Review

Drug targets in the cytokine universe for autoimmune disease

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In autoimmune disease, a network of diverse cytokines is produced in association with disease susceptibility to constitute the 'cytokine milieu' that drives chronic inflammation. It remains elusive how cytokines interact in such a complex network to sustain inflammation in autoimmune disease. This has presented huge challenges for successful drug discovery because it has been difficult to predict how individual cytokine-targeted therapy would work. Here, we combine the principles of Chinese Taoism philosophy and modern bioinformatics tools to dissect multiple layers of arbitrary cytokine interactions into discernible interfaces and connectivity maps to predict movements in the cytokine network. The key principles presented here have important implications in our understanding of cytokine interactions and development of effective cytokine-targeted therapies for autoimmune disorders.

Cytokine interactions and drug discovery in autoimmune disease

There are hundreds of inflammation-related cytokines described to date, and additional cytokines are continually being identified. Cytokines are produced by diverse sources of immune and nonimmune cells and form a highly complex network or 'cytokine universe' that is essential for immune system homeostasis [1]. Under physiological conditions, inflammation occurs as a self-limiting process, and homeostasis is restored through a delicate interplay between immune cells and their cytokine milieu composed of a dynamic mix of cytokines in tissue environment and between functionally opposing cytokines [2]. When immune tolerance is broken in autoimmune pathologies, the equilibrium of the cytokine milieu is lost in disease target tissues, shifting the local environment towards a proinflammatory state and resulting in tissue damage [3,4]. Targeting cytokines and their receptors with monoclonal antibodies has become a mainstream therapeutic approach for autoimmune disorders, which has shown some initial promise (Table 1) [5,6]. However, the development of effective cytokine-targeted therapies has been hampered by limited knowledge and an oversimplification as to how individual cytokines work in the network in autoimmune disease [7]. First, although genetic association studies have increased our knowledge of disease susceptibility [8–10], it remains unknown how self-limiting inflammatory processes *in situ* transition to autoimmune pathologies and which cytokines are responsible for this aberrant process. Second, it is not fully understood how different cytokines act in concert in highly complex networks to form a cytokine milieu that varies depending upon the nature of the disease or the involvement of the target organ. Consequently, it has been difficult to pinpoint which cytokine should be targeted for a given autoimmune condition. Often we have to rely on data from autoimmune animal models that sometimes do not exactly translate into human pathological situations. A deeper understanding of how cytokines interact and operate in the context of human disease is required to predict clinical efficacy and safety profile reasonably. Here, we discuss the principles that can guide us in calibrating and predicting the role and behavior of individual cytokines within the network through its interfaces and connectivity.

The universe of cytokines in Taoism

Taoism is the centerpiece of Chinese philosophy and has been practiced for more than 2000 years. It describes the basic principles of the universe and the patterns of change that exist within the natural world. Tao has two central modalities, that is, 'origin' and 'effect'. The origin modality is the originator of the universe and the effect modality uses the principle of *Yin* and *Yang* to drive interfaces and guide all movements in the universe [11]. Cytokines interact and move without form (not often calibratable) in their own universe to dictate the fate of inflammation. Their pattern of movements and interactions follow the principle of Taoism (Box 1), which allows us to convert them into critical interfaces and measurable connectivity maps.

In line with the principles of Taoism, infiltrating immune cells located at the site of inflammation constitute the origin of the cytokine universe. As illustrated in Figure 1, the origin comprises diverse populations of both proinflammatory cells (*Yang*) such as T helper (T_H)1/T_H17 cells and M1 macrophages, and anti-inflammatory cells (*Yin*) such as T regulatory (T_{reg}) or Tr1 cells and M2 macrophages. Aberrantly activated or hyperactive autoreactive T cells, for example, of the T_H1 and T_H17 phenotypes, can be considered the origin in many T cell-mediated autoimmune diseases, including multiple sclerosis (MS) [12], psoriasis [13], rheumatoid arthritis (RA) [14], and type 1 diabetes [15]. Data suggest that the abnormal functional state of autoreactive T cells is attributable to a combination of genetic susceptibility and environmental factors that vary between different autoimmune pathologies [16,17]. There are three crucial interfaces operating in

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 1471-4906/$ – see front matter http://dx.doi.org/10.1016/j.it.2012.10.003 Trends in Immunology, March 2013, Vol. 34, No. 3

Table 1. Current cytokine-targeted therapy for autoimmune diseases.

Target	Drug	Mechanism of action	MS	RA	PS	CD	UV	UN
IL-1	Anakinra	Recombinant IL-1R antagonist		+				
	Canakinumab	IL-1β antibody		II				
	XOMA052	IL-1β antibody		II				
	Rilonacept	Dimeric fusion IL-1 Trap		I				
IL-2	Daclizumab	IL-2 receptor α chain antibody	II		I/II		II	
IL-6	Tocilizumab	IL-6 receptor antibody		+		+		
	REGN88	Humanized IL-6 receptor antibody		I				
	CNTO136	Humanized IL-6 antibody		II				
	ALD518	Humanized IL-6 antibody		II				
	C326	Avimer therapeutic protein				I		
	CDP6038	IL-6 antibody						I
IL-7	GSK2618960	IL-7 receptor α chain antibody						Pre
	Pfizer 28G9	IL-7 receptor α chain antibody						Pre
IL-8	ABX-IL-8	Anti-IL-8 antibody		–	–			
IL-10	Ilodecakin/Tenovil	Recombinant protein		–	–	–		
IL-11	Oprelvekin/Neumega	Recombinant protein		II	II	III		
IL-12 IL-23	Ustekinumab	Humanized antibody targeting p40 common subunit	–		+	II	II	
	ABT874	Humanized p40 antibody	II		III	II		
	Apilimod	Oral small molecule inhibitor of IL-12/IL-23 production		II		II		
IL-15	HuMax-IL-15/AMG-714	Humanized anti-IL-15 antibody		II				
IL-17	Secukinumab/AIN457	Humanized anti-IL-17 antibody		II	II	II	III	
	Ixekizumab/LY2439821	Humanized anti-IL-17 antibody		II				
	AMG827	Humanized IL-17R antibody		II	II			
IL-18	IL-18 binding protein	Recombinant protein		II	II			
IL-21	ATR-107	Humanized IL-21R antibody				I		dcd
IL-22	Fezakinumab	Humanized anti-IL-22 antibody		II	I			
IL-23	Anti-p19,	Anti-p19 subunit antibody						I
	LY2525623	Anti-p19 subunit antibody						I
GM-CSF	Sargramostim	Recombinant protein				III		
TNF-α	Infliximab	Chimeric TNFα antibody		+	+	+	I	UC, +
	Adalimumab (Humira)	Humanized TNFα antibody	–	+	+	+	III	
	Etanercept (Enbrel)	TNF receptor p75 fusion protein		+	+			
	Lenercept	TNF receptor p55 fusion protein	–					
	Certolizumab	PEGylated, humanized TNFα Fab		+	+			
	Golimumab	Humanized TNFα antibody		+				
	ART621	TNFα domain antibody		II	II			
	Ozoralizumab	TNFα nanobody		II				dcd
IFN-γ	Fontolizumab	Humanized anti-IFN-γ antibody		-		I/II		
	AMG811	Humanized anti-IFN-γ antibody						I
		Recombinant protein	–					
IFN-β	IFN-β-1a	Recombinant protein	+					
	IFN-β-1b	Recombinant protein	+				II	

+, approved; –,failed; I, Phase I; II, Phase II; III, Phase III; CD, Crohn's disease; dcd, discontinued; MS, multiple sclerosis; Pre, preclinical; PS, psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis; UN, unspecified autoimmune disorders; UV, uveitis.

the cytokine network that can be considered as the effect of aberrant T cell function. The first interface involves tissue-infiltrating T cells (e.g., T_H1, T_H17, and T_{reg} cells) and the cytokine milieu that surrounds them [18]. At this interface, the interaction between inflammatory T cells and cytokines leads to dynamic changes in activation, differentiation, and survival of infiltrating inflammatory cells at different stages of disease. The second interface dictates how polarizing cytokines (i.e., proinflammatory and anti-inflammatory) interact to achieve equilibrium in the network. The third interface involves the hierarchical relationship of 'driver' and 'follower' cytokines in their own network of connectivity.

Inflammatory T cells as the origin of the cytokine universe

The origin (i.e., inflammatory T cells for the purpose of discussion) is particularly relevant to the pathogenesis of autoimmune disease, which links to disease susceptibilities and is unique to distinct disease entities. However, the origin may in itself be an effect, which could in part explain the variability between autoimmune disorders resulting from different intrinsic or extrinsic factors. Disease susceptibility is influenced by genetic predisposition and aberrant expression of critical genes in activated immune cells, which is exacerbated by environmental factors. These disease susceptibility genes often encode cytokines and

Box 1. Roles and complexity of the cytokine milieu in autoimmune disease

- Cytokine milieu is highly diverse and produced by mixed and dynamic populations of inflammatory cells (the origin as in Taoism) in target tissue in autoimmune disease.
- The composition of cytokine milieu is closely associated with autoimmune disease susceptibility and varies among different disease entities. Together with inflammatory cells, it ultimately drives the tissue pathology and disease phenotype.
- How each individual cytokine behaves in cytokine milieu is dictated by the critical interfaces as discussed within this review. The principles governing the cytokine movements and interfaces in the network help dissect the complexity.
- Disease-associated cytokine milieu can be altered therapeutically by targeting single or multiple key cytokines to offer an effective treatment for autoimmune disease. Critical considerations are discussed within this review.

their receptors, transcription factors, and proteins involved in apoptosis-related pathways that control T cell activation, differentiation, and survival, thus rendering inflammatory T cells to sustain chronic inflammation in target tissue [10]. For example, in a recent genome-wide association study (GWAS) involving 9772 MS patients and 17 376 matched healthy individuals, polymorphisms in the JAK-STAT pathway genes, known to drive T_H1 and T_H17 differentiation and function, were found to be associated with an increased risk of MS [9] and other autoimmune conditions [8]. Autoimmune disease susceptibility is also reflected in prolonged survival of tissue-infiltrating inflammatory T cells through an altered apoptotic process. In many autoimmune pathologies, the balance of pro- and antiapoptotic processes in inflammatory cells, a mechanism contributing to the self-limiting nature of inflammation, is lost as a result of an altered apoptosis-related gene profile associated with disease susceptibility [19–21].

Disease susceptibility in autoimmune conditions is not only linked to the functional state of inflammatory T cells but also influences the functional properties of regulatory T cells that keep inflammatory T cells in check [22,23]. Increasing evidence suggests that functional defects in T_{reg} cells are a major hallmark of many autoimmune conditions [24]. T_{reg} cells are a heterogeneous population comprising forkhead box (Fox)p3$^+$ naturally occurring (nT_{reg}) and inducible T_{reg} (iT_{reg}) cells [25], interleukin 10 (IL-10)-producing Tr1 cells, transforming growth factor (TGF)β-producing Tr3 cells, and other minor subsets with a suppressive function such as CD4$^-$CD8$^-$ T cells and γδ T cells [26]. These regulatory T cells control the functioning of effector T cells, such as T_H1 and T_H17 cells [27]. Conversely, proinflammatory cytokines such as tumor necrosis factor (TNF)α, IL-6, IL-12, IL-7, IL-15, and IL-21 have been shown to compromise the function of T_{reg} cells [28–31]. For example, TNFα inhibits the function of human T_{reg} cells by altering Foxp3 transcription and expression [28] and acts together with IL-6 to render effector T cells resistant to suppression by T_{reg} cells [32]. Furthermore, cytokines, such as IL-15, can induce resistance of effector T cells to T_{reg} cells by activating phosphatidylinositol 3-kinase (PI3K) signaling [30]. Therefore, failure to maintain suppressive function by T_{reg} cells contributes, at least in part, to persistent inflammation.

Our immune system has evolved to produce, as well as regulate, a variety of functionally diverse cytokines to maintain homeostasis. However, in autoimmune pathologies, disease susceptibility fundamentally alters how inflammatory cells are predisposed to react to an initial trigger (e.g., environmental insult), which leads to altered activation, differentiation, and prolonged survival of inflammatory cells *in situ*. As a consequence, inflammatory T cells inherently carrying disease susceptibility act as the origin that creates an aberrant cytokine milieu in target tissue.

Interface between proinflammatory T cells and their cytokine milieu

This interface involves the bidirectional interaction between inflammatory T cells (the origin) creating the cytokine milieu, which in turn influences the functional state of inflammatory T cells, sustaining a feedback mechanism (Figure 1). What is the feedback mechanism operating at this interface and what are the transcription factors and cytokines involved? In MS, the inflammatory processes seem to be driven largely by T_H17 and T_H1 cells [33,34]. Aberrant expression and function of JAK/STAT pathway genes is likely to lead to persistent differentiation and prolonged survival of pathogenic T cells through the production of a cytokine milieu enriched for IL-6, IL-2, IL-12, IL-7, and their receptors, which constitutes a feedback loop to sustain chronic inflammation [35–37]. It is noteworthy that such a proinflammatory cytokine milieu is detrimental to differentiation and function of T_{reg} cells, which seemingly affects the interplay between inflammatory T cells and T_{reg} cells as described above.

This bidirectional feedback mechanism of the cytokine milieu goes beyond sustaining activation, differentiation, and prolonged survival of functionally specialized T cell subsets of particular phenotypes. It can also cause T cell subsets to switch across functionally opposing phenotypes [38]. This notion is reinforced by several recent observations. For example, TGFβ can trigger CD4$^+$ T cells to differentiate into a T_H17/T_{reg} intermediate phenotype that expresses both RAR-related orphan receptor gamma (RORγ) and Foxp3 [39]. A changing cytokine milieu enriched for IL-6 and IL-1β renders differentiated Foxp3$^+$ T_{reg} cells to become IL-17-producing T cells [39,40]. Another example relates to interferon (IFN)-γ$^+$/IL-17$^+$ double-positive cells that are readily detected in central nervous system (CNS) lesions of postmortem tissue taken from MS patients and experimental autoimmune encephalitis (EAE), a commonly used animal model for MS. The model is routinely induced by immunization with myelin autoantigens, such as myelin basic protein, proteolipid protein and myelin oligodendrocyte glycoprotein, in complete Freund's adjuvant [41,42]. These cells express both RORγ and T-bet transcription factors and can polarize into T_H1 or T_H17 cells, depending upon the given cytokine milieu [41]. Thus, T cell subsets characterized as either anti-inflammatory or proinflammatory can actually display remarkable plasticity that is influenced by the cytokine milieu. Similarly, a proinflammatory cytokine milieu enriched for cytokines, such as granulocyte–monocyte colony stimulating factor (GM-CSF), drives initially

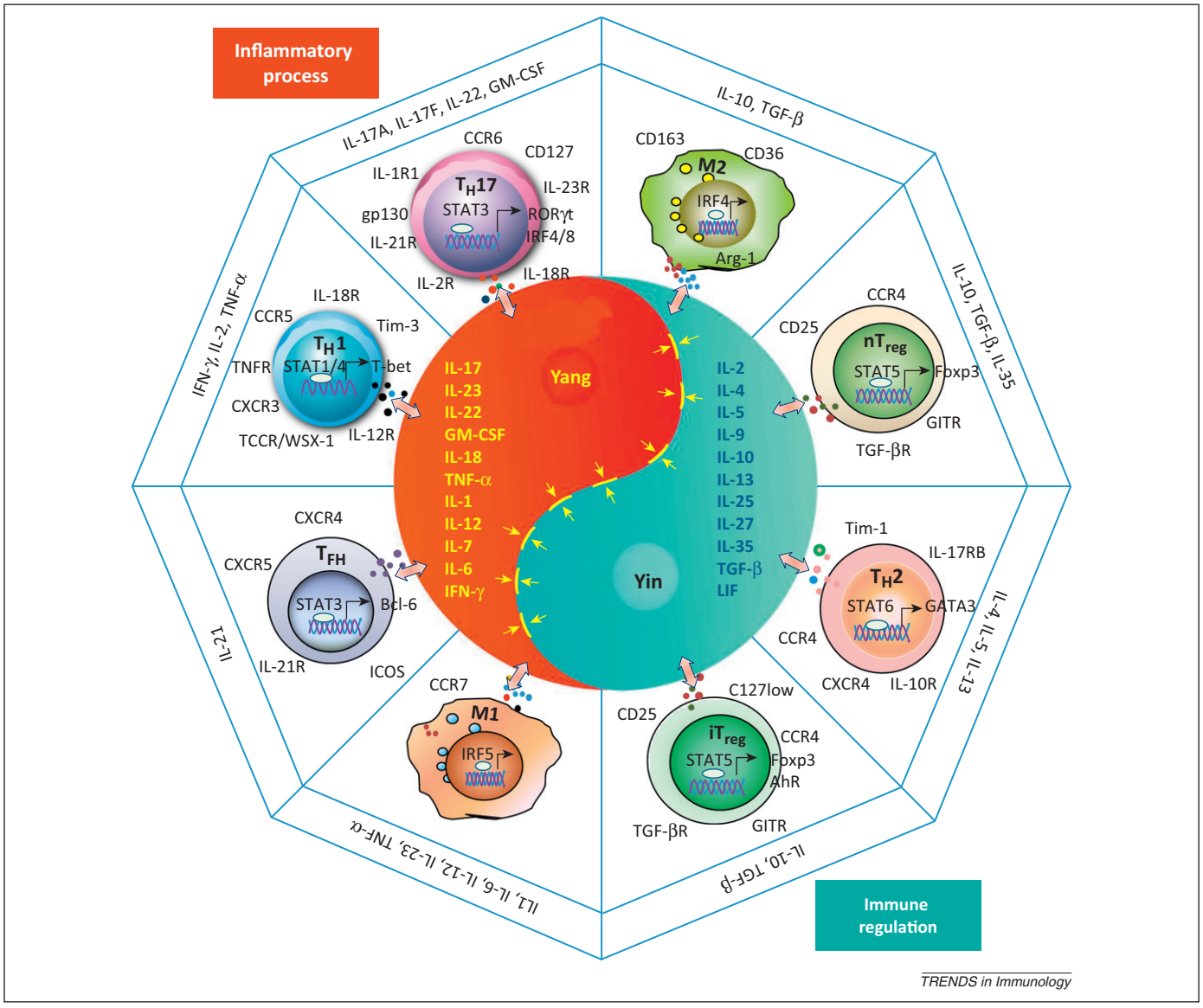

Figure 1. Interaction between inflammatory cells and cytokine milieu in Taoism. Interfaces and interactions between immune cells and their cytokine milieu are best illustrated in Taoism (Tai-chi – the 'Great Ultimate'). Diverse lineages of pro- and anti-inflammatory cells, referred to here as the origin, when activated, produce and constitute a cytokine milieu comprising anti-inflammatory (*Yin*) or proinflammatory *(Yang*) cytokines. The actions of the cytokines in relation to tissue inflammation are dictated by critical interfaces, that is, between the origin and cytokine milieu and between cytokines of opposing properties. When an inflammatory process (*Yang*) is initiated through activation and differentiation of infiltrating proinflammatory T cells, such as T helper (T_H)1 and T_H17 cells, proinflammatory cytokines (some are indicated) are produced to form a milieu that drives tissue inflammation. This cytokine milieu is dynamic and in turn drives further differentiation and prolonged survival of inflammatory cells *in situ*, forming a unique feedback mechanism to sustain chronic inflammation. In parallel, regulatory mechanisms (*Yin*) exemplified by regulatory T cells and anti-inflammatory cytokines (also indicated) are activated to keep tissue inflammation in check. In autoimmune pathologies, as tissue inflammation intensifies, the area of *Yang* expands whereas the opposite (*Yin*) is compressed, shifting the process towards persistent inflammation at the target tissue.

diverse infiltrating macrophages to polarize towards a highly proinflammatory M1 macrophage subset, termed M1 [43]. When combined with disease susceptibility associated with nuclear factor (NF)κB pathway genes implicated in multiple autoimmune pathologies [9], the ratio of M1 to M2 macrophages is markedly altered in target tissue [44]. M1 macrophage polarization and accumulation in target tissue is a dominant hallmark for many autoimmune diseases, such as MS, RA [44], and diseases of a nonautoimmune origin, such as arthrosclerosis [45] and amyotrophic lateral sclerosis (ALS) [46].

Interface and movements between opposing cytokines

Zhang Zai (1020–1077 AD), a Chinese philosopher of Taoism, said, 'Material force moves and flows in all directions and in all manners. Its two elements (*Yin* and *Yang*) interact and unite to establish *he* (harmony), so it gives rise to the concrete. Thus, the multiplicity of things is produced. In their ceaseless successions, the two elements of *Yin* and *Yang* constitute the great principles of the universe' [47]. Proinflammatory cytokines, including IL-1, IL-2, and IL-6, promote differentiation and influence the function of inflammatory cells, whereas anti-inflammatory cytokines, such as TGFβ, IL-10, IL-13, IL-15, and leukemia inhibitory factor (LIF), produce opposing effects. Although there is a wealth of knowledge as to how individual cytokines function, we know very little about how multiple cytokines of mixed properties act in concert in a complex network. Elegant preclinical and clinical reports have revealed that an individual cytokine of known properties

can act in an opposite or paradoxical manner depending on within which network it is operating. This is not surprising because there are mixed forces influencing the behavior of an individual cytokine within a network. For example, IL-12 is considered to be a crucial initiator of proinflammatory T_H1 cell differentiation in multiple disease settings. However, analysis of EAE models has demonstrated that IL-12 is dispensable for CNS inflammation because IL-12p35- or IL-12Rβ2-deficient mice, rather than being resistant, are actually more susceptible to developing EAE [48].

The proinflammatory cytokine IFN-γ also has a diverse and paradoxical role in autoimmune disease. Once inflammation is initiated, IFN-γ is produced and acts through various signaling pathways to intensify the inflammatory process. There is an extensive body of literature documenting the proinflammatory nature of IFN-γ, which has led to the mainstream opinion that IFN-γ is a prime proinflammatory cytokine in inflammation and autoimmune disease [49]. However, emerging evidence indicates that our current thinking does not accurately reflect the complex properties of IFN-γ when it functions within a cytokine network. Early indications of the paradoxical roles of IFN-γ were demonstrated either by administration or by blocking of IFN-γ in models of autoimmune disease or by attempts to induce autoimmune inflammation in *Ifng*-knockout mice [50]. For example, there was increased susceptibility and severity of EAE in mice genetically deficient in IFN-γ or the IFN-γ receptor [51,52]. Furthermore, knockout of the gene encoding IFN-γ renders mouse strains genetically less susceptible to exhibit full-blown disease and is accompanied by markedly increased T cell responses and high titers of specific antibodies [53]. However, these contradictions have not been satisfactorily explained and were often considered exceptions to the role of IFN-γ as a T_H1 cytokine. The paradoxical actions of IFN-γ appear to follow the principle of *Yin* and *Yang*, as do many of the paradoxes of nature. When inflammation culminates, high levels of IFN-γ induce a negative feedback response to the inflammatory process by activating regulatory mechanisms. The underlying process that allows a single cytokine to act in opposing roles during inflammation is unclear.

Interface between driver and follower cytokines in network connectivity

In addition to the two interfaces discussed above, cytokine interactions through network connectivity provide a third level of interface. The connectivity is not random and involves a hierarchical relation of cytokines in terms of their roles within the network. Some can be viewed as driver cytokines (e.g., IL-2, IFN-γ, and IL-6) because they are positioned at crucial nodal points in the network to drive initial differentiation and survival of inflammatory cells, whereas others are followers (e.g., IL-22) that amplify the magnitude of the response induced by driver cytokines (Figure 2). In some cases, the role of a follower cytokine may be redundant and can be readily compensated for. Here, we used multiple bioinformatics tools to provide a 2D connectivity map illustrating the network relations of 31 cytokines most commonly involved in T_H1, T_H17, and T_{reg} cell differentiation and survival, as well as their relations with key transcription factors. The relation between IL-6 and IL-22 is that of driver–follower, owing to their distinct roles in T_H17 differentiation, as demonstrated in EAE studies using the respective gene knockout mice [54]. It is reasonable to predict that targeting driver cytokines, such as IL-6 for T_H17 cell differentiation, would produce better clinical efficacy in an autoimmune disease in which T_H17 cells are critically involved in the disease process. By the same token, blocking follower cytokines involved in the T_H17 differentiation process, such as IL-22, may not achieve equivalent clinical efficacy. Although the concept of driver and follower cytokines applies to many inflammatory and autoimmune diseases situation, the level of this hierarchical relation may vary in different autoimmune diseases or target organs.

Considerations for designing effective therapy for autoimmune disease

In this review, we have discussed the principles of the origin and the three critical interfaces that dictate how cytokines behave in a network. How do we apply these principles to design effective cytokine-targeted therapy for autoimmune disease? The origin concept is a consideration that directly applies to selecting the right cytokines as drug targets for the treatment of different human autoimmune diseases according to specific disease susceptibility. The origin concept is difficult to validate in animal models of autoimmune disease that are artificially induced with eliciting autoantigens and whose genetic background cannot replicate the complexity of human disease susceptibility. Genetic modification to introduce 'fit-for-disease susceptibility' offers some value, provided that there is a true rodent homolog for the human risk gene of interest. First, one obvious therapeutic approach is to correct the origin by suppressing or depleting inflammatory cells or their subsets carrying disease susceptibility traits [55,56]. These approaches have not been very successful because they are associated with severe side effects owing to poor selectivity. Therefore, generalized immunosuppression is no longer the preferred treatment option for autoimmune diseases, and earlier attempts to suppress or deplete $CD3^+$ or $CD4^+$ T cells have not been productive due to lack of efficacy and poor safety profile [57,58]. However, there are a few exceptions in which more general immunosuppressive agents have demonstrated clinical efficacy and an acceptable safety profile, (e.g., alemtuzumab, a CD52-depleting antibody, and bone marrow transplantation with either autologous or allogenic hematopoietic stem cells that have been registered for the treatment of MS [59,60]). Lessons from these clinical studies indicate that transient or intermittent eradication of major immune cell lineages enables the system not only to reduce output of inflammatory cells but also to 'reset' and 'correct' itself [61]. One of the caveats is that the reconstituted immune system seems to carry the same T cell repertoire and that the disease susceptibility traits do not change with renewed immune cells [62]. Other therapeutic strategies aiming to modulate the origin appear to be more successful. As an example, glatiramer acetate (Copaxone), a random polymer of four amino acids for the treatment of MS, appears to act through shifting macrophages from a proinflammatory

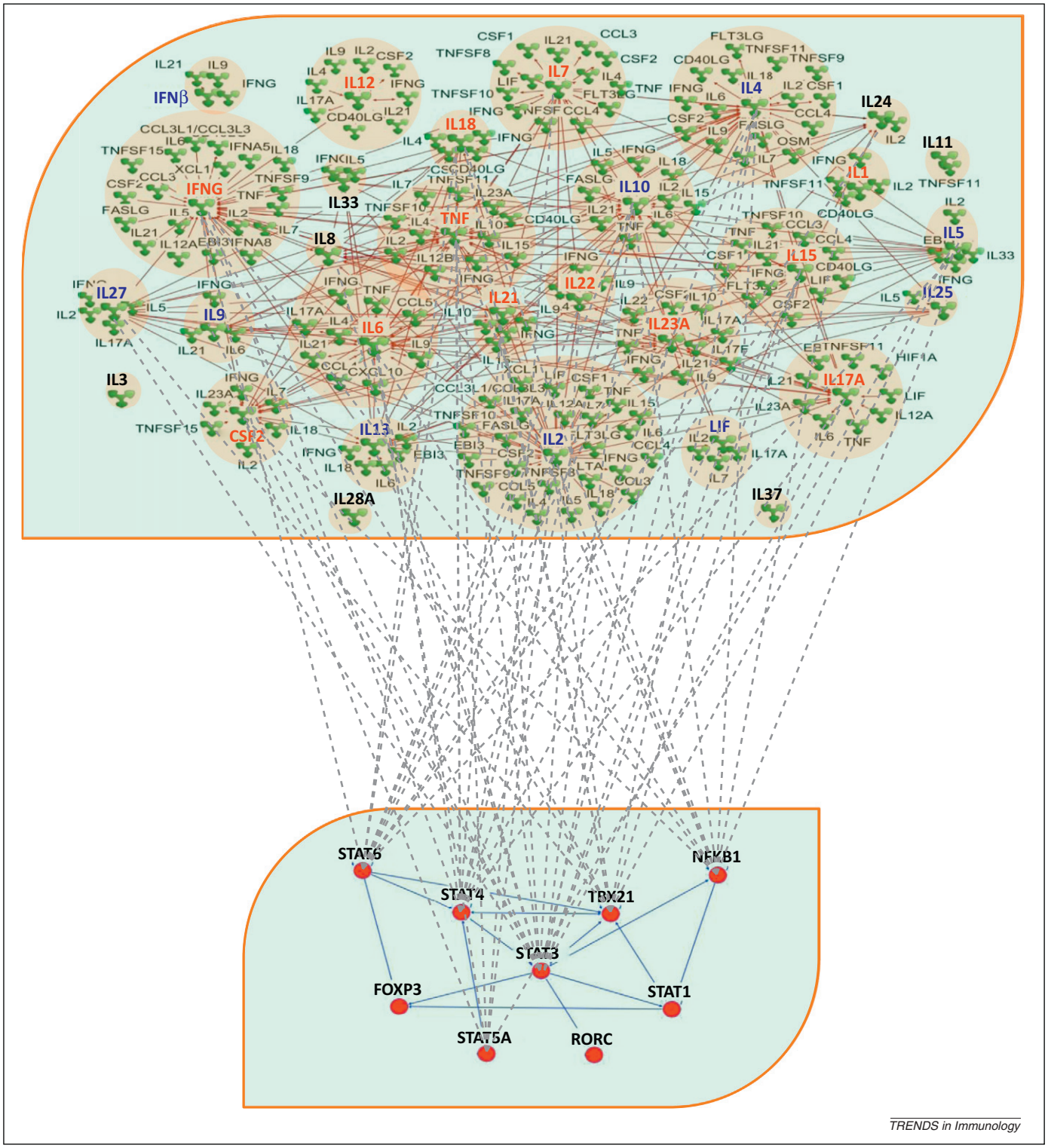

Figure 2. Interface involving hierarchical relations of cytokines in a connectivity map. Thirty-one cytokines and nine transcriptional factors involved in T helper (T_H)1 and T_H17 differentiation are applied as seed genes to create this connectivity map. Individual cytokines are first connected to neighboring cytokines through a first-degree connection that includes direct physical or indirect nonphysical contacts. All seed genes are connected to complete this connectivity map. Ingenuity pathway analysis (IPA) is applied to create and visualize the network (http://www.ingenuity.com). The upper plate represents the connectivity map of the cytokines through solid lines, which connects through dotted lines to the transcription factors in the lower plate. The size of the round shaded area represents arbitrarily the volume of connectivity for each cytokine analyzed.

M1 phenotype towards a 'protective' M2 phenotype [63] and modulating T cell responses by reducing T_H1 and T_H17 cells, as well as promoting T_{reg} cells [64,65].

Second, in some cases, drug targets for cytokine therapy may be derived from genes implicated in disease susceptibility. The connection, however, is not as straightforward as it appears, because these disease susceptibility genes are not directly associated with cytokines or their receptor genes. These genes encode proteins that reside in key signaling pathways that render proinflammatory cells to produce certain driver cytokines in the cytokine milieu to perpetuate an ongoing inflammatory process. Therefore,

targeting cytokines along pathways implicated by specific disease susceptibility would be of therapeutic relevance. A recent example is anti-IL-17 antibody therapy in psoriasis, which has demonstrated efficacy in Phase II clinical trials [66]. IL-17 is implicated in the pathogenesis of psoriasis by the involvement of *IL23R* and *IL23A* genes [8] and the presence of infiltrating IL-17-producing γδT cells in psoriatic lesions [67]. In other cases, identification of disease susceptibility genes may directly point to the aberrant role of cytokines in the disease. The gene encoding IL-7 receptor α chain was recently identified as the first non-human leukocyte antigen (HLA) MS susceptibility gene in a GWAS study [68]. In a separate study, IL-7 signaling was discovered to be required by differentiated T_H17 cells and, to a lesser degree, T_H1 cells for survival and expansion in EAE [35]. The findings are indicative of the role of IL-7 and its receptor in driving a tissue cytokine milieu that prolongs survival and persistent expansion of T_H17 and T_H1 cells in MS lesions. The data provide a strong rationale for developing an antagonist of IL-7/IL-7 receptor for the treatment of MS.

Third, the principles of the cytokine interfaces presented here can be directly applied to predict potential effects of targeting an individual cytokine in its own network for autoimmune disease. One consideration is that, although several human T cell-mediated autoimmune pathologies share mechanisms involving T_H1 and T_H17 cells [69], they are seemingly associated with distinct cytokines. Thus, targeting one particular cytokine may be effective for a given autoimmune condition but may have little efficacy for another autoimmune disease considered in the same disease category. For example, TNFα blockers are effective treatments for RA but showed no efficacy in MS [70], whereas IFN-β, a first-line treatment for MS, is not effective for RA [5]. Is there an opportunity to develop a more universal cytokine-targeted therapy for autoimmune diseases? The answer may lie in identifying a common pathway shared by multiple diseases or down-stream cytokines acting as common effectors in multiple autoimmune pathologies. As indicated in Figure 3, some of the non-HLA susceptibility genes identified in MS GWAS overlap with those implicated in RA, psoriasis, Crohn's disease, and ulcerative colitis [8,9], which suggests some degree of shared susceptibility for autoimmune pathogenesis. Thus, it is not unlikely that a cytokine-targeted therapy may be more universal for a cluster of autoimmune conditions in which disease susceptibility converges onto shared pathways.

Another consideration is how to apply the driver and follower concept of cytokine behavior and how to calibrate the effects of each participant. In this regard, although it is tempting to target driver cytokines for the purpose of achieving optimal clinical efficacy, we must consider that better efficacy often comes at a cost. Manipulation of a driver that is high up in the cytokine hierarchy will mediate broader effects with a greater magnitude, which may

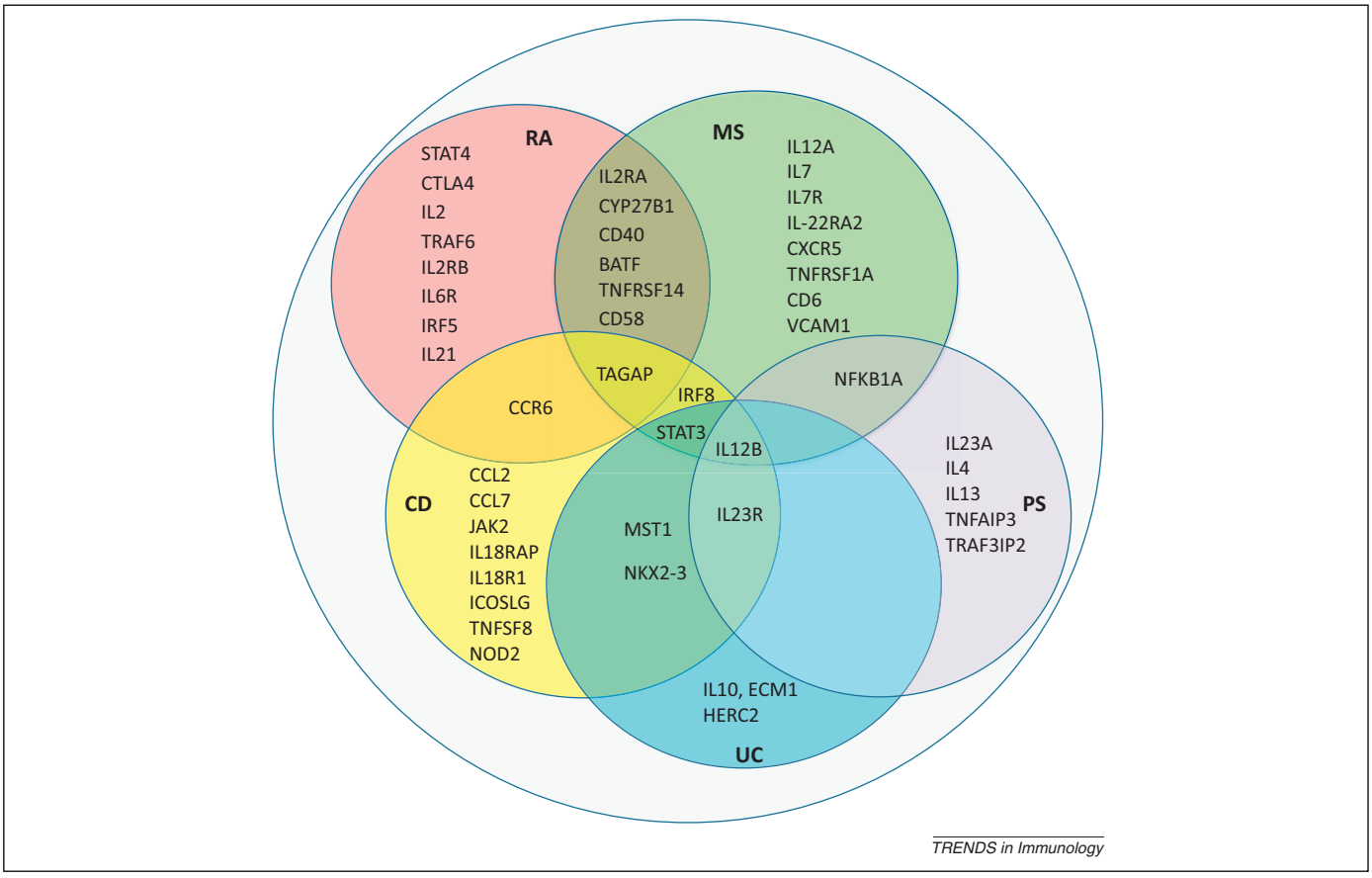

Figure 3. Distribution pattern of disease susceptibility genes among selected T cell-mediated autoimmune diseases. Disease susceptibility genes identified in genome-wide association studies (GWASs) involving patients with T cell-mediated autoimmune diseases, including multiple sclerosis (MS), rheumatoid arthritis (RA), psoriasis (PS), and Crohn's disease (CD) are grouped together in a Venn diagram to illustrate overlapping susceptibility genes among different disease entities.

lead to mechanism-based immune system suppression resulting in deleterious side effects. Natalizumab (targeting α4 integrin) effectively blocks influx of inflammatory cells into the CNS and has demonstrated superior clinical efficacy to all the approved medicines for the treatment of MS. However, in a subset of individuals, the very mechanism and magnitude of this particular antibody treatment can lead to a devastating life-threatening condition known as progressive multifocal leukoencephalopathy (PML) in which the oligodendrocytes, instead of being destroyed by inflammatory cells, are killed by the John Cunningham (JC) virus that has become activated due to failed CNS immunosurveillance [71]. There are other examples of cytokine-targeted therapy, such as ustekinumab (blocking IL-12 and IL-23 for psoriasis) and tocilizumab (blocking IL-6 receptor for RA), that carry significant risks of infections, malignancies and reversible posterior leukoencephalopathy [5]. Thus, we must maintain a sophisticated balancing act to achieve desired clinical efficacy while avoiding significant immune system suppression by targeting driver cytokines. Therefore, it may be desirable to target driver cytokines crucially required within the tissue cytokine milieu to sustain chronic inflammation rather than initiate inflammation. This notion can be exemplified in a scenario to target T_H17 cells for MS therapy. That is, targeting IL-7 and its receptor may be advantageous over targeting IL-6 signaling because the former achieves T_H17 inhibition through its selective effect on prolonged survival of differentiated T_H17 cells. This would block a persistent T_H17 response but not the initiation or differentiation of T_H17 cells, which would affect a normal immune response. As more clinical trials conclude within the next 5 years, we will enter an exciting era when the principles discussed in this review can be validated to guide us in designing more effective cytokine-targeted therapy for autoimmune disease.

Concluding remarks

An aberrant cytokine milieu is a prerequisite for chronic tissue inflammation in autoimmune disease. Cytokines work through interactions within a network; therefore, it is important to understand the pattern of change and movements in the cytokine milieu through discernible interfaces for the purpose of therapeutic intervention. The principles derived from critical interfaces and the cytokine connectivity map, as presented here, offer a unique guide for our understanding of potential consequences or network effects when a given cytokine is selected as a therapeutic target for the treatment of autoimmune disease.

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