Commentary
Interleukin-18: a therapeutic target in rheumatoid arthritis?

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Abstract

Interleukin 18 (IL-18), a member of the IL-1 superfamily of cytokines has been demonstrated to be an important mediator of both innate and adaptive immune responses. Several reports have implicated its role in the pathogenesis of rheumatoid arthritis (RA). Although biologic therapy is firmly established in the treatment of a number of inflammatory diseases including RA, partial and non-responder patients constitute residual unmet clinical need. The aim of this article is to briefly review the biology of, and experimental approaches to IL-18 neutralisation, together with speculation as to the relative merits of IL-18 as an alternative to existing targets.

Keywords: cytokine, IL-18, inflammation rheumatoid arthritis

Whereas TNFα antagonists provide impressive clinical benefits in rheumatoid arthritis (RA), partial and non-responder patients constitute residual unmet clinical need. Establishing the therapeutic potential of individual cytokines in rheumatoid arthritis, therefore, assumes increasing importance. Rational choice of an appropriate target however poses significant challenges as we move from linear models of cytokine effector function in chronic inflammation, to a 'network concept' of interacting activities contributing in synergy across distinct tissue events. In particular, cytokine mediated pathology may be distinct in cartilage and bone as opposed to synovial tissue or draining lymph node. For many given cytokines, establishing tissue expression and local function is now relatively straightforward. However, we believe that critical decision making with respect to therapeutic utility remains elusive. One must unravel functional pleiotropy and redundancy for a cytokine, and explore patient variation in expression and regulation prior to 'rational' progress.

IL-18, originally described as IFNγ inducing factor, is a member of the IL-1 superfamily that includes IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra) and the recently described IL-1F5-F10 cytokines [1,2]. Synthesised as an 23 kD pro-molecule (often pre-existing in resting leukocytes), IL-18 is cleaved by caspase-1 to an active 18 kD ligand, that binds a heterodimeric receptor, consisting of IL-18Rα and IL-18Rβ, that in turn mediates signalling through the canonical IL-1R superfamily signalling cascade that includes MyD88, IRAK (interleukin-receptor-associated kinase) to NF-κB. IL-18 mRNA and pro-protein are widely distributed, as are IL-18R complexes suggesting an important role in early innate immune responses. *In vitro*, IL-18 induces Th1 cell maturation, migration and activation in synergy with IL-12 and IL-23, but can promote default Th2 differentiation of T precursor cells even in the absence of IL-4 [2]. IL-18 activates and induces cytokine production by natural killer cells, macrophages and neutrophils, promotes angiogenesis and reverses endothelial cell apoptosis, retards fibroblast apoptosis and modulates function in varied tissue cell lineages including keratinocytes, osteoclasts and chondrocytes [2]. Importantly, IL-18 often acts in synergy rather than independently, and for some activities it remains unclear whether direct or indirect effects predominate. A further intriguing activity is the potential to promote nociceptor function [3]. Numerous recent *in vivo* studies using both IL-18-gene-targeted mice and neutralising agents such as anti-IL-18 antibody or IL-18 binding protein, implicate IL-18 in components of

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DMARD = disease modifying anti-rheumatic drug; GM-CSF = granulocyte macrophage colony-stimulating factor; IFN = interferon; IL = interleukin; IL-1Ra = IL-1 receptor antagonist; IRAK = interleukin-receptor-associated kinase; NF-κB = nuclear factor- κB; RA = rheumatoid arthritis; Th = T helper cells; TLR = toll-like receptor; TNF = tumor necrosis factor.

host defence and in responses in autoimmune models of disease [1,4–7], increasing interest in it as a therapeutic target. Commensurate with the foregoing inflammatory profile, IL-18 is subject to close regulation. Cleavage and degradation of caspase-1 limits generation of active 18 kD IL-18 prior to release mediated in part via P2X7 dependent pathways. In the extra cellular domain IL-18 is antagonised by IL-18 binding protein and in part by soluble IL-18Rα, although lower affinity binding of the latter suggests it is a minor contributor.

We first reported IL-18 expression in RA synovial membrane in macrophages, together with lining layer fibroblasts. IL-18 promoted TNFα, IFNγ, granulocyte macrophage colony-stimulating factor (GM-CSF) and nitric oxide release in primary synovial cultures [8]. Osteoarthritis tissues, in contrast, exhibit virtually no IL-18 protein expression [8]. Several subsequent studies have confirmed and extended these observations, in particular in the intriguing observation that RA synovial IL-18 expression correlates not only with tissue TNFα and IL-1β expression but also with erythrocyte sedimentation rate [9,10]. Moreover, Bresnihan and colleagues correlated synovial IL-18 expression with disease activity in inflammatory arthritis following DMARD therapy [11]. Before treatment, tissue IL-18 expression correlated with serum C reactive protein levels, but interestingly not with serum IL-18. After DMARD treatment, there was decreased tissue expression of IL-18 that correlated significantly with change in serum IL-18 and C reactive protein. The effects of IL-18 extend beyond T cell activation. Recently, we have shown that IL-18 is an important activator of synovial neutrophils [12]. Others have demonstrated effects upon synovial fibroblast activation, and on chemokine release [13–15] although contradictory data have been reported [16].

In vivo observations further support a proinflammatory role in articular inflammation. Thus, IL-18 can replace the requirement for complete Freund's adjuvant to induce arthritis in collagen immunized DBA/1 mice [17]. Utilising adenoviral delivery of IL-18 and TNFα/IL-1 deficient mice, Joosten and colleagues subsequently demonstrated that whilst IL-18-induced joint inflammation is independent of IL-1, cartilage degradation requires IL-18 induced IL-1β production [18]. Furthermore they suggest that TNF is partly involved in IL-18-induced joint swelling and influx of inflammatory cells, but cartilage proteoglycan loss occurs independent of TNF. These findings indicate that IL-18, in contrast to TNF, contributes through distinct pathways to joint inflammation and cartilage destruction. IL-18-deficient DBA/1 mice exhibit reduced incidence and severity of collagen induced arthritis associated with amelioration of articular damage [19]. Neutralisation of IL-18 by antibody or IL-18 binding protein ameliorates collagen induced arthritis [4,6] although the dose response of the latter is

unclear. IL-18 neutralisation also ameliorates streptococcal induced arthritis. Moreover local overexpression of IL-18 binding protein c by adenoviral delivery also ameliorates articular destruction [5]. Thus, IL-18 is present in the synovial lesion and is tractable in relevant *in vivo* model systems.

Whereas the foregoing *in vivo* data suggest a pro-destructive role, the effect of IL-18 in bone and cartilage biology is controversial at this stage. Previous reports have suggested that IL-18, independent of IFNγ, inhibits osteoclast formation via increased production of GM-CSF by T cells and osteoblasts [20,21]. However supporting the notion that IL-18 facilitates bone destruction in RA, it has been shown that IL-18 indirectly stimulates osteoclast formation through upregulation of both soluble and membrane bound RANKL (receptor activator of nuclear factor κB ligand) by RA synovial derived T cells [22]. In this study IL-18 stimulation failed to induce GM-CSF or osteoprotegrin from T cells.

Several potential approaches to IL-18 targeting are proposed [1,23,24]. Although synovial IL-18 expression has been considered the primary target, expression elsewhere in the circulation and in the lymphoid system may also be therapeutically important – we recently reported IL-18 expression in human lymph node, although its function therein is unclear [25]. No consensus exists to the optimal therapeutic modality. Generation of anti-IL-18 monoclonal neutralising antibodies represents an attractive approach, although at this time clinical studies have not yet commenced. Antibody offers the potential to select binding site and affinity to optimise therapeutic neutralisation – this in turn may offer advantages midst the complex milieu of regulatory pathways described for IL-18. High affinity binding by IL-18 binding protein a and c isoforms renders these obvious neutralising agents, and early clinical studies to establish the safety of this approach are in progress. Whether the dose response will prove useful in clinical studies is however unclear. In contrast, the lower affinity of native soluble IL-18Rα has dissuaded use of this moiety thus far. Directly targeting the IL-18R receptor, e.g. via antibody or specific antagonist, is also of potential interest, although shared utilisation with other IL-1 cytokines, e.g. IL-1F7, may reduce the specificity of such an approach [26]. Small molecule approaches include inhibitors of caspase-1, antagonism of P2X7 receptors and generation of inhibitors to components of the IL-18 receptor signalling pathway. The latter approaches will provide limited specificity for IL-18 since generation and release of other IL-1 superfamily members may also be inhibited. Whether this offers therapeutic disadvantage is however unclear and need not be assumed. They provide potential advantages in oral delivery, patient tolerance and cost in the longer term.

Is IL-18 therefore a good therapeutic target in RA? IL-18 functions in synergy with numerous cytokines present within the synovial compartment including IL-12 and IL-15 and as such it probably serves to amplify ongoing inflammatory responses ('adjuvant-like'). Blockade could therefore usefully impinge on the optimal function of a number of proinflammatory pathways therein. IL-18 also apparently acts upstream of TNF release in some model systems [18]. The foregoing offer likely therapeutic advantage. However, whether the IL-18R signalling pathway is sufficiently distinct from that of IL-1, which in turn has proven disappointing as a target in clinical trials is not yet clear. The effects of IL-1 and IL-18 *in vitro* are not synonymous, e.g. IL-1 directly activates synovial fibroblasts and chondrocyte metabolism whereas IL-18 appears to operate via indirect means including IL-1 itself [16,18]. This could reflect distinct receptor expression or divergent signalling. Similarly, IL-18 has potent effects on T lymphocyte maturation that are distinct from IL-1. Nevertheless, toll-like receptor (TLR) dependent signals have been shown to bypass IL-1 in serum transfer arthritis [27] and it is possible that the IL-1R superfamily exhibits too much functional redundancy to offer utility in practice. As TLR signalling has unravelled, discrete functions have emerged for distinct signalling pathways and adapter moieties, offering opportunity for future, more specific intervention [28]. IL-18 targeting also offers further potential disadvantages. Infectious models in which IL-18 has been targeted or in IL-18 deficient mice clearly show a role for this cytokine in host defence to bacterial and fungal infection [2,29], although IL-18 function has not yet appeared critical. At this stage IL-18 appears little different from other cytokines targeted in RA – close attention to the potential for infectious complications should be anticipated in clinical development.

The foregoing discussion clearly indicates that IL-18 offers potential as a therapeutic target in RA. Caution with respect to effects on bone biology should be balanced with the potential for broad anti-inflammatory effects within and beyond the synovium. IL-18 overexpression has been variously reported in psoriasis, pulmonary inflammatory diseases, inflammatory bowel diseases, and various tumours, and therapeutic utility likely extends to a range of inflammatory conditions. We recently detected IL-18 expression in psoriatic arthritis synovium and demonstrated that such expression is maintained despite three months methotrexate therapy [30]. The balance of evidence strongly supports progression into clinical studies at this time – only these however will determine whether improvement in disease activity can be achieved. We believe that carefully designed proof-of-concept studies are indicated to ensure that pathogenetically useful information at least is obtained. Indeed one might usefully consider this as we progress with a range of novel therapeutic targets in RA.

Competing interests
The author(s) declare that they have no competing interests.

Acknowledgements

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