Interleukin 20 - A Potential New Biologic Treatment Candidate in Psoriasis

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Interleukin 20 (IL-20) has recently been proposed as a new biologic target in psoriasis treatment. Its discovery originated from a library search for cytokines with helical structures, and was published in 2001 (1). Since then, it has been shown that expression levels of both IL-20 mRNA and protein were elevated in psoriasis plaques, compared to the non-lesional and normal skin. Moreover, established psoriasis treatments such as cyclosporine, calcipotriol, alefacept (anti-CD2), and infliximab (anti-TNFα) decreased the elevated levels of IL-20 (2). IL-20 polymorphisms are also supportive of the proposed importance of IL-20 in psoriasis, as the IL-20 gene carries single nucleotide polymorphisms (SNPs) that are associated with the risk of plaque-type psoriasis.

Psoriasis is a strictly human disease; however, experimental animal models have been developed to study psoriasis pathogenesis, *in vivo*. Anti-IL-20 antibodies have been developed and their effect as biological treatment was investigated in a psoriasis xenograft transplantation model where skin from psoriasis patients is transferred to immune-deficient mice in such a way that the grafted skin maintains its psoriatic characteristics (3). It was shown that blocking IL-20 signalling with anti-IL-20 antibodies ameliorated psoriasis, and that administration of IL-20 exacerbated the disease. Both these experiments highlight the important role of this interleukin in psoriasis pathogenesis an its potential use as target in psoriasis treatment (4).

Biological treatments embracing both antibodies and fusion proteins that target either T cells or the cytokine tumor necrosis factor α (TNFα) are already in use in psoriasis treatment. In general, these new biological treatments display an improved safety profile as compared to the more classical systemic psoriasis treatments such as PUVA, methotrexate, and cyclosporine. However, they do have an impact on the immune system with consequences such as increased risk of infections and development of cancer, which are, obviously, of major concern. For instance, the anti-TNFα treatments have been associated with an increased risk of reactivating latent tuberculosis. Discovery of IL-20 and its putative role as a tissue specific mediator of the psoriasis pathogenesis thus presents itself as an interesting and welcome new target in psoriasis treatment.

IL-20 expression was primarily found in the skin and a putative role of IL-20, in the psoriasis pathogenesis, was suggested by the observation that IL-20 transgenic mice displayed a psoriasis-like phenotype of the skin. These mice displayed hyperproliferative keratinocytes with an altered differentiation profile. IL-20 was therefore suggested to play a direct or indirect role in epidermal function by dysregulating keratinocyte proliferation and differentiation. A direct effect of IL-20 on keratino-

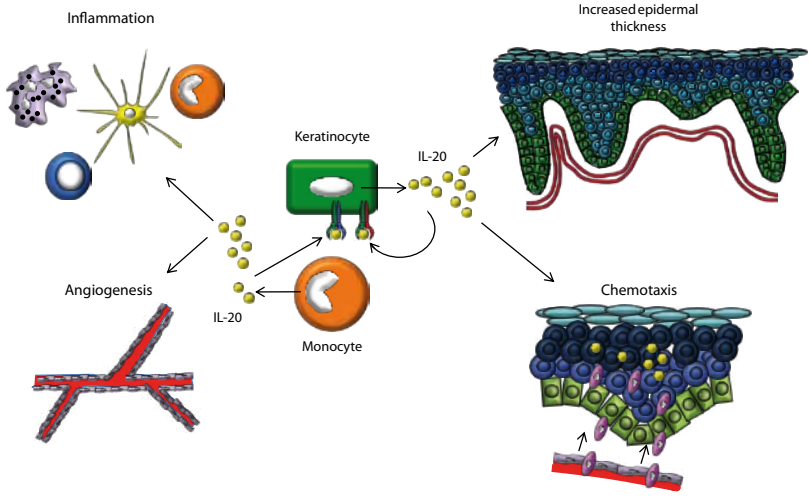

Fig. 1. Production and biological functions of IL-20.

cyte proliferation *in vitro*, however, was not possible to ascertain, even at very high concentrations of IL-20 (5). In contrast to the keratinocytes, endothelial cells respond directly to IL-20 stimulation *in vitro*, by increasing their proliferation. Besides proliferation and angiogenesis, IL-20 has also been implicated in chemotaxis (Fig. 1). Keratinocyte proliferation, angiogenesis, and chemotaxis are all important features of psoriasis as the disease is characterized by increased epidermal thickness, an increased capillary network, and an increased influx of lymphocytes.

IL-20 signals through two receptor complexes: the IL-20R1/IL-20R2 complex that also binds IL-19 and IL-24, and the IL-22R/IL-20R2 complex that also binds IL-24. IL-19, IL-20, IL-22, IL-24, and IL-26 all belong to the IL-20 subfamily of cytokines. Although sharing of receptors is shown among these family members, IL-19 and IL-24, the two cytokines employing the same receptors as IL-20, have not yet been implicated to play a role in psoriasis. IL-19 may play a role in the pathogenesis of asthma and IL-24 may act as a tumour-growth suppressor. All three receptors were found in the skin; IL-20R1 predominantly above the basal layer of the keratinocytes, IL-20R2 evenly distributed in all layers of the epidermis, and IL-22R differentially expressed in the most superficial part of the epidermis just beneath the stratum corneum (2).

Proinflammatory stimuli induce the expression of IL-20 in keratinocytes (IL-1β and UVB light) and monocytes (TNFα and LPS). Intra-cellularly the expression is regulated by the p38 MAPK pathway and by NF-κB (6). Upon transcription and translation the IL-20 protein is secreted into the extra-cellular environment where it encounters its receptors (one or both of the two receptor complexes described above) on the surface of a target cell. Each receptor complex consists of a type I and a type II receptor and the intracellular domains of the type I receptor (IL-20R1 and IL-22R) have been demonstrated to possess two and four stat3 recruitment sites, respectively.Upon binding of IL-20, stat3 is activated by phosphorylation (Fig. 2). The primary source of IL-20 in the skin is a matter of debate but both keratinocytes and monocytes have been suggested to fulfil this role. Identification of the main target cell of IL-20 is debated as well.

Elevated levels of IL-20 are not exclusively found in psoriasis but also in atopic dermatitis and spongiotic dermatitis such as contact eczema. Its role in these skin diseases remains unknown. Besides the skin, elevated IL-20 expression was also found in rheumatoid arthritis in synovial fibroblasts (RASF), endothelial cells and macrophage-derived foam cells lining the microvessel of atherosclerotic lesions. Both rheumatoid

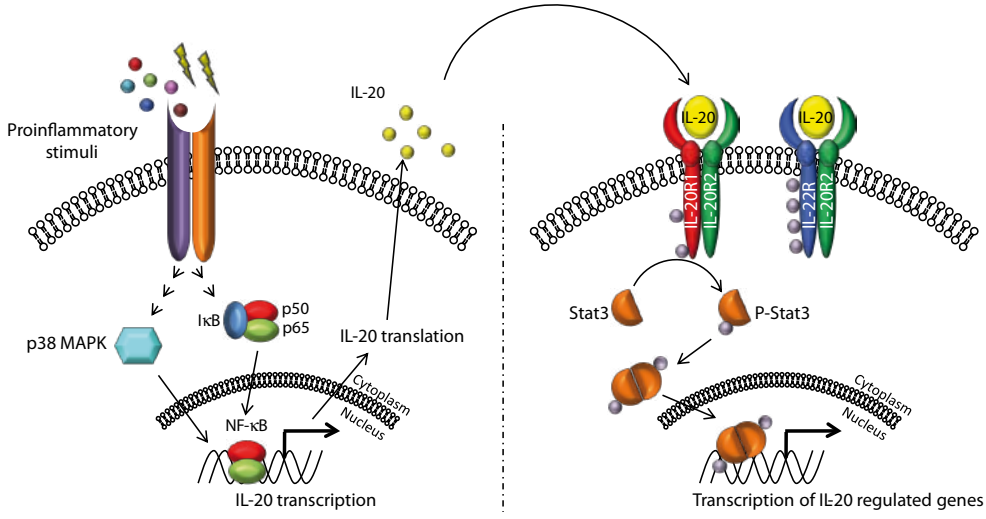

Fig. 2. Stimulation and effect of IL-20 in source and target cells.

arthritis (RA) and atherosclerosis are chronic inflammatory diseases suggesting a common role of IL-20 in inflammation.

Since the discovery of IL-20, much information on its actions and regulation has emerged. IL-20 has been demonstrated to play an important role in psoriasis and is a likely new therapeutic target. IL-20 is a pleiotropic cytokine with potent inflammatory, proliferative, angiogenic and chemoattractive effects. The exact role of IL-20 in the psoriasis pathogenesis, however, is still under investigation.

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