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Therapeutic Targeting of the Inflammome

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Abstract

Inflammatory responses can vary depending on a myriad of factors including: 1) the initiating stimulus or trigger, 2) the cell types, involved in the response, and 3) the specific effector cytokine-chemokine milieus produced. The compilation of these and other factors in a given mechanistic context is sometimes referred to as the “inflammome”. Humans and other higher order mammals have evolved (over time) several discrete inflammomes to counter the effects of pathogens. However, when these inflammomes are induced inappropriately, they drive the development of chronic inflammatory diseases. The vast majority of biological anti-inflammatory treatments currently being developed are focused on the *post hoc* inhibition of downstream effectors by anti-cytokine monoclonal antibodies and receptor antagonists. This prevailing “end-point treatment” has even directed a new disease classification paradigm, namely a cytokine-based disease classification, as opposed to a traditional diagnosis based on a particular tissue or organ system dysfunction. Although this approach has a number of advantages, it omits the processes that led to the generation of the inflammatory effectors in the first place. In this review, we will expand the cytokine-based disease taxonomy into an inflammome-based taxonomy that includes interventions that subvert *a priori* cytokine development that can complement *post hoc* inhibition.

1.0 INTRODUCTION

Inflammation, to use a timeworn axiom, is a double-edged sword. Under normal physiological circumstances, it operates as an integral component of a defense system that the human body utilizes to ward off the incursion of foreign pathogens [1]. However, if inappropriately directed or poorly regulated, inflammation can lead to significant morbidity and mortality [2]. It is truly a unique circumstance within physiology that one of the greatest assets for developing Darwinian fitness can abruptly become one of the most significant contributors to tissue dysfunction, destruction, and disease.

Although the mechanisms by which inflammation develops has become more complex and efficient over evolutionary time, there are only but a handful of molecular signaling

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pathways and professional immune cell types that drive inflammatory processes [3]. Nevertheless, the term inflammation is used very broadly, particularly as it is portrayed to the general public. This oversimplification has contributed to the stagnation in therapeutic options for patients suffering from “inflammatory” diseases, until the advent of cytokine-specific biologicals in the 1990s [4, 5]. In reality, inflammation can vary depending on a myriad of factors including: 1) the initiating stimulus or trigger (e.g. pathogenic infection, cell injury, molecular mimicry, or inappropriate responses to a self-antigen), 2) the cell types, receptors, and signaling pathways involved, 3) the generation of specific effector cytokine and chemokine milieus, 4) temporality of the response (e.g. acute vs. chronic, or early vs. late phase), and 5) the type of pathology that results (e.g. systemic vs. local, tissue destruction vs. tissue repair). The compilation of these factors in a given mechanistic context is the “inflammome” [6].

Humans and other higher order mammals have, over evolutionary time, developed several discrete inflammomes designed to counter specific types of pathogens (Fig. 1). However, when these inflammomes are induced inappropriately, they drive the development of distinctive disease-causing effector molecules that have become the basis of many new interventional therapies [7]. The vast majority of biological anti-inflammatory treatments currently being developed are focused on the *post hoc*, direct inhibition of downstream effectors by anti-cytokine monoclonal antibodies or receptor antagonists. This prevailing predilection for “end-point treatment” has even directed a new approach to disease classification, namely, a cytokine-based disease taxonomy [8], as opposed to a traditional diagnosis based on a particular tissue or organ system dysfunction. Although this approach can be beneficial for categorizing inflammatory diseases, it omits the underlying processes that led to the generation of these effectors in the first place. In this review, we will focus on delineating not only the pathogenic sequelae of inflammation-driving effector cytokines, but also the distinct inflammomes that lead to their synthesis. Through this, we discuss the benefits of expanding the present cytokine-based disease taxonomy into an inflammome-based disease taxonomy, while directing the focus of future therapeutic development toward those interventions that subvert *a priori* cytokine development, in addition to their *post hoc* inhibition.

2.0 THE MAJOR INFLAMMOMES

2.1 INNATE (TNF DOMINANT)

The innate immune response is composed of different cell types that respond to diverse endogenous or exogenous signals and mediate distinct downstream effects within minutes to hours of activation. However, there are at least three major cytokine milieus that can be generated based on all of these factors: tumor necrosis factor (TNF) dominant, interferon (IFN) dominant, and inflammasome dominant. The word “dominant” is used because, in reality, all of these responses are generated to varying degrees with any given inflammogen. For clinical purposes, thinking about the innate response in the context of these three major divisions allows one to clearly see that these milieus are generated by distinct signaling cascades that provide an opportunity for specific therapeutic interventions.

A TNF dominant response can be generated by either a pathogenic infection or trauma that results in cell injury [9]. These initiating triggers are recognized by the innate immune system through pathogen associated molecular patterns (PAMPs), or in the case of cell injury, damage-associated molecular patterns (DAMPs) [1, 10, 11]. PAMPs, as the name implies, are usually structural components of bacteria, viruses, or fungi that are recognized through pattern recognition receptors (PRRs) on immune cells such as macrophages, dendritic cells, and B cells [12]. On the other hand, DAMPs are factors from host cells that are normally sequestered away from immune recognition, but in the face of cell injury or death, are released from cells. DAMPs, such as the nucleosome associated protein HMGB1, can be recognized by the same PRRs as PAMPs [13].

PRRs, such as the toll-like receptors (TLRs), activate two distinct signaling pathways following ligation, depending on which PAMP is recognized. In TNF dominated responses, the major contributing pathway involves activation of the MyD88 adaptor protein, which is activated most strongly in the context of lipopeptides (TLR1/2 or 2/6), LPS (TLR4), flagellin (TLR5), profilin (TLR11, 12), ribosomal RNA (TLR13), or CpG oligodinucleotides (TLR9) [12]. MyD88 is responsible for coupling TLR ligation to the activation of the pro-inflammatory transcription factor NF-κB through a complex signaling pathway involving interleukin-1 receptor-associated kinase (IRAK) 1 and 4, TNF receptor associated factor 6 (TRAF6), TAK1, IκB kinase (IKKα/β/γ), and finally poly-ubiquitinylation and degradation of the inhibitor of NF-κB, IκBα [14]. NF-κB function results in the transcription of genes important for cell survival, as well as initiating a pro-inflammatory program. Specifically, in conjunction with MAPK signaling, this leads to synthesis of the transcription factor activator protein 1 (AP-1), which induces transcription of the *TNF* gene. After TNF protein is produced, it exerts pleiotropic effects on the body including: activation of the underlying tissue endothelium which directs other immune cells to sites of inflammation, activation of the pro-inflammatory acute phase response proteins from the liver (interleukin-6, C-reactive protein, serum amyloid A, etc.), enhancement of phagocytosis and oxidative burst by phagocytic cells, and during prolonged or systemic exposure, insulin resistance, muscle wasting, and vasodilation [9, 15]. Additionally, TNF signaling through its receptors can lead to further activation of NF-κB, and subsequently more TNF production, creating a very potent and potentially dangerous cycle of activation [16].

TNF is produced in nearly every inflammatory disease; however, there are several in which TNF predominates the response, so much so that anti-TNF interventions have been introduced as therapies. These include inflammatory bowel diseases (Crohn’s disease and ulcerative colitis), rheumatoid arthritis, ankylosing spondylitis, psoriasis, several vasculitides including giant cell arteritis, and asthma that is refractory to other therapies [5, 17]. Systemic TNF, via activation of the acute phase response, can also result in a “cytokine storm”, which leads to the initiation of systemic inflammatory response syndrome (SIRS) or sepsis for triggers involving bacteremia, viremia, or mass tissue damage (e.g., from electrocution or severe burns)[18].

Current anti-TNF therapies being used in the clinical setting include: anti-TNF monoclonal antibodies (infliximab, adalimumab) and soluble TNF decoy receptors (etanercept) [19, 20].

However, many disease processes do not respond to anti-TNF therapy. In fact some, as in the case of multiple sclerosis [21], are exacerbated with anti-TNF therapy. The number of adverse effects of anti-TNF treatments is also growing and to date include increased risks of infection, autoimmune disease, and malignancy.

As anti-TNF treatment was the first biologic anti-cytokine therapy to be FDA approved (in 1998)[22], it is not surprising that this field is also the first to realize the need for *a priori* therapeutics, exemplified by the recent wave of NF-κB inhibitors and TLR antagonists currently in clinical trials [23] to prevent sepsis and treat other TNF-centric inflammomes [24]. Some of the drugs under development for the innate/TNF-dominated inflammome are shown in Table I. These agents act on a range of dysregulated targets in this inflammome. Resatorvid acts at a very early stage by inhibiting the TLR4 receptor and inhibiting lipopolysaccharide-induced inflammatory mediator production [25]. Other compounds, such as apremilast, cool this inflammome by inhibiting intermediate steps; apremilast inhibits the phosphodiesterase PDE4, which promotes cellular cAMP accumulation and suppresses NF-κB activity and inflammatory mediator production [26]. Understanding the details of this inflammome has helped identify novel treatments that target dysfunctional signaling pathways at the root of the disease.

2.2 INNATE (IFN DOMINANT)

The innate IFN dominant inflammome is initiated in a manner analogous to the TNF dominant inflammome (i.e. PAMP-TLR interaction); however, the ligands recognized in these responses are generally nucleic acids from viruses, and to a lesser extent bacteria, or even endogenous DNA and RNA in the context of autoimmune diseases like systemic lupus erythematosus. The signaling mechanisms of type-I IFN generation are complex but are becoming well described. Briefly, nucleic acid PAMPs are recognized by endosomal (TLR3, TLR7, TLR8) or cytoplasmic (RIG-I, MDA-5, STING) sensors, and converge downstream at the level of interferon regulatory factor 3 (IRF3) and IRF7 phosphorylation [27, 28]. IRF3 and IRF7 act to initiate the transcription of type-I IFNs (IFNα/β/δ/ε/ω) which, like TNF, can enhance their own production via a positive feed-forward loop. Type-I IFNs can be made by most cell types, but plasmacytoid dendritic cells (pDCs) have been identified as professional IFNα producing cells in response to nucleic acid PAMPs [29]. The importance of pDCs in type-I IFN production is exemplified by the fact that they have a cell-type specific alteration in their signaling machinery that permits IFNα production directly after stimulation with TLR7 and TLR9 ligands through a TRAF3-independent mechanism involving IKKα and IRF7. Type-I IFNs, like TNF, also have pleiotropic effects at different levels of the immune system including activation of anti-viral response genes, the establishment of CXCR3-mediated chemokine gradients via CXCL9 and CXCL10, and the enhancement of IFNγ production from Th1 and Tc1 T cells and NK cells [30]. Type-I IFNs can also lead to STAT3 phosphorylation in macrophages and Tregs which induce an anti-inflammatory response via up-regulation of IL-10 and PD-L1 [31].

Some diseases associated with altered type-I IFN production include SLE [32], psoriasis [33], multiple sclerosis (therapeutic) [34], insulin-dependent diabetes mellitus [35], rheumatoid arthritis (therapeutic) [36], myasthenia gravis [37], and some hematologic

malignancies [38]. Therapeutically, anti-IFN treatments for diseases like SLE and polymyositis have shown some promise in reducing symptom severity [39, 40], although responses in SLE was limited to a subpopulation of patients. However, inhibition of IFNα theoretically increases the risk of viral infections, so trials of anti-IFN therapies are carefully monitored and exclude patients with chronic viral infections. The anti-viral activity of type-I IFNs highlights the drawback of targeting effector cytokines and supports the further development of inflammome-targeting therapies. Interestingly, recombinant IFNβ has been established as a treatment for relapsing-remitting multiple sclerosis [34]. Although this treatment has proven to be effective for many, it can potentially exacerbate existing autoimmune tendencies, again pointing to the risks of cytokine interventions.

Janus kinase (JAK) inhibitors may be a particularly effective for treating the IFN-dominant inflammome, given the critical role of JAKs in IFN signaling (Table I). The expression specific JAK isotypes in different cell types provides an additional layer of specificity. Ruxolitinib has been developed as a JAK1 and JAK2 inhibitor, whereas tofacitinib is specific for the JAK3 isotype. Since JAK3 is predominantly expressed by hematopoietic lineage cells (including T cells and NK cells), JAK3 inhibitors can achieve some novel anti-inflammatory effects. Recent clinical data have shown tofacitinib to be superior to methotrexate for the treatment of rheumatoid arthritis [41]. Inhibition of JAK2 by Ruxolitinib has side effects that limits its use, but has shown some effectiveness for treating myelofibrosis, a disease frequently driven by activating mutations in JAK2 [42]. Additional study of the JAK inhibitors could further establish their utility as part of a comprehensive treatment plan for the innate/IFN-driven inflammome.

2.3 INNATE (INFLAMMASOME DOMINANT)

The third major inflammome driven by innate immune cells centers on activation of inflammasomes, which are pentameric or heptameric protein complexes that serve to couple PAMP and DAMP sensing with the proteolytic cleavage of pro-IL-1β and pro-IL-18 via caspase 1 [43]. Several different inflammasomes exist and differ somewhat in structure, but each contains a PRR-like protein [a NOD-like receptor protein (NLRP) or the interferon-inducible AIM2] connected to pro-caspase 1 by the adaptor protein ASC [44]. Inflammasomes also have been reported to confer resistance to different kinds of pathogens based on the PRR that is affiliated with them. For example, the NLRP3 inflammasome responds to *Staphylococcus spp.*, *Listeria spp.*, and influenza viruses, the NLRC4 inflammasome is activated by intracellular pathogens bearing flagella, and the AIM2 inflammasome responds to dsDNA from *Francisella tularensis* and herpes viruses [45, 46]. The exact nature of inflammasome activation and regulation are still active areas of investigation; however, several consensuses have been reached. First, inflammasomes usually require two signals in order to become fully responsive: 1) a signal is required to drive expression of substrates for the inflammasome (i.e. pro-IL-1β and pro-IL-18), which usually occurs in response to signaling cascades downstream of other PRRs and 2) the inflammasome requires a second signal that stimulates the cleavage of pro-caspase 1 into bioactive caspase 1, and subsequently the production of mature IL-1β and IL-18. There is much conjecture as to what can provide the second signal and present data point to intracellular potassium efflux [47], extracellular ATP sensing [48], exposure to lysosomal

enzymes like cathepsin B [49], and reactive oxygen species [50]. Following activation, inflammasome regulation is less well understood, but factors associated with chronic infection, such as prolonged IFNγ, exposure can lead to inflammasome destabilization through nitric oxidize-mediated nitrosylation [51].

The inflammasome dominant inflammome becomes medically relevant in response to bacterial and viral pathogens, but also in the context of situations involving “frustrated phagocytosis” which can result from exposure to particulate antigens. Diseases associated with the inflammasome dominant inflammome include gout (uric acid crystals), asbestosis (asbestos fibrils), berylliosis (beryllium), silicosis (silica), sarcoidosis, and amyloidosis (protein deposits) [52]. Each of these diseases lead to localized inflammation of the area where these particulates are deposited which is usually the lung (beryllium, silica, asbestos), joints (uric acid), or small blood vessels and soft tissue (amyloid). Inflammasomes are also implicated in both metabolic disease and atherosclerosis, and may be a central player in the development of insulin resistance in type-2 diabetes mellitus [53].

Antagonistic IL-1 therapies such as anakinra (receptor antagonist [54]), canakinumab (anti-IL-1 mAb [55]), and rilonacept (soluble decoy receptor [56]) have proved efficacious in these types of diseases, including gout [57]. Many of these therapies were initially developed for the treatment of rheumatoid arthritis; however, they have shown limited long-term efficacy in humans [58]. This illustrates that the presence of a particular cytokine within the inflammatory milieu in a given disease, and thus an attempt to block it therapeutically, is not necessarily sufficient to effectively decrease symptom severity. However, a full understanding of the inflammome of a given disease can better guide clinicians to more rational interventions.

With regard to the inflammasome inflammome, direct inflammasome inhibition is one obvious approach. Pre-clinical studies have supported the benefit of inflammasome inhibition for some inflammatory animal models. Interestingly, the IκB kinase-β inhibitor Bay-11-7082 was found to potently inhibit the NLRP3 inflammasome, most likely through inhibiting the NLRP3 ATPase activity [59]. Although studies with inhibitor are still at the preclinical stage, data showing efficacy for protection in a mouse model of diabetic nephropathy has been reported [59]. The selective deployment of newly developed inflammasome inhibitors in the clinic could therefore serve to control inflammation close to the root cause.

2.4 ADAPTIVE (T CELL CENTRIC)

T cells are perhaps the best studied of all immune cells due to their importance in mediating nearly every immune and inflammatory response [60]. T cells are activated after their T cell receptor (TCR) encounters a peptide antigen that has been processed and presented by an APC in the context of the major histocompatibility complex (MHC)[61]. Naïve T cells also require a second signal from co-stimulatory molecules, which together with the antigen signal, drives their proliferation (clonal expansion) via the production of IL-2 [62]. Co-stimulation usually arises from the interaction between CD28 on the T cell and CD80/CD86 on the APC; however, ligation of other co-stimulatory molecules such as ICOS, OX40, and 4-1BB can also provide this necessary signal [15]. Finally, a third signal in the form of

cytokines directs differentiation of the activated T cell towards a specific effector subtype, and in some cases (IL-33) enhances their ability to produce effector cytokines. Thus, the T cell centric inflammome can take on different characteristics depending on the context in which it was induced. The major T cell subsets include Th1 (driven by IL-12, IL-18, IFNα/β), Th2 (IL-4, IL-33), Th17 (TGFβ & IL-1, IL-6, IL-21, IL-23), and T regulatory cells (TGFβ), but other, less well defined subsets also exist, including cytotoxic T helper cells, Th9, Th22, Tfh, and Tr1 [63, 64]. For the purpose of this review, we will focus on Th1, Th2, and Th17 subtypes, as they have been the best studied in the context of mediating human disease.

Th1 T cells are produced when activated in the context of IL-12, IL-18, and Type-I IFNs and the absence of IL-4 [65]. They are defined by the major transcription factor T-bet which is necessary for their ability to produce the effector cytokine IFNγ. Th1 T cells also provide help to $CD8^+$ cytotoxic T lymphocytes (CTLs) that respond to cells infected with intracellular pathogens or expressing altered self-antigens (cancerous cells), and kill them by production of several soluble effector molecules including IFNγ, granzymes, granulysin, and perforin [66]. CTLs can also induce death through contact-mediated, caspase 8 dependent apoptosis by Fas-FasL (CD95-CD95L) and TNF-related apoptosis-inducing ligand (TRAIL)-DR5 [67]. Th1 cells have been implicated in the pathogenesis of numerous autoimmune diseases through inappropriate activation by self-antigens. They can also potentiate the innate immune response through the positive feedback effects of IFNγ.

Th17 T cells are produced in the context of TGFβ and other pro-inflammatory cytokines such as IL-6, IL-1β, IL-21, IL-23, and others [68]. Their differentiation to Th17 can be enhanced through the autocrine production of IL-21, and are stabilized by IL-23 after the up-regulation of IL-23R following TCR activation [69]. Th17 polarization is controlled by the master transcription factor RORγT/RORC2 [70], which facilitates IL-17A, IL-17F, IL-21, and IL-23 production from Th17 T cells [71]. A major function of IL-17 is to recruit neutrophils to the sites of infection by stimulating the production of CXCL8, CCL2, CCL7, CXCL1, and CXCL5 [72]. IL-17 can also promote synthesis of TNF, IL-6, and IL-1β from epithelial cells and macrophages. Th17 cells have been implicated as pathogenic in mouse models of RA, IBD, psoriasis, and type-1 diabetes mellitus, as well as several diseases in humans: multiple sclerosis, RA, SLE, psoriasis, and IBD [73]. These associations have been largely based on finding elevated IL-17 levels in either sera or tissue biopsies from afflicted patients, or the direct visualization of Th17 cells within diseased tissue biopsies [74]. Several therapies that target the Th17 pathway are available or under development, including a monoclonal antibody called ustekinumab that targets the IL-12p40 subunit shared by IL-12 and IL-23 [75], and several anti-IL17 antibodies that are not yet FDA approved (brodalumab, ixekizumab, and secucinumab). Ustekinumab treatment has seen some success in treating patients with psoriasis, but that success has not translated to other Th17 implicated diseases to date [76, 77].

The final T cell subset that can define a T cell centric inflammome are the Th2 T cells that differentiate in the presence of IL-4 or IL-33 and the absence of IFNγ [78, 79]. Th2 cells are potent promoters of IL-4, IL-5, and IL-13 production and are defined by their master transcription factor GATA3. Th2 cells can also efficiently stimulate B cell expansion

through CD40-CD40L interactions. In the presence of IL-4, B cells secrete antibodies of the IgE isotype, which are critical for protection against helminthic infection, but can also drive allergic responses in humans [80]. The concomitant actions of IgE binding to its receptor (FcεRI) and the Th2-associated cytokines potently induce granulocyte chemotaxis and the degranulation of mast cells, eosinophil, and basophils. This degranulation releases vasoactive amines (e.g. histamine), serine proteases, and eicosanoids (such as prostaglandins and leukotrienes), all of which trigger allergic symptoms (erythema, pruritus, bronchoconstriction) [81]. Once again, most therapies currently approved for treatment of allergic reactions are typically based on *post hoc* approaches. These interventions involve the blockade of histamines and leukotrienes, or management of symptoms through the use of bronchodilators [82]. Investigation into blocking these responses at the level of T cell (or B cell) initiation is an area that requires attention.

The T cell centric inflammome can assume very diverse outcomes, and be the driving force behind many different types of inflammatory diseases. However, because T cells undergo clonal expansion in response to activation, they are susceptible to many of the broadly immunosuppressive agents that kill dividing cells [83]. For example, corticosteroids block the production of IL-2, and immunophilins (such as tacrolimus and cyclosporine) prevent calcineurin-mediated activation of NFAT, a transcription factor critical for T cell responses [84]. Also, cyclostatic drugs (e.g. methotrexate, azathioprine, mercaptopurine) that block all cell proliferation, and are typically used in cancer therapy, are sometimes used to prevent T cell expansion in inflammatory diseases [85]. All of these therapeutic options prevent pro-inflammatory cytokine production; however, they also suffer from lack of specificity. Future studies aimed at improving T cell-based therapeutic interventions should seek to combine the *a priori* blockade of cytokine synthesis with the specificity of a biologic treatment in order to prevent complications associated with broad immunosuppression.

One potential example of this *a priori* cytokine inhibition strategy is blockade of Raf 1 kinase inhibitor protein (RKIP) by the small molecule inhibitor locostatin. RKIP has been implicated as an important signaling molecule in both the NF-κB and MAPK signaling cascades [86, 87]. Although the exact molecular mechanism by which RKIP functions *in vivo* remains elusive, it is preferentially activated in recalled T cells and its inhibition by locostatin can significantly attenuate the production of IFNγ from antigen-specific $CD8^+$ effector T cells in a T-cell dependent model of SIRS [88], as well as IFNγ and TNF synthesis from human flu specific CTLs and LPS stimulated PBMCs [89]. Identification and development of other agents that target over-active signaling pathways in activated T cells could enable clinicians to suppress T cell inflammomes prior to the excessive expression of cytokines.

2.5 ADAPTIVE (B CELL CENTRIC)

The main effectors of the B cell centric inflammome are antibodies, which are generated after the integration of signals from B cell receptor ligation, T cell help, PRR signaling, and the cytokine milieu [90]. The effector functions of antibodies are well defined and include opsonization and neutralization of pathogens, initiation of the complement cascade, and activation of other effector cells. Different antibody isotypes are generated by activation-

induced cytodine deaminase (AICD) in response to sensing the cytokine milieu by B cells. For example, in humans the presence of IFNγ will trigger production of IgG1 whereas IL-4 will promote IgE production and TGFβ will yield IgA [91].

B cells can also be significant contributors to cytokine synthesis in their own right. B cells that are primed by Th1 cells and BCR ligation will begin to produce a “Th1-like” cytokine profile including synthesis of IFNγ and even IL-12, a cytokine not made explicitly by Th1 cells but key for Th1 differentiation (B effector type 1 or Be-1 cells). By analogy, those primed with Th2 cells will produce IL-2, IL-4, and IL-13 (Be-2 cells) [92]. Additionally, B cells can also produce regulatory cytokines, such as TGFβ and IL-10, in some circumstances (Bregs). Each of the B cell cytokine-producing subtypes have been identified *in vivo* [93], and have documented functional significance, especially in the context of pathogen clearance and autoimmune diseases that result from the inappropriate production of autoantibodies like SLE and many others [94]. Nevertheless, much remains to be studied regarding the role of B cell generated cytokines in inflammatory disorders.

2.6 REVERSE-PHASE IMMUNITY

Recently, more evidence is coming to light that exemplifies the bi-directionality of the immune response, in that exposure to molecules that directly activate T cells, such as superantigens, can lead to T-cell mediated activation of the innate immune system [95]. This concept outlines an emerging reverse-phase inflammome that relies on bystander activation of the innate immune response through cytokines produced by the adaptive arm of the immune system, rather than PAMP or DAMP exposure. The exact mechanism(s) by which this activation occurs is still an area of active investigation; however, production of IL-17 by TCRγδ T cells after cooperative activation by TCRαβ T cells has been implicated [96, 97]. This novel route of innate immune system activation will generate an inflammatory-milieu that is largely similar to those generated by the innate inflammomes discussed above. In cases such as *Staphyloccal* enterotoxin A (SEA) mediated acute lung injury or SIRS, a physician may see a cytokine profile that implicates the innate immune system as the main driving force in disease pathogenesis; however, treating such a disease with therapeutics such as anti-TNF may not be productive because the actual pathogenic mechanism is directed by T cells. In this instance a better outcome would be obtained using agents that target IL-17 or IL-2 production. Although a cytokine-based disease taxonomy allows for a better understanding of how to treat diseases that share related milieus, it may in some cases lead clinicians to incorrect assumptions that could be insignificant, or even deleterious to the patient. An understanding of a patient’s underlying inflammome would enable physicians to administer targeted and timely therapeutic interventions, which could improve a patient’s condition with fewer side-effects.

3.0 CONCLUSIONS

Inflammation is one of our body’s greatest assets as it is responsible for the defense against harmful pathogens and facilitates removal and repair of dead or dying cells. However, inflammation is also the pathogenic mechanism by which many diseases are manifest, leading to significant medical and financial burdens for patients. Our ability to

therapeutically intervene in these pathophysiological processes is key to preventing undue morbidity and mortality in these patients. Before the 1990s, the standard of care for many auto-inflammatory diseases involved broad immunosuppression using corticosteroids or direct killing of proliferating cells, both of which lead to significant immunosuppression and the inability to ward off potential infections. With the advent of cytokine-specific biologics, clinicians and scientific investigators became much more interested in specific, targeted therapies that attenuated disease, while allowing for most of the immune response to continue unabated. This led many to consider a disease diagnostic schema that centered on a particular cytokine milieu. This has resulted in the development of successful therapeutic endeavors for some diseases (IBD, RA), but also to significant failures (anti-TNF in MS, anti-IL-1 in sepsis, and anti-IL-17 in Crohn's disease) [98-100]. These failures are due in large part to the exclusive focus on *post hoc* cytokine production rather than an examination of the underlying inflammome that led to the generation of these cytokines in the first place. By understanding the inner workings of the body's different inflammomes, better therapies can be developed that stop altered cytokine production at the source, rather than treating them as the sole cause of the disease.

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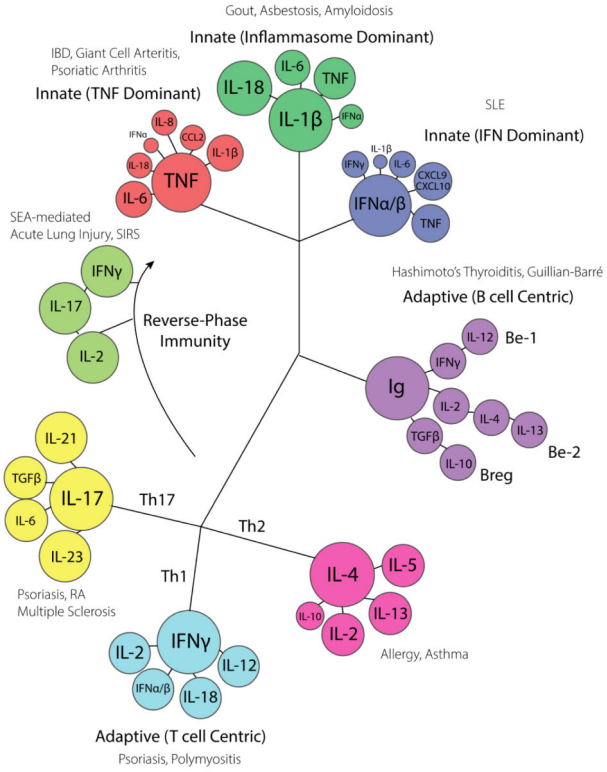

Figure 1. An Inflammome-based Disease Taxonomy

A schematic representation of the cytokine networks established by the host's major inflammomes; the size of each circle pictorially represents the relative abundance of a given cytokine within its respective inflammome. Human diseases associated with each inflammome are listed in non-bold script.

TABLE I

Examples of *a priori* Inflammome Inhibitors Currently Under Investigation

Drug	Mechanism of Action	Point in Pipeline	Inflammome Affected	Potential Diseases Interventions
Apremilast (Otezla) GSK256066	PDE4* inhibitor- ↑ PKA ↓ NF-κB	Approved† Phase 2	Innate TNF & Inflammasome dominant	Psoriatic Arthritis Ankylosing Spondylitis Allergic Rhinitis
Atreleuton (VIA-2291)	5-LO** inhibitor- ↓ Leukotrienes	Phase 2	T cell centric (Th2) & B cell centric (Be2)	Allergy, Atherosclerosis, Vasculitis
Apilimod (STA-5321)	PIKfyve inhibitor- ↓ IL-12 ↓IL-23	Phase 1	T cell centric (Th1/Th17)	Inflammatory Bowel Disease
Dilmapimod (SB-681323) Losmapimod (GW856553X) BMS-582949	p38 MAPK inhibitor- pleiotropic	Phase 1 Phase 2 Phase 2	Multiple	COPD Rheumatoid Arthritis Atherosclerosis
Diacerein	Xanthine Oxidase inhibitor - ↓IL-1β	Phase 4	Innate Inflammasome dominant	Gout
Resatorvid (TAK-242)	TLR4 inhibitor	Phase 3	Innate TNF & Inflammasome dominant	Sepsis, ARDS
Tofacitinib (CP-690550) Ruxolitinib (INC424)	Janus Kinase (JAK) Inhibitors‡	Phase 3	Innate & Adaptive Inflammomes	Rheumatoid Arthritis, Psoriasis, Myelofibrosis, Leukemia
BAY-11-7082	Inhibits TNFα induced IκB-α phosphorylation & NLRP3 inflammasome	Pre-clinical	Innate TNF & Inflammasome dominant	Diabetic Neuropathy Cardiac Ischemia-Reperfusion
Locostatin	RKIP inhibitor- ↓ IFNγ ↓IFNα	Pre-clinical	T cell centric (Th1) & Innate IFN dominant	SIRS

*Phosphodiesterase 4

**5-Lipoxygenase

†FDA approval for Psoriatic Arthritis (March 2014)

‡Provide both *a priori* and *post hoc* inhibition due to prevention of cytokine-induced cytokine release