FAX (303) 315-8054, cdinare333@aol.com.

Cytokines in evolution

Cytokines evolved from the earliest forms as intracellular molecules before the appearance of receptors and signaling cascades. Cytokine-like activities have been demonstrated in invertebrates such as star fish and *Drosophilia*, where they played an essential role in host defense and repair. A cytokine-mediated rise in body temperature as survival mechanism was demonstrated in poikilothermic lizards [3]. Some cytokines function as transcription factors (likely their initial functions) as well as extracellular ligands for specific receptors (evolved later). Recorded history is full of examples of the devastating effect of infection on societies and one can argue that cytokine-mediated events underlie the pathological processes of these epidemics.

Cytokine biology springs from the host production of “pus”. Long before the microscope, exudates containing pus and the presence of fever and local swelling and pain were well-documented by writers in the ancient world. Pus was visible and later could be studied in the laboratory. The field had its earliest advance with interest in soluble “factors”, as they were then called, which were studied in the mid-1940’s as products of white blood cells (pus). Indeed, most cytokines are best defined as soluble factors produced by one cell that acts on another cell. Today, however, we recognize that cytokines can also function as integral membrane proteins and some are never released from the cell. Initially, cytokines were called “lymphokines” to distinquish them from “monokines” in an attempt to classify these soluble factors by their primary sources but that nomenclature was short lived and yielded to “cytokines”. With the exception of the red blood cell, every cell can produce as well as respond to a cytokine.

The pioneering days

Soluble factors released from neutrophils from the peritoneal cavity of rabbits were the first to establish a link between a disease (in most cases infection) and the response of the host (fever). The biological properties of these soluble factors included fever, resistance to viral infections, elevated white blood cell count, the synthesis of acute phase proteins, death of cancer cells and migration of inflammatory cells. Soluble factors as regulators of lymphocyte functions were not studied until the mid-1970’s, with the first description of “lymphocyte activating factor” by Igal Gery and Byron Waksman [4] and later as T-cell growth factor [5]. A paradigm developed that a disease process induces the production of these soluble factors (cytokines) from cells and it is the property(s) of these “factors” that account for the manifestations of the disease. The concept is best appreciated with the non-specific physiological and immunological upheaval that the host initiates with infection. The “innate immune response” is nothing more than a cytokine storm to infection or to cell damage triggered by Toll-like receptors (TLR). The hallmark of the innate immune response is its non-specific nature as the response occurs repeatedly, regardless of triggering event. The effect of the response on the specific or adaptive immune response is actually collateral.

The good and bad of cytokines

Here lies the conundrum in cytokine biology, particularly for the immunologist. The innate response is required for host survival but is also causative in disease. For example, interferon-γ (IFNγ), essential for defense against several intracellular microorganism such as *Mycobacterium tuberculosis*, is also a major cytokine in the pathogenesis several autoimmune diseases. The issue of the “good cytokine versus the bad cytokine” has its greatest impact in therapeutic arena. IL-2 is needed for the generation of cytotoxic T-cells (CTL) and forms the basis for several vaccines but the same cytokine drives graft versus host disease and limits the success of bone marrow transplantation.

Cytokine as hormones of the immune system

For sure, the definition of a cytokine as a soluble factor produced by one cell and acting on another cell, in order to bring about a change in the function of the target cell, was based on the endocrine system of hormones. In a way, one can consider cytokines as the “hormones” of immune and inflammatory responses. However, there are several properties of cytokines that escape this definition. For example, hormones are the primary product of a specific tissue or cell whereas cytokines are products of most cells. Most importantly, on a molar basis, cytokines are far more potent than hormones. For example, the concentration of the cytokine IL-1 that induces gene expression and synthesis of cyclo-oxygenase-1 (COX-2) is 10 pM and the ability of IL-12 to induce IFNγ is 20 pM. In fact, during purification of several cytokines from cell cultures, it was not uncommon to have a biological response in the absence of a visible band on gel electrophoresis.

The interleukins nomenclature

Being non-structural proteins, biological properties were and still are the gold standards for defining a cytokine. The interleukin nomenclature was invented to deal with the issue of multiple biological properties of cytokines. At the time of the naming these molecules with an interleukin number, primary amino acid sequences of the active molecules were not known. The term IL-1 was used to define a monocyte product and the term IL-2 was used to define a lymphocyte product. But the nomenclature did nothing to resolve the broader issue of multiple biological properties ascribed to a single molecule. IL-1 was reported to cause fever, induce acute phase protein synthesis, activate B-cells and act as a co-factor for T-cell proliferation in the presence of antigens or mitogens. IL-2 was reported to expand T-cell proliferation and also activate B-cells. IL-2 was initially termed T-cell growth factor and expanded human T-cells in vitro [5]. T-cell growth factor produced in the laboratory of Robert Gallo at the NIH allowed for the isolation of the human immunodeficiency virus-1 (HIV-1).

The skeptics are rained in

The concept that a single molecule could possess multiple and diverse biological activities was viewed with considerable skepticism by cell biologists but it was the immunological community that provided increasingly convincing data that indeed this was the case. The issue was particularly problematic for those working with IL-1, as its properties ranged from effects on control of body temperature to liver protein synthesis to T-cell responses to antigens and mitogens. Despite highly purified preparations of IL-1 and IL-2, it was the molecular cloning of the cDNA and the expression of recombinant forms of these cytokines that broke the impasse. All doubts were pushed aside using recombinant forms of cytokines [6]. A great deal of biology was accomplished using recombinant cytokines and immunological research advanced greatly with receptor identification. Recombinant cytokines were used not only to confirm the biological properties of the natural molecule derived from cell cultures but more importantly used to discover new properties. Recombinant cytokines also provided antigens for monoclonal antibody production and the ELISA kit. The ELISA kit liberated the immunologist from the tedium of bioassays and provided for a rapid method for determining the quantity of a cytokine.

Genes and more genes

Today we speak not only of a cytokine as a single gene product but also of cytokine families. The family of TNF includes over 20 members, each a separate gene product but with a considerable over lap in biological properties such cell death. Although there are presently 33 interleukins, the IL-1 family has 11 members and include IL-1α, IL-1β, IL-18

and IL-33. Although each member of the IL-1 family is a separate gene, their products overlap in functions as proinflammatory cytokines. The family of IL-6 includes several members such as IL-6, leukemia inhibitory factor, IL-11, oncostatin, ciliary neurotropic factor and cardiotropin-1. Each member induces hepatic acute phase proteins in addition to other unrelated biological properties. The IL-10 family includes IL-22 and represents a family of cytokines that inhibit inflammation and immune responses. IL-15 accomplishes nearly the same functions as does IL-2. Colony stimulating factors (CSF) such as IL-3, granulocyte-CSF, granulocyte-macrophage CSF, macrophage CSF, have overlapping functions but remain distinct gene products with specific receptors. The most impressive families are the chemokine families. In total, there are xx individual human genes for chemokines. Although there are two structural classes, the CC chemokines and the CXC chemokines, regardless of structure, chemokines orchestrate cell migration from the blood compartment into the tissues. Why this duplication of function? Such duplication in function is not found in the endocrine system of hormones.

Duplication of function

The duplication in cytokine function is best explained from the viewpoint of host defense and immune function. Challenged with death from microbial invasion, the host turns on most cytokine genes. There are probably few persons reading this review who have not cleared a pneumococcal bacteremia without antibiotics. In doing so, cytokines mobilize several mechanisms for defeating microbial invaders. For example, cells migrate to the site of infection, reactive oxygen species are produced to aid in phagocyte-mediated killing and pro-coagulant activities are initiated to wall-off the invader and limit spread of the infection. At the same time, several cytokines assist dendritic cells in the process of antigen (microbial) presentation, which results in the generation of cytotoxic T-cells and production of neutralizing antibodies. It is unlikely that evolution could depend on a few cytokines to rescue the host from a lethal infection. The large number of cytokines induced during an infection also includes cytokines that aid in repair. For example, fibroblast growth factors (FGF) and vascular endothelial growth factor (VEGF) should be considered cytokines that participate in the healing process. But again, we are faced with the duality in cytokine biology as FGF is a pathological molecule in lung and liver fibrosis and VEGF is a pathological molecule in cancer.

Dysregulation of cytokine production

Cytokines wreak havoc with the immune system turning against itself in autoimmune diseases. During infection, the cytokine “storm” subsides as the infection is eliminated and the genes return to their normal state of being repressed by histone acetylases. When cytokines genes fail to shut down, their products drive the host into a state of chronically activated cells, which now dominate an otherwise resting immune system. Auto-reactive T-cells are cells that persist and fail to die. There are likely other mechanisms of “failure to die” that account for the persistence which are influenced genetically. Most anti-cytokine therapies for autoimmune disease target the effects of cytokines on inflammatory and tissue remodeling processes but seem unable to shut down the persistently activated auto-reactive T-cell.

Gene deletions and gene screenings advance the field

The major impact for cytokine studies remains molecular cloning of biologically active molecules, the testing of recombinant cytokines and the identification of their specific receptors [7]. The most recent example of this area is the identification of IL-33. IL-33 is the specific ligand for the orphan receptor ST2 [8]. A great deal about the function of this receptor for the Th2 response and allergic diseases was gained over the past 12 years

without knowing the ligand [9]. With the cloning of IL-33, the recombinant cytokine fulfills each of the biological properties attributed to the receptor and closes the circle. Although neutralizing antibodies greatly advanced cytokine studies, deleting a specific cytokine gene or receptor in a mouse was also a major advance. However, in the gene deletion studies, the unexpected finding was that most cytokine or cytokine receptor deletions did not affect the mouse unless the mouse was challenged with infection or an immunological challenge. The lack of a phenotype in cytokine deficient mice supports the concept that most cytokines are not needed for health but rather for infections, trauma or immunological challenge. For example, mice deficient in IL-1α, IL-1β, caspase-1, TNFα, or IL-6 are fertile, and their off-spring develop normally and for the most part age normally without a spontaneous disease. Only when challenged with disease-inducing events does the deficiency reveal a role for the cytokine. In contrast mice, deficient in IL-10, IL-1 receptor antagonist (IL-1Ra) or IL-2 develop spontaneous diseases. The diseases are inflammatory such as inflammatory bowel disease and arthritis. In the case of IL-18 deficient mice, spontaneous disease develops only as the mice age when they begin to eat excessively, become obese, diabetic and atherosclerotic [10]. Thus IL-18 deficiency reveals a property of the cytokine never anticipated as a mediator of Th1 and Th2 responses.

Another advance in cytokine biology came as the genomic make-up of a species was sequenced yielding thousands of genes without known function. The cDNA for human IL-32 was deposited in the gene bank 13 years ago but remained without function until the recombinant cytokine was tested and anti-IL-32 antibodies used to detect its presence in disease [11]. IL-32 is a proinflammatory cytokine inducing TNFα, IL-1β and several chemokines and is found in tissues from rheumatoid arthritis and Crohn's Disease [12]. One can asked the question: how many other genes presently with unknown function are actually cytokines and may have a role in immunological functions or disease?

The failures and benefits of cytokines for treating human disease

With progress in the late 1970's on the biological activities of "soluble factors" came increasing interest from the pharmaceutical industry. In fact, the development of the biotech industry can be linked to developments in cytokine biology, particularly as cDNA and recombinant cytokines validated the field. The molecular cloning of the first cytokines in the early 1980's (IFNα, IL-1, IL-2 and TNFα) coincided in 1984 with the discovery of HIV-1 as the causative agent in the acquired immunodeficiency syndrome (AIDS). Therapeutic use of IL-1 and IL-2 held great promise as natural immuno-stimulants to combat the immune deficiency of AIDS. At the same time, it was thought that the immunosuppression of cancer could be reversed by injecting patients with immuno-stimulating cytokines. There was no dearth of animal and in vitro studies to support trials for treating cancer patients or patients with AIDS with these cytokines. At the same time TNFα held promise for treating patients with cancer. The fact remains, however, that injecting humans with IL-1, IL-2, IL-3, IL-4, IL-6, IL-12 or TNFα induces unacceptable systemic inflammation and the use of these cytokines as therapies was abandoned.

The only cytokine to receive approval for treating cancer is IL-2 but its pro-inflammatory effects are not easily tolerated by most patients and its efficacy in treating melanoma and renal cell carcinoma is low. IL-10 was an outstanding candidate for treating a variety of autoimmune diseases as IL-10 suppressed IFNγ, IL-1, TNFα, and IL-6 production as well as possessing other anti-inflammatory activities. Several trials of recombinant human IL-10 showed limited efficacy in psoriasis, rheumatoid arthritis and Crohn's disease but the cytokine, has never been approved for therapeutic use. On the other hand, colony stimulating factors such as G-CSF or GM-CSF are used to treat bone marrow suppression associated with radiation, chemotherapy or transplantation. GM-CSF has also been used to

treat Crohn's Disease. Erythropoietin (EPO) is routinely used to large numbers of patients with anemia and bone marrow failure. Impressively, IFNα is administered to millions of patients to treat hepatitis B and C. IFNβ for the treatment of multiple sclerosis is also effective.

Blocking cytokines in humans

The use of agents that specifically block the activity of a cytokine truly defines the role of that cytokine in disease or in an immunological response. Although blocking cytokines in animal models with neutralizing strategies established the importance of a cytokine in the pathogenesis or progression of disease, approval for use in humans remains the ultimate goal. The first studies of blocking a cytokine in humans was based on reducing IL-1 and TNFα activity in animal models of lethal endotoxemia or live infections. The animal studies were impressively revealing in that blocking either of these cytokines reduced mortality and therefore it was logical to reduce IL-1 and or TNFα in patients with sepsis. Despite sophisticated intensive care units, death from sepsis has an unacceptable mortality rate with over 500,000 cases in the USA each year. Therefore, billions of dollars were invested in the development of blocking agents and testing in placebo-controlled trials in over 12,000 patients. Only marginal reductions in all-cause 28 mortality were achieved, insufficient to gain approval. A meta-analysis of the clinical trials concluded that like the animal studies, a mortality benefit of blocking IL-1 or TNFα was only observed in patients at the highest risk of death [13]. Blocking IL-4 or IL-5 for treating asthma was based a well-established animal model of airway antigen challenge but the results in several placebo-controlled trials did not show sufficient efficacy. Blocking chemokines were also thought to be a therapeutic strategy; neutralizing anti-IL-8 failed to affect psoriasis.

Blocking cytokines in autoimmune disease succeeds

The same agents that failed in clinical trials for sepsis were also tested in patients with rheumatoid arthritis, Crohn's disease and plaque psoriasis. In the case of blocking TNFα, monoclonal antibodies to TNFα or soluble TNF receptors have been highly successful in these autoimmune diseases and used in over 800,000 patients. As a result, nearly every anti-cytokine agent, whether an orally active inhibitor of a cytokine-regulated intracellular pathway, a neutralizing antibody or soluble receptor or a receptor antagonist, is tested in patients with rheumatoid arthritis, Crohn's Disease or psoriasis. Blocking IL-1, IL-6, IL-12, IL-23 have been successful. Blocking IL-15 or IL-18 have been marginal. In general, animal models can predict which cytokines are likely to improve rheumatoid arthritis as well as Crohn's Disease [14], but do not predict which anti-cytokine is efficacious for one patient but not another.

Autoimmune versus auto-inflammatory disease

As the properties of various cytokines were investigated, understanding the linkage between inflammation and immune responses expanded. For some cytokines, the ability to induce inflammatory mediators such a prostaglandins, nitric oxide, reactive oxygen species impacts greatly on immune responses in chronic diseases. Autoimmune diseases have both dysfunctional immune responses as well as a prominent inflammatory component. For example, in the treatment of rheumatoid arthritis, psoriasis or Crohn's Disease by blocking TNFα or IL-12 activities, there is both a reduction in chronic inflammation and a partial restoration of suppressed immune responses. Other chronic diseases appear to be mostly inflammatory in nature and due to dysregulation of IL-1β processing and secretion. These diseases are called auto-inflammatory to distinguish them from autoimmune diseases.

As shown in Table 1, examples of auto-inflammatory diseases are Familial Mediterranean Fever, Neonatal Onset Multiple System Inflammatory Disease and Systemic Onset Juvenile Idiopathic Arthritis. Patients with these diseases suffer from chronic fevers, systemic inflammation and painful joints. However, upon blocking IL-1β activity there is a rapid reversal of disease severity. The pathological abnormality in auto-inflammatory diseases appears to be a failure to control the processing and secretion of IL-1β in that blood monocytes from patients with these diseases release more active IL-1β compared to cells from non-disease subjects. The processing and secretion of IL-1β is controlled by caspase-1, an intracellular cysteine protease that cleaves the IL-1β precursor as well as those of IL-18 and IL-33 into active cytokines. Caspase-1 is controlled by the caspsase-1 inflammasome, a complex of intracellular proteins. The discovery of the inflammasome is one of the hallmarks of cytokine biology since inflammation mediated by IL-1β, IL-18 and IL-33. Figure 1 illustrates the caspase-1 inflammasome.

Th1, Th2, Th17 polarization and the generation of T-regulatory cells

Fundamental to the pathogenesis of autoimmune diseases is the polarization of the immune response and generation of T-regulatory cells as controlled by cytokines. The Th1 response is dominated by the activities of IL-2 and IFNγ in orchestrating expansion of cytotoxic T-cells in auto-immune diseases and allograft rejection whereas IL-4 and IL-13 and possible IL-33 function to promote a Th2 response dominated by antibody production. IL-18 in the presence of IL-12 or IL-15 is a Th1 cytokine inducing IFNγ but alone, IL-18 induces a Th2 response. In the case of Th17, a polarization towards autoimmune disease, the production of IFNγ is driven by IL-17 via the intermediate production of IL-23. The differentiation of T0 into IL-17-producing T-cells plays a greater pathogenic role in models of autoimmune disease compared to Th1 T-cells producing IFNγ or IL-12. Similarly, the function of T regulatory cells (Treg) is also controlled by the cytokine expressed in T-cells. The ability of Treg to suppress autoimmune processes and allograft rejection is dependent on the expression of IL-10 and TGFβ.

Dual function cytokines

Most cytokines function solely by binding to specific cell surface receptors, which initiates a cascade of intracellular signals affecting gene expression mediated by transcription factors such as NFκB and AP-1. Increasingly, there are cytokines that function as classic ligands for specific receptors but, in addition, have another life as transcription factors. For example, the N-terminal amino acids of the IL-1α precursor binds to DNA and participates in transcriptional machinery [15], whereas the carboxyl domain (mature) binds to the IL-1 cell surface receptor as induces the same portfolio of genes as does IL-1β. High-mobility group B-1 (HMGB-1), a nuclear DNA-binding protein that regulates gene transcription and steroid hormone receptors, binds to the RAGE receptor and functions as a pro-inflammatory cytokine inducing IL-1β and TNFα [16]. Antibodies to HMGB-1 reduce disease severity in animal models of inflammation. It is likely that the original function of these signaling immune and inflammatory responses but others cytokines seem to have another life. IL-33, the specific ligand for the IL-1 family receptor ST2 is a Th2 cytokine. However, IL-33 is homologous to the nuclear factor high endothelial venules (NF-HEV) binding chromatin [17]. Chromatin binding and transcriptional repression are due to the N-terminal domains of IL-33 whereas the C-terminal part of the molecule is homologous to IL-1. IFNγ has intracellular targets.

Surprises in cytokine biology

The field had its first major surprise when TNF, long studied for its effect in killing tumors in vivo and in vitro, was shown to be a proinflammatory cytokine sharing many properties

with the proinflammatory effects of IL-1 such a fever, induction of PGE2 and adhesion molecules. For many years, nearly all investigations on TNF had focused on the eventual administration of the cytokine to treat cancer. It was the work of the Cerami laboratory that proposed that “cachetin” (one of the names used for TNF) accounted for several of the pathological changes in chronic autoimmune and inflammatory diseases. Today using TNF as a cancer therapy remains primarily a laboratory exercise whereas blocking the cytokine has become a therapeutic success and a multi-billion dollar business. IL-4, studied as a B-cell growth factor and agonist in the Th2 paradigm, was shown to possess significant anti-inflammatory effects. The combination of IL-12 and IL-18 induces IFNγ, the classic Th1 cytokine; however, in the absence of IL-12, IL-18 is a Th2 response [18]. Not unexpectedly, mice deficient in IL-18 produce lower amounts of IFNγ and exhibit reduced inflammation compared to wild-type mice but unexpectedly mice deficient in the IL-18 receptor produce more IFNγ and an accelerated rejection of allographs [19]. Another surprise came when mice deficient in IL-18 became increasingly obese as they aged and developed frank metabolic syndrome with diabetes, insulin resistance and atherosclerosis just by eating more normal mouse food [10,20].

Functional classes of multifunctional cytokines

What defines a cytokine? Although the interleukin nomenclature streamlined the dilemma of multiple names describing biological activities into a numbering system, the nomenclature provides no indication of the properties of the molecules. The interleukin numbers are assigned solely by order of description of the human cDNA associated with an activity(s). Once it had become clear that recombinant IL-1 and TNFα possessed multiple and often unrelated activities, other cytokines were shown to induce varied effects depending on the target cell. However, most cytokines have one or two prominent properties along with other effects. As shown in Table 2, some cytokines act primarily as T-lymphocyte or B-cell growth factors, others function as prominent mediators of inflammation, whereas yet others suppress inflammation as well as immune responses.

Since each cytokine binds to its specific receptor and initiates a cascade on intracellular signals, what then explains the multiple and varied properties of a single cytokine? In some cases, the cytokine receptor is found primarily on one type of cell, accounting for its primary function, for example, IL-33 receptor is expressed on mast cells [8]. In other cases, the receptor is found on nearly every cell, for example, IL-1 and TNFα. In these cases, the cell type defines the property of the cytokine. For example, activation of NFκB by either IL-1 or TNFα induces COX-2 resulting in high levels of proinflammatory PGE2 but in cells lacking COX-2, such as T-cells, IL-1 and TNFα act as co-activators of IL-2 production. Indeed, another explanation for the pleiotropic nature of cytokines is their ability to induce or to function as co-activators. IL-18 in the presence of IL-12 induces IFNγ but alone induces Fas ligand and death of hepatocytes [21].

The adipokines

The adipokines (see Table 2) are a recent grouping of cytokines based on their production from white adipose tissue, including resident macrophages in fat, and their role in the metabolic syndrome, particularly in insulin resistance [22]. Several adipokines, such as IL-1α and TNFα, are already known for their pro-inflammatory role in the atherosclerotic processes [23]. Leptin, although initially described as a naturally occurring suppressor of appetite, appears to function primarily as a mediator of cytokine-induced inflammation and immune functions [24]. Adiponectin is an anti-inflammatory adipokine inhibiting macrophage functions. Resistin increases insulin resistance in muscle and liver tissue but also induces chemokines and vascular adhesion molecules. Adipokines have a role in

obesity-related diseases. For example, in type 2 diabetes, fatty tissue-derived cytokines likely accounts for the progressive loss of the insulin-producing beta cells in the pancreatic islets. From a historical perspective, the ability of IL-1β to kill the beta cell, first reported in 1986 [25], opened the field of cytokines to diabetologists. In response to glucose challenge, the beta cell produces IL-1β in a suicidal process [26]. The importance of IL-1 in type 2 diabetes has been demonstrated in a placebo-controlled trial of IL-1Ra, in which blocking IL-1 prevented the loss in beta cell function [27].

The systemic cytokine versus the micro-environmental cytokine

There is no dearth of reports measuring circulating cytokines and their association with disease severity. Despite highly statistically significant correlations, an important lesson in cytokine biology is that a causative role of a particular cytokine in disease can only be established by specific blockade in animals or humans. For example, serum IL-6 levels often correlate with mortality in patients with septic shock but the administration of high doses of IL-6 to humans does not affect blood pressure or the physiological parameters of shock. On the other hand, nanogram per kg doses of IL-1 or TNFα injected into humans induces life-threatening hypotension [28] yet there have been few studies that correlate serum levels of IL-1 or TNFα with any disease. In the past 10 years, another property of cytokines has emerged – one of being both an extracellular molecule engaging its specific cell surface receptor as well as being an integral membrane proteins using a juxtacrine mechanism of cell-cell contact for its activity [29]. For example, a considerable amount of the biological activity of TNFα in rheumatoid arthritis and Crohn's Disease is likely mediated by membrane TNFα. It is likely that many cytokines effects take place in the micro-environment [30] whereas systemic levels of cytokines, such as IL-6 levels, are primarily markers of disease severity.

Anti-cytokine genes found in viruses

A major advance in cytokine biology and the immune response came with discovery that viral genomes code for molecules highly homologous to mammalian cytokines, including soluble cytokine receptors and inhibitors of caspases [31]. Viruses use these gene products to prevent the host's immune response intended to eliminate the infection. Deletion of these genes from a viral genome dramatically reduces the virulence of the virus and allows an immune attack by the host. The best example is viral IL-18 binding protein (IL-18BP), which being highly homologous to the mammalian molecule [32], neutralizes the activity of human IL-18 [33]. Skin infection with Poxviruses such as *Molluscum contagiosum* is remarkable for its near total lack of infiltrating immune cells allowing for a persistent infection. The virus actually teaches us of the importance of IL-18 in the immune response. Some viral genes code for biologically active IL-10 as part of their attempts to suppress IFNγ during an immune response to the infection.

Endogenous inhibitors limit the biological impact of cytokines

With the increasing numbers of cytokines being discovered, it became clear that some possessed pro-inflammatory properties whereas others inhibited inflammation. The message was that nature had provided mechanisms to limit or balance exuberant cytokine responses. For example, soluble [34,35] and decoy [36] receptors limit cytokine action of their respective ligands As listed in Table 2, cytokines with anti-inflammatory and immunosuppressive properties are IL-4, IL-10, IL-22 and TGFβ; even IL-6 appears to reduce inflammation since mice deficient in IL-6 have more inflammation than wild-type mates and produce higher levels of TNFα. TLR agonists, for example, induce both pro and anti-inflammatory cytokines. IL-10 deficient mice develop spontaneous inflammatory bowel disease. In the case of the IL-1 receptor antagonist, mice deficient in this antagonist

spontaneously develop inflammatory arthritis and arteritis [37] since without IL-1Ra, there is no counter balance against the effects of IL-1β.

Another mechanism for controlling inflammation or during an immune response is the action “suppressors of cytokine signaling” of (SOCS). In the absence of these gene products, increase inflammation and immune responses are observed. But perhaps the most common mechanism for controlling runaway immune stimulation or inflammation is the effect of prostaglandins on cytokine production and cytokine activity. PGE2 is perhaps the most potent suppressor of T-cell function; PGE2-induced cAMP inhibits the production of IL-2, IFNγ, TNFα and other cytokines. A great number of persons routinely use aspirin and other inhibitors of COX-1 or 2, which affect cytokine responses, particularly immune responses. A short course of daily aspirin increases the production of IFNγ from primary human blood T-cells [38]. In contrast, PGE2 augments the production of IL-6. Oral cyclooxygenase inhibitors reduce serum IL-6 and acute phase proteins in patients with rheumatoid arthritis. The discovery that nutritional status and the balance between cell membrane composition of N-3 and N-6 fatty acids affect cytokine production and activity [39] likely explains a large body of epidemiological evidence on dietary affects on health, disease and the aging process.

Abbreviations (not finished)

LAF	lymphocyte activating factor
TCGF	T-cell growth factor
LEM	leukocytic endogenous mediator
MIF	migration inhibition factor
IFN	interferon
TNF	tumor necrosis factor
MNC	mononuclear cell factor
NFκB	nuclear factor B
AP-1	activating protein-1
TLR	Toll-like receptors

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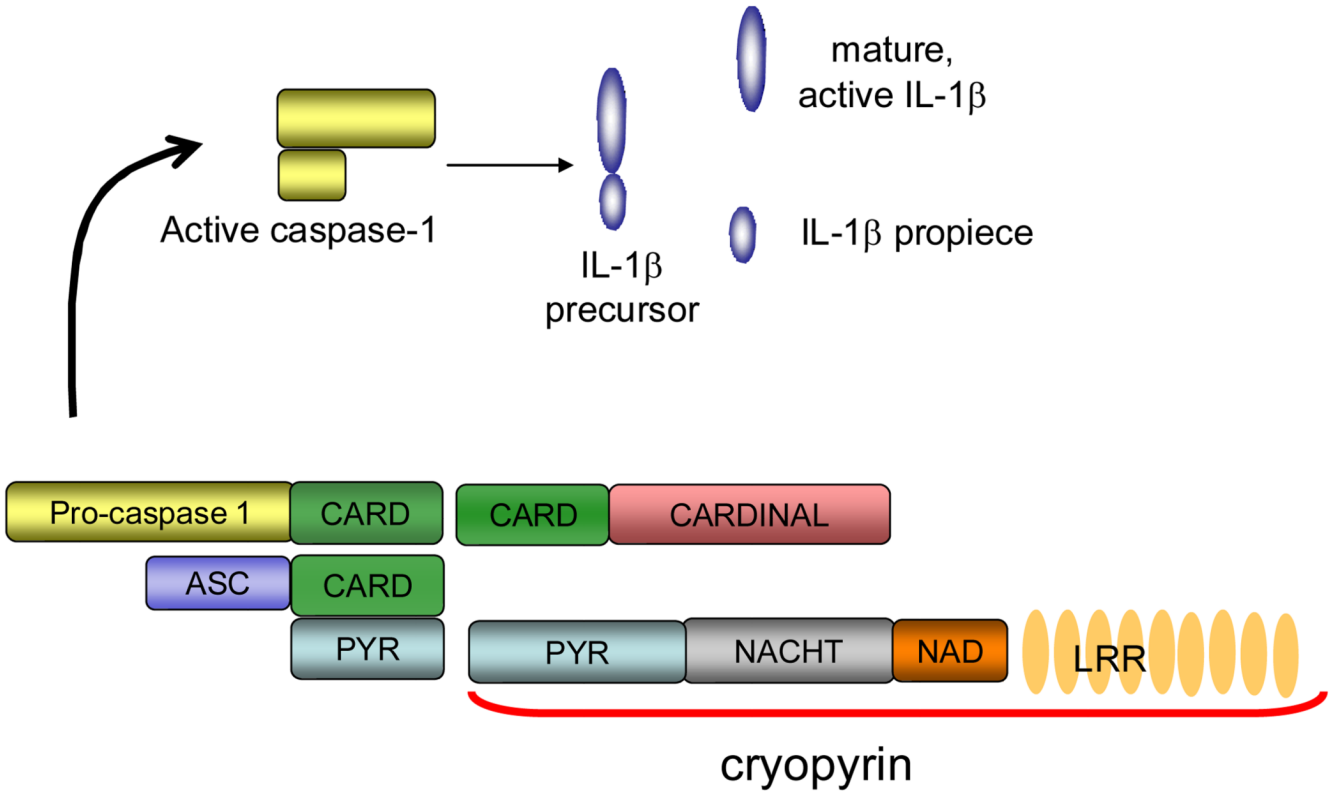

Figure 1.
Cryopyrin Inflammasome. The function of the cryopyrin inflammasome is to activate inactive procapsase-1 into an active heterodimeric enzyme. Active caspase-1 cleaves the N-terminal 116 amino acids from the inactive IL-1β precursor. The inflammasome is a complex of interacting intracellular proteins and each component assembles to form the complex. Cryopyrin (also known as NALP3) binds to procaspase-1 via CARD (caspase-1 recruitment domain) and the CARD on ASC (apoptosis-associated speck-like protein containing CARD) and its pyrin (PYR) domain. Cryopyrin is a large protein with four domains: PYR, a pyrin domain; NACHT (a domain found in NAIP, CIITA, HET-E and TP-1), NAD (NALP-associated domain) and LRR (Leucine Rich Repeats). Mutations in cryopyrin are associated with three autoinflammatory diseases (FCAS, MWS, NOMID) [40–42]. Other proteins are part of the cryopyrin complex such as Cardinal (CARD Inhibitor of NFκB-Activating Ligands). The processing of pro-caspase-1 results in the formation of the active caspase-1 heterodimer and the cleavage of the IL-1β precursor. The enzymatic processing of the IL-1β precursor by caspase-1 may take place in the cytosol or in the secretory lysosomes [43] or both.

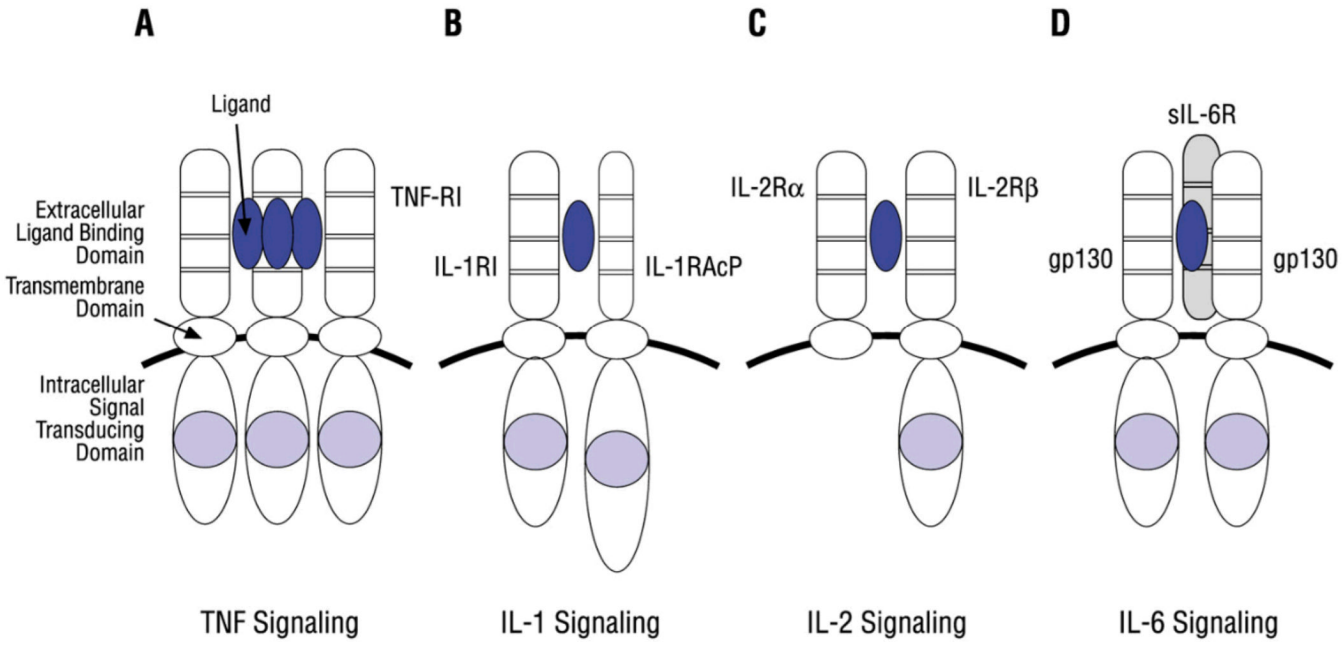

Figure 2.

Four examples of cytokines and their receptors. A. TNF. TNFα is biologically active as a trimer. The TNF receptor is comprised of three chains (homotrimer) of either the TNF type 1 receptor (TNF-RI, also known as p55) [34] or a homotrimer of the type 2 receptor, not shown (also known as p75) [34] and initiates signal transduction. The cytoplasmic domains of the TNF R (I or II) contains death domains. B. IL-1. IL-1 binds to the type I IL-1 receptor (ligand binding chain) with a low affinity [7]. The IL-1 receptor accessory protein (IL-1RAcP) [44] is then recruited to form a high affinity heterodimer. The cytoplasmic domains of the IL-1 receptors (type I and IL-1RAcP) contain the Toll-IL-1 receptor (TIR) domains, which are essential for signaling [45]. The cytoplasmic domains of the IL-1 receptors share a high level of homology with the TLR and signaling is also similar. C. IL-2. IL-2 binds to the IL-2Rα chain with a low affinity [46,47]. The signaling chain IL-2Rβ forms the dimeric complex. D. IL-6. Like IL-1 and TNF, IL-6 is a pleiotropic cytokine [48]. IL-6 first binds to the soluble IL-6 receptor. The soluble IL-6 receptor binds to two chains of the gp130 receptor initiating a signal.

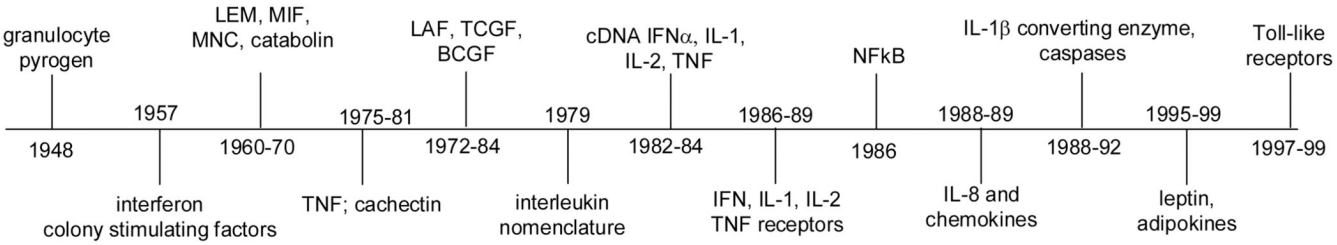

Figure 3.

Time-line of milestones in cytokine biology. The early work on cytokines focused on soluble factors that were active in vivo models such as fever in rabbits [49] [50–52]. Colony stimulating factors (CSF), first reported by Leo Sachs and Donald Metcalf, interferon and migration inhibitory factor (MIF) [53] were some of the first cytokines studied in vitro. MNC, mononuclear cell factor, an inducer of PGE2 and collagenases [54] and catabolin [55] for breakdown of cartilage were studies focused on the role of soluble factors affecting cartilage in models of rheumatoid arthritis. LEM, leukocytic endogenous mediator, was studed primarily as an inducer of hepatic acute phase proteins [56,57]. LAF (lymphocyte activating factor), a macrophage product first described by Gery and Waksman [4], was shown to be mediated by leukocytic pyrogen purified from human monocytes [52,58]. TNF was initially described as a serum factor in animals injected with endotoxin [59]. Later, the endotoxin-induced macrophage product cachetin was purified and shown to be identical to TNF [60]. B-cell growth factors (BCGF) included several factors reviewed in [61]. IL-2 was originally described as T-cell growth factor [5]. IL-8 was the first chemokine [62,63] of a very large family. The term IL-1β converting enzyme was changed to caspase-1 and the caspase family expanded.

Table 1

Auto-inflammatory Diseases
Dominant Cytokine = IL-1β; secondary cytokine = IL-6 Dominant Cell = Macrophage > T-cell> B-cell
Examples[a]
Familial Mediterranean Fever
Familial Cold Auto-inflammatory Syndrome
Muckle-Wells Syndrome
Neonatal Onset Multi-inflammatory Disease
Hyper IgD Syndrome
Adult and juvenile Still's Disease
Anti-Synthetase Syndrome
Macrophage Activation Syndrome
Urticarial vasculitis
Behçet's's Syndrome; Blau's Syndrome; PAPA Syndrome
Schnitzler's Syndrome; Sweet's Syndrome
Urate Crystal Arthritis (Gout)
Type 2 Diabetes

Auto-immune Diseases
Dominant Cytokine = TNFα; secondary cytokines = IFNγ/IL-17/ Dominant Cell = T-cell > Macrophage; secondary cell = B-cell
Examples [a]
Rheumatoid arthritis
Juvenile rheumatoid arthritis
Ankylosing spondylitis
Crohn's disease
Psoriasis
Lupus erythematosus
Pemphygus
Wegener's granulomatosis
Sarcoidosis

[a]Blocking IL-1β effective therapy; blocking IL-6 effective; blocking TNFα minimally effective or exacerbation of disease

[a]Blocking TNFα, IL-23, CD20, CTLA-1 Ig, IL-1β effective therapy

Table 2

Functional Classes of Cytokines

Functional Class	Primary Property	Other Effects	Examples
lymphocyte growth factors	clonal expansion	Th1/Th2/Th17 polarization	IL-2, IL-4, IL-7, IL-17, IL-15
Th1 cytokines	↑ Th1 response	clonal expansion of CTL[a]	IFNγ, IL-2, IL-12, IL-18
Th2 cytokines	↑ Th2 responses	↑ antibody production	IL-4, IL-5, IL-18, IL-25, IL-33
Th17 cytokines	↑ Th17 responses, IFNγ	autoimmune responses	IL-17, IL-23, IFNγ
pro-inflammatory cytokines	↑ inflammatory mediators	↑ innate immune responses	IL-1α, IL-1β, TNFα, IL-12, IL-18, IL-23
			MIF, IL-32, IL-33, CD40L
anti-inflammatory cytokines	↓ inflammatory genes	↓ cytokine-mediated lethality	IL-10, IL-13, TGFβ, IL-22, IL-1Ra, IFNα/β
adipokines	pro-inflammatory	↓ autoimmune disease pro-atherogenic	IL-1α, TNFα, IL-6, leptin, adiponectin, resistin
gp130 signaling cytokines	growth factors	B-cell activation, acute phase	IL-6, CNTF, IL-11, LIF, CT-1
nerve growth factors	↑ nerve/Schwann cells	B-cell activation	BNDF, NGF
osteoclast activating cytokines	bone resorption	immune stimulation	RANK L
colony stimulating factors	hematopoiesis	pro and anti-inflammatory	IL-3, IL-7, G-CSF, GM-CSF, M-CSF
angiogenic cytokines	neovascularization	pro-metastatic	VEGF, IL-1, IL-6, IL-8
mesenchymal growth factors	fibrosis	pro-metastatic	FGF, HGF, TGFβ, BMP
type II interferon	macrophage activation	increase class II MHC	IFNγ
type I interferons	anti-viral; ↑ class I MHC	anti-inflammatory, anti-angiogenic	IFNα, IFNβ
chemokines[b] others	↑ cellular emigration	↑ cell activation	IL-8, MCP-1, MIP-1α,

[a] does not include soluble cytokine receptors such as sTNFRp55, sTNFRp75, sIL-1R type II, IL-18 binding protein, osteoprotegerin

[b] the chemokine family includes CC and CXC chemokines with over xx members

[a] CTL, cytotoxic T-cell; BMP, bone morphogenic protein;