Nature Reviews Rheumatology | Published online 10 Dec 2015; doi:10.1038/nrrheum.2015.171

PERSPECTIVES

OPINION

Cytokines in rheumatoid arthritis — shaping the immunological landscape

Iain B. McInnes, Christopher D. Buckley and John D. Isaacs

Abstract | Cytokine-mediated pathways are central to the pathogenesis of rheumatoid arthritis (RA). The purpose of this short Opinion article is to briefly overview the roles of cytokine families in the various phases and tissue compartments of this disease. In particular, we consider the combinatorial role played by cytokines in mediating the overlapping innate and adaptive immune responses associated with disease onset and persistence, and also those cytokine pathways that, in turn, drive the stromal response that is critical for tissue localization and associated articular damage. The success of cytokine inhibition in the clinic is also considerable, not only in offering remarkable therapeutic advances, but also in defining the hierarchical position of distinct cytokines in RA pathogenesis, especially IL-6 and TNF. This hierarchy, in turn, promises to lead to the description of meaningful clinical endotypes and the consequent possibility of therapeutic stratification in future.

Rheumatoid arthritis (RA) is associated primarily with articular inflammation, synovial joint damage and increasing disability over time. This disease is increasingly recognized to comprise a broader syndrome that includes, for example, increased cardiovascular morbidity, psychological impairment, risk of cancer and osteoporosis[1]. The past decade has seen the advent of novel therapeutics in the form of both biologic agents and small-molecules. At least as important as these unparalleled advances in drug development has been the introduction of strategic management approaches that have made remission or low disease activity the target of treatment. However, remission rates, particularly off-therapy, remain low, and long-term cure, or re-establishment of immune homeostasis, is elusive for all but a minority. Furthermore, the cellular targets that should be used to best achieve remission, and the relative contribution of different cells types during the development of the disease, remain unclear.

Unravelling the pathogenesis of RA, therefore, remains an exciting and critical challenge to address unmet clinical need[2]. Genome-wide analysis studies (GWAS), together with epigenetic studies, clearly implicate the immune system as central to disease pathophysiology. Epidemiological studies as well as *ex vivo* model and synovial tissue studies are consistent with this thesis, as are the emerging mechanisms of disease-related co-morbidities. Furthermore, the composition of the human microbiome is similarly postulated to contribute to RA, operating at least in part via immune polarization and subsequent regulation that arises from the oral, gut and pulmonary mucosae[3]. Thus, an early breach of immune tolerance in the face of an as-yet poorly defined environmental challenge(s), leading to core immune dysregulation that integrates with altered tissue homeostasis, seems to underlie the disease.

This view of RA pathogenesis begs several questions. What are the most tractable immune parameters for therapeutic intervention or biomarker utility? At what stage should these interventions and biomarkers be applied to optimize outcomes? Should therapeutic interventions be tailored (personalized) for a given disease phase, or even a 'pre-disease' phase? Do discrete and therapeutically useful disease endotypes exist that will permit a more rational taxonomy based on underlying immune pathology?

Many clinical studies have crystallized and validated the pivotal contribution of cytokines in the pathogenesis of RA. A diverse range of circulating cytokines emerges shortly before the onset of articular disease and particularly during the transition from systemic to localized disease. Cytokines regulate cellular phenotype, localization, activation status and longevity in the synovial and lymphoid micro-environments[4]. The critical role of TNF and IL-6 therein has been unequivocally demonstrated by successful clinical targeting of these cytokines in RA using biologic therapies[5]. As such, there is now an imperative to define other cytokines that are of hierarchical importance, that drive the tissue components of RA, and that could provide additional therapeutic targets in refractory disease, where remission is difficult to achieve. For example, granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-17 are currently of particular interest. A new taxonomy for RA based on patterns of cytokine dominance could facilitate stratification of patients for therapy; this stratification should emerge from a systematic analysis of cytokine expression across disease phases (FIG. 1) in parallel with studies of appropriately targeted intervention.

In this Opinion article, we consider the contribution of cytokines across the 'pathologic compartments' of the RA immune response — namely innate, adaptive and stromal responses. In the past few years, evidence has emerged that these responses, though usefully considered in isolation, together represent a more holistic 'RA tissue response'. It is also now clear that cytokines serve to integrate the various compartments of the RA pathobiology (systemic and synovial) as well as phases of disease (early and established). The key contributing

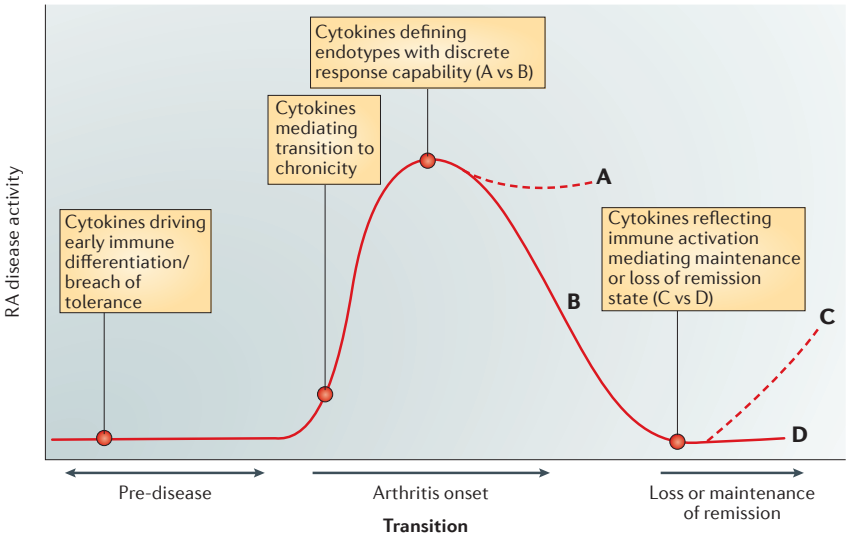

Figure 1 | **Cytokine profiles that subserve the biology of discrete phases of the rheumatoid arthritis disease process.** This figure depicts the notion that groups of cytokines (e.g. IL-6, IL-21, IL-23, IL-17) likely drive adaptive immune activation/differentiation and loss of tolerance in preclinical or early arthritis, whereas distinct profiles might dominate the transition to chronicity or the maintenance of established disease (e.g. TNF, IL-6), and perhaps phases of disease dominated by response to damage (e.g. cytokines released by activators of damage-sensing pathways). Such cytokine profiles could yield new biomarker profiles, or novel insights into the rational, 'pathogenesis stage-dependent' application of cytokine-targeting therapeutics. For example, cytokine signatures could separate those patients destined to fail (A) or respond to (B) a given intervention, and once in remission those patients destined to flare (C) or remain in a low disease activity state (D).

cytokines are reviewed in detail in a series of articles in this journal, covering TNF, IL-1, JAK-dependent cytokines (including IL-6), GM-CSF and chemokines, respectively[6–10]; herein, we aim only to provide an overview to these detailed discussions.

Cytokines of the 'innate response'

Infiltration of the synovial membrane and fluid space with leukocytes is characterized primarily by cells of the innate immune compartment. Thus, macrophages (probably including resident as well as infiltrating populations), mast cells, natural killer (NK) cells and neutrophils (usually trafficking to the synovial fluid) have long been identified as important components of the synovial infiltrate and their effector functions clearly link to disease manifestations. More recently, innate lymphoid cell lineages have been characterized that further extend the contribution of innate effector components to tissue destruction[11]. Synovitis is characterized by wide cellular expression of damage-associated molecular patterns and pathogen-associated molecular patterns that facilitate dysregulated activation of these various cell lineages, in the presence of chronic damage but without recourse to specific antigen[2]. Critically, the kinetics of immune function in RA tissues are unlikely to be 'synchronized' by an initiating event and, as such, the normal sequential regulatory homeostasis that is integral to classical innate immune responses in relation to antigen-triggered responses is unlikely to operate in the rheumatoid joint. From the pathological perspective, the net effect of this cellular profile is the generation of tissue-destructive enzymes, reactive oxygen and nitrogen intermediates, prostaglandins and leukotrienes, and a broad range of effector cytokines, outside their normal homeostatic 'on–off' regulatory cycle.

TNF and IL-6

The pivotal cytokines that regulate innate responses are now well-defined. The hierarchical importance of TNF and IL-6 is strongly supported by the accrual of clinical benefits upon their inhibition. The functional profile of TNF in particular is central to RA pathophysiology[12]. This cytokine primes for, or directly mediates, leukocyte activation, adhesion and migration, endothelial activation and angiogenesis, nociception, chemokine expression, stromal-cell activation, chondrocyte activation, and, with RANKL (receptor activator of NFκB ligand, also known as TNF ligand superfamily member 11), contributes to the activation and effector function of osteoclasts. The broader benefits of clinical therapeutics that specifically block TNF suggest that TNF also mediates other effects: in the central nervous system, altering cognition, depression and fatigue; in metabolism, via altered cholesterol homeostasis and insulin receptor resistance; and in the vasculature, where it can directly regulate endothelial dysfunction and repair. IL-6 mediates effects rather similar to those of TNF in the local synovial environment, with the added role of directly driving the acute-phase response[13]. IL-6 also seems to offer more extensive integration with lipid metabolism than does TNF. IL-6 and TNF differ in the capacity of the former to signal via *cis* and *trans* pathways, with the *trans* pathway facilitated by circulating soluble IL-6 receptor (IL-6R) and widespread expression of the co-receptor gp130. Results of clinical studies are consistent with the notion that there may be distinct inflammatory subgroups emerging that are elicited by these two pivotal cytokines[14]. In a head-to-head comparison of TNF inhibition and IL-6 receptor blockade, for example, discrete predictive serum immune profiles were detected by reciprocal expression of soluble intercellular adhesion molecule 1 and CXC-chemokine 13 (REF. 14).

IL-1, IFNs and GM-CSF

Numerous other cytokines associated with innate immune responses are detected in the RA synovium. Several members of the IL-1 family, including IL-1α, IL-1β, IL-1Ra, IL-18, IL-33 and IL-36, are present and functionally active, as are upstream regulatory factors such as IL-32 (REFS 2,4,15). Despite an encouraging effector biology profile, however, IL-1 inhibition has not been successful for RA in the clinic. This failure does not denote a lack of functional involvement of IL-1 in synovial processes, but rather a lack of a 'pivotal' regulatory role for this cytokine in the inflammatory cascade. Thus, many of the effector pathways that lead to symptoms are potentially mediated by IL-1, often in synergy with TNF, such as prostanoid synthesis and activation of chondrocytes and fibroblast-like synoviocytes (FLSs).

The type I interferons (IFNs) are similarly widely detected and functionally active in RA[16]. These cytokines mediate immune regulation via modulation of many leukocyte subsets, and thereby achieve effective viral defence, which, in a

chronically inflamed tissue lesion, could equally drive tissue deficit. However, a substantial proportion of the effects of type I IFN are anti-inflammatory, leading to trials of IFNs as therapeutic agents in RA (which were ultimately unsuccessful[17]). Numerous transcriptional profiling studies in RA synovia and peripheral blood leukocytes clearly indicate that type I IFNs are biologically active; that such interferon response elements (IREs) offer prognostic utility for some biologic therapies further supports their functional importance.

Finally, focus on the GM-CSF pathway is increasing. GM-CSF mediates plausible effector function via activation of macrophages, neutrophils and dendritic cells, driving the differentiation of these cells to an inflammatory phenotype and promoting downstream cytokine release, prostanoid synthesis and enhanced cellular activation[18]. GM-CSF administration to correct neutropenia in patients with RA promotes disease flare. Most persuasively, the administration of mavrilimumab, an inhibitor of GM-CSF receptor-α, in phase II RA trials suggests GM-CSF antagonism has efficacy similar to that of TNF blockade, clearly indicating a regulatory role for this pathway in the synovial response[19].

Cytokines of the 'adaptive response'

As discussed in this section, 'adaptive' cytokines regulate a rich panoply of interactions, not only between innate and adaptive immune responses, but also between different adaptive responses, and even autocrine positive-feedback loops. Furthermore, a number of novel paradigms are emerging, such as antigen-independent adaptive immune pathology, cytokine families with both proinflammatory and regulatory members, and a role for cytokines in the 'licensing' of cell function rather than simply as strict differentiation factors.

IL-17

The dominant interest in adaptive biology in RA has lately been defining the role of the type 17 T helper (T_H17)-cell axis. The archetypal proinflammatory T-cell cytokine, IL-17A, has multiple overlapping functions with both TNF and IL-6 (REFS 20,21). IL-17A promotes the release of additional proinflammatory cytokines (including TNF, IL-6, IL-1 and GM-CSF), chemokines (CXC-chemokine 8 and CC-chemokines 2 and 3) and matrix metalloproteinases, as well as facilitating osteoclast activation and angiogenesis. In synergy with other growth factors, IL-17A is an important antiapoptotic, or survival, factor for FLSs, as well as for B cells and T cells, which support germinal centre formation. Thus, while IL-17A levels correlate with disease activity and tissue damage in RA, redundancy and pleiotropism could explain the somewhat disappointing efficacy of IL-17 blockade in this condition compared with other inflammatory immune diseases such as psoriasis. Alternative explanations include specific IL-17-dependent disease endotypes (the presence of which would permit therapeutic stratification), a more dominant role for IL-17 in epithelial tissues such as the skin, or more-complex interdependencies. For example, some studies suggest reciprocity between TNF and IL-17, such that TNF blockade might lead to increased IL-17 levels or, tantalizingly, that lack of response to TNF blockade is underpinned by IL-17 pathobiology[21,22]. Similarly, a key cytokine for IL-17 generation is IL-6, whereas IL-17 provokes IL-6 production by FLSs, thereby creating a vicious proinflammatory circle. Therapeutically, cautious use of combinations of cytokine blockade might therefore be necessary to broach the 'therapeutic ceiling' seen with current biologic therapies.

IL-6

Despite being a key innate cytokine, IL-6 has an essential immunoregulatory role in adaptive immunity, acting at a checkpoint in the differentiation of naive T cells towards proinflammatory T_H17 cell or regulatory T (T_{REG}) cell pathways with a probable role in early disease and in driving cardiovascular comorbidities[13,23]. Although GWAS provide few clues of IL-6 dysfunction, at least in seropositive RA, the potential for a strong IL-6 dependent contribution is vast, as suggested by the 'IL-6 amplifier' pathway[24]. This pathway introduces an important concept, namely that adaptive immunity can be nonspecifically activated in the absence of an ongoing cognate antigenic stimulus[25]. In this way, nonspecific stimuli, such as trauma, could precipitate an apparent autoimmune disease via dysregulated feedback circuits involving players such as IL-17, IL-6, STAT3 and NFκB.

Other common-γ-signalling cytokines

IL-21 is not only a differentiation factor for T_H17 cells, but also an adaptive response cytokine produced by these cells, with downstream effects on follicular T helper (T_{FH}) cells, dendritic cells, NK cells, osteoclasts and B cells[26]. In particular, the effects of IL-21 on B-cell maturation and the development of plasma cells and T_{FH} cells effectively link the T-cell and B-cell arms of the adaptive immune response. Blockade of IL-21 has, however, proven disappointing in RA thus far. IL-21 shares the gamma chain of its receptor with a number of other cytokines, including the 'homeostatic' cytokines IL-7 and IL-15 (REF. 27). Both IL-7 and IL-15 have been linked to RA via reports of elevated levels of these factors in synovial fluid; IL-15, in particular, has a clearly defined proinflammatory role in T-cell and NK-cell activation and in promoting crosstalk between T cells and macrophages in RA synovitis. IL-15 has been targeted in phase II clinical trials, with equivocal outcomes[28]. These cytokines are antiapoptotic and co-stimulatory, typically promoting T-cell expansion in response to lymphopenia. Their predominant effect is the expansion and activation of memory T cells, but evidence now suggests they might additionally sensitize the TCR to subthreshold stimuli, potentially including autoantigens, and at the same time favour pro-inflammatory pathways, thereby facilitating autoreactivity[25].

IL-23 and the IL-12 family

IL-23 stabilises IL-17 expression by T_H17 cells and seems to 'license' T_H17 cells to become pathogenic. By inducing expression of its own receptor, IL-23 also induces an autocrine positive-feedback loop[29]. IL-23 is a member of the IL-12 family (which also includes IL-27 and IL-35), an interesting group of heterodimeric cytokines that share receptor components and signalling pathways. Despite this promiscuity, IL-12 (comprising p40 and p35 subunits) and IL-23 (p40 and p19) are predominantly proinflammatory whereas IL-35 (EBI3 and p35) is immunoregulatory. IL-27 (composed of EBI3 and p28 subunits) seems capable of dual effects, which are possibly dependent on the stage of T-cell maturity — in some situations IL-27 inhibits T_H17 cell differentiation and in others promotes T_H1 cell development. IL-35 has emerged as a key cytokine in immunoregulatory circuits. It provides an important effector mechanism for natural T_{REG} cells but is also important for the generation of T_{REG} cells, including a population that does not express FOXP3, IL-10 or transforming growth factor (TGF)-β (iTr35 cells). Perhaps for reasons similar to those defined above for IL-17 inhibition, efforts to block IL-23, or indeed to capitalize on the wider regulatory biology of this cytokine family in RA, have been unsuccessful thus far.

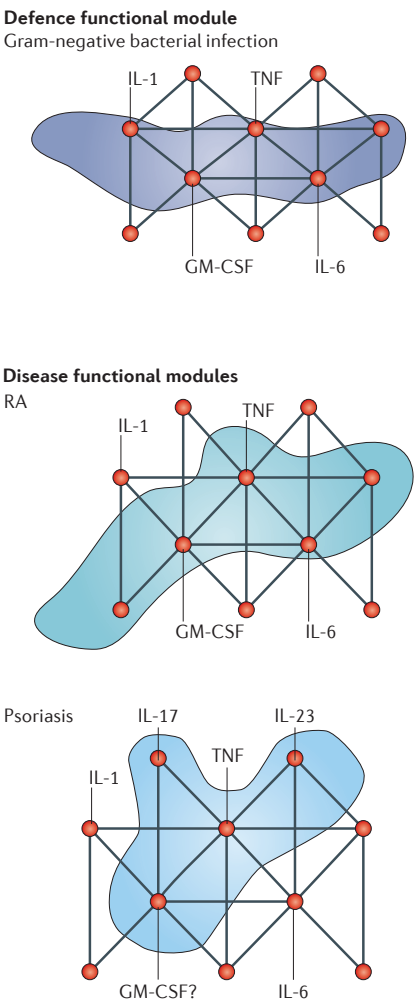

Figure 2 | **Functional modules exist within complex cytokine networks.** Modules of cytokines provide optimal host defence with minimal tissue damage, through functional cooperation involving critical 'cytokine checkpoints'. Cytokines that cooperate, or dominate, in host defence need not necessarily share a functional hierarchy with diseases such as RA. Herein we depict a group, or functional module, of cytokines that might be optimal to mediate host defence to a gram-negative bacterium, and propose that the group of cytokines that is essential for RA synovitis is distinct from this, and does not necessitate IL-1 (even though the latter may be present and functionally contribute albeit in a nonessential role). We have excluded IL-17 from the essential RA module on the basis of clinical trial data, although we recognize that the role of IL-17 may be disease-duration related; indeed, modules may need to be adjusted for disease duration. Similarly, in psoriasis the functional module is distinct from that shown for RA and contains TNF, IL-17 and IL-23 as essential contributors, on the basis of clinical intervention studies. GM-CSF, granulocyte-macrophage colony-stimulating factor.

T-cell plasticity

In contrast to early models of rigid T-cell differentiation, it is now recognized that considerable plasticity exists between key T-cell subsets, for example with potential interchangeability between T_H1, T_H17 and T_{REG} cells. While such plasticity provides the template for 'nimble' and appropriate tissue responses to a range of extraneous insults, it might also underpin dysregulated tissue responses in autoimmunity, at the same time providing therapeutic opportunities[30].

B-cell cytokines

B-cells have traditionally been viewed as antibody-producing and antigen-presenting cells, but it is now recognized that certain B-cell subsets can express RANKL and produce cytokines, including the key proinflammatory cytokines TNF, IL-6 and IL-1. Analogous to T cells, both proinflammatory and regulatory B (B_{REG}) cells are now recognized, the latter producing IL-10 and TGF-β. Of interest, IL-6 is also involved in the generation of B_{REG} cells in the gut. In parallel to observations in T cells, IL-35 also promotes the generation of B_{REG} cells, including IL-35-producing B_{REG} (iBr35) cells. Unlike iTr35 cells, their B-cell counterparts utilize both IL-35 and IL-10 for their suppressive function[31]. Other cytokines supporting B-cell lineages, including TNF ligand superfamily member 13B (also known as BAFF or BLyS) and TNF ligand superfamily member 13 (also known as APRIL), although of interest in defining B-cell maturation and expansion, have not proven of value or impact thus far in clinical targeting[32].

Cytokines of the 'stromal response'

Why chronic inflammation persists indefinitely within the RA synovium, and why some patients with early synovitis progress to persistent disease while others do not, remain enigmatic. In contrast to the outdated paradigm of stromal tissue as immunologically inert, it is now clear that FLSs have a role both in driving disease persistence and in providing the cellular basis for the tissue tropism that means inflammation occurs in particular joints in RA[33]. FLSs regulate the transition from acute to chronic inflammation through a variety of immune-mediated processes, and thereafter are probably central to the maintenance and fluctuations of local tissue inflammation[33].

FLSs express Toll-like receptors (TLRs) and other pattern-recognition receptors that facilitate responses to a variety of tissue-derived stress-related or damage-related moieties, which, in turn, drive cytokine release. In RA, FLSs express a specific pattern of coding and non-coding (small and long) RNA that distinguishes them from non-RA FLSs, and are endogenously activated owing to epigenetic imprinting for tissue-destructive pathways[34]. The basic biology of FLSs is altered in RA; for example, they exhibit anchorage independence, ongoing cell division and loss of contact inhibition. Interestingly, rheumatoid but not control FLSs can traffic between organs via the circulation, providing one mechanism for 'spreading disease' (REF. 35). In chronic synovitis, FLSs maintain a state of permanent transformation. RA FLSs possess a more 'anaerobic glycolytic' metabolic phenotype, which is stable even after long-term culture *in vitro* in atmospheric oxygen and the absence of external stimulation, including by leukocytes. These 'Warburg-like' cells could be one of the sources of blood metabolites identified in studies in patients with RA, which showed that low-molecular-weight metabolite signatures are associated with the extent of inflammation[36] and can also be used to predict treatment response[37]. Taken together, these observations demonstrate that FLSs create a distinctive synovial microenvironment that is intrinsically imprinted and stable.

Stage-specific FLS cytokines

The mechanisms responsible for the breach of tolerance and the cytokines implicated in this process (as discussed above) are in some measure distinct from those responsible for disease localization and persistence. Indeed, FLSs probably contribute substantially to the inflammatory milieu in the context of chronicity. They are capable of releasing a broad range of moieties including cytokines, growth factors and chemokines, including (but not limited to) IL-6, IL-1, platelet-derived growth factor, fibroblast growth factor and vascular endothelial growth factor. Clinically, disease remission is unusual after 6 months of synovitis. This observation is consistent with a switch from predominantly leukocyte-derived to a mix of leukocyte-derived and fibroblast-derived cytokines, which could contribute to driving disease persistence; this notion provides a molecular interpretation of the so-called therapeutic window of opportunity[38]. Support for this concept has come from the observation that the synovial fluid of patients with synovitis of <12 weeks' duration that subsequently progressed to RA has a unique cytokine/chemokine profile,

with a mixture of T-cell, macrophage and FLS-derived cytokines. This profile was restricted to the earliest phases of disease and was not present in the synovial fluid of patients with synovitis that did not persist or that developed into other forms of non-RA-driven persistent arthritis, such as psoriatic arthritis[38]. These findings strongly support the concept that the nature of the immune response, and consequent cytokine milieu, during the early phases of RA need not be identical to that involved during the phases of disease where inflammation localizes to the synovium and becomes persistent. This concept has important implications for the interpretation of animal model systems, and especially in the selection of therapeutic targets across discrete phases of disease.

Targeting the stromal response

As outlined earlier in this article, cytokines such as IL-1, IL-6 and TNF are key effectors of the tissue response in RA. Stromal elements might act upstream of these cytokines (acting as sentinel cells that recognize danger and damage) and are, therefore, possible drivers of persistent synovitis. Many ongoing studies are aimed at identifying those markers that define activated or pathogenic FLSs[39]. Cadherin-11 is an attractive candidate as it is specific to the inflammatory synovium. Intriguingly, anti-cadherin-11 reagents have been shown to ameliorate synovitis in models of arthritis[40]. Finally, targeting cyclin-dependent kinases in rheumatoid FLSs has anti-inflammatory effects mediated via modulation of IL-6 (REF. 41). These findings suggest that targeting pathways intrinsic to FLSs could be a useful strategy, especially during the phase of RA when inflammation begins to localize to the synovium.

Defining the RA cytokine landscape

Computational biology and the expanding array of clinically relevant RA biobanks (as well as the data sets arising from them) are facilitating a paradigm shift driven by systems biology[42]. A move towards a systematic approach to the categorization of biological pathways will probably yield new insight into the effector roles played by, and the presumed synergy of, cytokines in RA.

Molecular taxonomy

The linear, hierarchical models of cytokines in RA pathogenesis originally proposed to support TNF inhibition were remarkably successful in driving clinical innovation but are now less tenable, as broader cytokine effector profiles become relevant in the clinic and as experimental approaches enable the study of the plasticity of host defence in response to microbial challenges. In the past 3–4 years, the inflammatory arthropathies and related immune-mediated diseases have been allocated a taxonomy based on the therapeutic profile of distinct biologic interventions[43]. Although necessarily 'simplistic' at present, such cataloguing of clinically relevant pathways should lead, eventually, to a pathology-driven approach to therapy selection; see FIG. 1 for a description of cytokine-dependent categories of disease that might beg distinct therapeutic choices. Thus, therapeutics that target cytokines will be assigned on the basis of a molecular taxonomy so that treatment to target is specifically informed by the underlying pathology. Achieving this aspiration will be aided by the current drive towards biomarker discovery but will also require detailed clinical phenotyping in order to truly elucidate the endotypes that would support such stratification for therapy. Such a classification might also enable rational selection of cytokine-receptor-dependent kinase inhibitors — for example, those targeting Janus kinases. Those inhibitors with an optimal receptor-inhibition profile (which might also vary during the course of the disease) could offer the most benefit.

Identifying functional groupings

One attractive development has been the recognition of functional modules within complex networks[42]. In this model, cytokines have evolved to deliver optimal host defence through functional cooperation (FIG. 2). Thus, modules (groups) of cytokines will aggregate to deliver the necessary recruitment and differentiation of cells that would offer defence with minimal tissue damage — they will likely contain hierarchically dominant cytokine members — critical 'cytokine checkpoints'. In the context of autoimmunity, a putative disease module will dominate and necessitate specific targeting of that module, and selection of the pivotal cytokine(s) will offer optimal therapeutic value (for example, TNF in RA). Such modules might arise from genetic and epigenetic susceptibility to disease, or the nature of a given environmental challenge; by corollary, it cannot be assumed that cytokines that cooperate, or dominate, in host immune-defence necessarily cooperate in disease in an obligatory and/or identical manner. This model would explain why TNF and IL-1 work synergistically in TLR-driven host defence or, for that matter, in animal models of adjuvant-driven arthritis, but do not share an obligatory functional hierarchy in diseases such as RA (FIG. 2). The implications of such a new taxonomic approach are broad; for example, placement of as-yet undescribed or therapeutically tested cytokines or inhibitors in such networks could characterize their therapeutic utility even before clinical trials, with the potential to model their likely benefits or, in anticipation of future combination therapies, their synergistic value.

Conclusions

Cytokine expression in RA has provided remarkable insight into disease pathogenesis and therapeutic utility thus far. More knowledge is now required to properly deliver on the potential of this exciting field as it moves from disease suppression to disease prevention and cure. As small-molecule inhibitors gain traction in the therapeutic armamentarium, allocating the appropriate inhibitors to the subsets of patients who are most likely to derive benefit will become even more important; this general approach will lead, in turn, to a molecular definition of RA endotypes, and earlier selection of appropriate therapeutics as well as their rational combination.

Iain B. McInnes is at the Institute of Infection, Immunity & Inflammation, University of Glasgow, 120 University Place, Glasgow G12 8QQ, UK.

Christopher D. Buckley is at Rheumatology Research Group, Centre for Translational Inflammation Research, University of Birmingham Research Laboratories, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham B15 2WB, UK.

John D. Isaacs is at the NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Institute of Cellular Medicine, Newcastle University, William Leech Building, Framlington Place, Newcastle-upon-Tyne NE2 4HH, UK.

All authors are affiliated with the Arthritis Research UK Rheumatoid Arthritis Pathogenesis Centre of Excellence.

Correspondence to I.B.M.
iain.mcInnes@glasgow.ac.uk

doi:10.1038/nrrheum.2015.171
Published online 10 Dec 2015

1. Firestein, G. S. The disease formerly known as rheumatoid arthritis. *Arthritis Res. Ther.* **16**, 114 (2014).
2. McInnes, I. B. & Schett, G. The pathogenesis of rheumatoid arthritis. *N. Engl. J. Med.* **365**, 2205–2219 (2011).
3. Zhang, X. *et al.* The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat. Med.* **21**, 895–905 (2015).
4. McInnes, I. B. & Schett, G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat. Rev. Immunol.* **7**, 429–442 (2007).
5. Smolen, J. S. & Aletaha, D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat. Rev. Rheumatol.* **11**, 276–289 (2015).

6. Kalliolias, G. D. & Ivashkiv, L. B. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. *Nat. Rev. Rheumatol.* http://dx.doi.org/10.1038/nrrheum.2016.169 (2016).
7. Schett, G. & Manger, B. Interleukin-1 function and role in rheumatic disease. *Nat. Rev. Rheumatol.* http://dx.doi.org/10.1038/nrrheum.2016.166 (2016).
8. Schwartz, D. M., Bonelli, M., Gadina, M. & O'Shea, J. J. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat. Rev. Rheumatol.* http://dx.doi.org/10.1038/nrrheum.2016.167 (2016).
9. Wicks, I. P. & Roberts, A. W. Targeting GM-CSF in inflammatory diseases. *Nat. Rev. Rheumatol.* http://dx.doi.org/10.1038/nrrheum.2016.161 (2016).
10. Szekanecz, Z. & Koch, A. E. Successes and failures of chemokine-pathway targeting in rheumatoid arthritis. *Nat. Rev. Rheumatol.* http://dx.doi.org/10.1038/nrrheum.2016.157 (2016).
11. Spits, H. & Cupedo, T. Innate lymphoid cells: emerging insights in development, lineage relationships, and function. *Annu. Rev. Immunol.* **30**, 647–675 (2012).
12. Feldmann, M., Brennan, F. M. & Maini, R. N. Rheumatoid arthritis. *Cell* **85**, 307–310 (1996).
13. Tanaka, T., Narazaki, M.& Kishimoto, T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb. Perspect. Biol.* **6**, a016295 (2014).
14. Dennis, G. Jr *et al.* Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics. *Arthritis Res. Ther.* **16**, R90 (2014).
15. Garlanda, C., Dinarello, C. A. & Mantovani, A. The interleukin-1 family: back to the future. *Immunity* **39**, 1003–1018 (2013).
16. Rönnblom, L. & Eloranta, M. L. The interferon signature in autoimmune diseases. *Curr. Opin. Rheumatol.* **25**, 248–253 (2013).
17. van Holten, J. *et al.* A multicentre, randomised, double blind, placebo controlled Phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis. *Ann. Rheum. Dis.* **64**, 64–69 (2005).
18. van Nieuwenhuijze, A. *et al.* GM-CSF as a therapeutic target in inflammatory diseases. *Mol. Immunol.* **56**, 675–682 (2013).
19. Burmester, G. R. *et al.* Efficacy and safety of mavrilimumab in subjects with rheumatoid arthritis. *Ann. Rheum. Dis.* **72**, 1445–1452 (2013).
20. Lubberts, E. T_H17 cytokines and arthritis. *Semin. Immunopathol.* **32**, 43–53 (2010).
21. Benedetti, G. & Miossec, P. Interleukin 17 contributes to the chronicity of inflammatory diseases such as rheumatoid arthritis. *Eur. J. Immunol.* **44**, 339–347 (2014).
22. Lubberts, E. The IL-23–IL-17 axis in inflammatory arthritis. *Nat. Rev. Rheumatol.* **11**, 415–429 (2015).
23. McInnes, I. B. *et al.* Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. *Ann. Rheum. Dis.* **74**, 694–702 (2015).
24. Murakami, M. & Hirano, T. A four-step model for the IL-6 amplifier, a regulator of chronic inflammations in tissue-specific MHC class II-associated autoimmune diseases. *Front. Immunol.* **2**, 22 (2011).
25. Deshpande, P. *et al.* IL-7- and IL-15-mediated TCR sensitization enables T cell responses to self-antigens. *J. Immunol.* **190**, 1416–1423 (2013).
26. Di Fusco, D., Izzo, R., Figliuzzi, M. M., Pallone, F. & Monteleone, G. IL-21 as a therapeutic target in inflammatory disorders. *Expert Opin. Ther. Targets* **18**, 1329–1338 (2014).
27. Kim, H. R., Hwang, K. A., Park, S. H. & Kang, I. IL-7 and IL-15: biology and roles in T-cell immunity in health and disease. *Crit. Rev. Immunol.* **28**, 325–339 (2008).
28. Baslund, B. *et al.* Targeting interleukin-15 in patients with rheumatoid arthritis: a proof-of-concept study. *Arthritis Rheum.* **52**, 2686–2692 (2005).
29. Vignali, D. A. A. & Kuchroo, V. K. IL-12 family cytokines: immunological playmakers. *Nat. Immunol.* **13**, 722–728 (2012).
30. Gagliani, N. *et al.* T_H17 cells transdifferentiate into regulatory T cells during resolution of inflammation. *Nature* **523**, 221–225 (2015).
31. Wang, R.-X. *et al.* Autoimmune disease. *Nat. Med.* **20**, 633–641 (2014).
32. van Vollenhoven, R. F., Kinnman, N., Vincent, E., Wax, S. & Bathon, J. Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a Phase II, randomized, placebo-controlled trial. *Arthritis Rheum.* **63**, 1782–1792 (2011).
33. Buckley, C. D. Why does chronic inflammation persist: an unexpected role for fibroblasts. *Immunol. Lett.* **138**, 12–14 (2011).
34. Klein, K., Ospelt, C. & Gay, S. Epigenetic contributions in the development of rheumatoid arthritis. *Arthritis Res. Ther.* **14**, 227 (2012).
35. Lefevre, S. *et al.* Synovial fibroblasts spread rheumatoid arthritis to unaffected joints. *Nat. Med.* **15**, 1414–1420 (2009).
36. Kapoor, S. R. *et al.* Metabolic profiling predicts response to anti-tumor necrosis factor α therapy in patients with rheumatoid arthritis. *Arthritis Rheum.* **65**, 1448–1456 (2013).
37. Young, S. P. *et al.* The impact of inflammation on metabolomic profiles in patients with arthritis. *Arthritis Rheum.* **65**, 2015–2023 (2013).
38. Raza, K. *et al.* Early rheumatoid arthritis is characterized by a distinct and transient synovial fluid cytokine profile of T cell and stromal cell origin. *Arthritis Res. Ther.* **7**, R784–R795 (2005).
39. Filer, A. The fibroblast as a therapeutic target in rheumatoid arthritis. *Curr. Opin. Pharmacol.* **13**, 413–419 (2013).
40. Kiener, H. P. *et al.* Cadherin 11 promotes invasive behavior of fibroblast-like synoviocytes. *Arthritis Rheum.* **60**, 1305–1310 (2009).
41. Perlman, H. *et al.* IL-6 and matrix metalloproteinase-1 are regulated by the cyclin-dependent kinase inhibitor p21 in synovial fibroblasts. *J. Immunol.* **170**, 838–845 (2003).
42. Vidal, M., Cusick, M. E. & Barabási, A. L. Interactome networks and human disease. *Cell* **144**, 986–998 (2011).
43. Schett, G. *et al.* How cytokine networks fuel inflammation: toward a cytokine-based disease taxonomy. *Nat. Med.* **19**, 822–824 (2013).

Acknowledgements
The authors receive funding support from Arthritis Research UK via the Arthritis Research UK Rheumatoid Arthritis Pathogenesis Centre of Excellence.

Author contributions
All authors researched data for article, made substantial contributions to discussions of the content, wrote the article and reviewed/edited the manuscript before submission.

Competing interests statement
I.B.M. declares that he has received research funding and honouraria from AbbVie, BMS, MSD, Pfizer, Roche and UCB, all of whom make biologic agents used in the treatment of rheumatoid arthritis. C.D.B. declares that he has received honouraria and research funding from Novartis, Pfizer, Roche and UCB. J.D.I. declares that he has received research funding and honouraria from AbbVie, BMS, Novartis, Janssen, Pfizer and Roche.