Letters to the Editors

Hypoxia-induced transcription factor 1α: a potent driving force behind rheumatoid arthritis

Sirs,

We read with interest the recently published research article "Identification of multiple, oxygen-stable HIF1 alpha isoforms, and augmented expression of adrenomedullin in rheumatoid arthritis" in *Clinical and Experimental Rheumatology* (1). During both phases of the study, Green *et al*. agreed that hypoxia-inducible transcription factor 1α (HIF-1α) target genes increased basal expression of the adrenomedullin gene in rheumatoid arthritis (RA) peripheral blood mononuclear cells, with resulting loss of further induction upon cell activation.

To date, RA is characterised by tumour-like expansion of the synovium and the subsequent destruction of adjacent articular cartilage and bone. At the same time, angiogenesis is required to maintain the chronic inflammatory state by transporting inflammatory cells to the site of synovitis and supplying nutrients to the pannus. The latest achievement obviously suggested the HIF-α was expressed abundantly in RA synovium and was related to both angiogenesis and inflammation, predominantly close to the intimal layer but also in the subintimal zone (2, 3). Although the exact causes of RA remain unknown, immunological dysregulation by inflammatory cytokines and VEGF-mediated angiogenesis have been shown to be involved in driving the inflammation and synovial cell proliferation that result in joint destruction in RA patients.

The latest achievements obviously suggested that the expression levels of IL-6, IL-8, IL-33, matrix metalloproteinase (MMP)-1, MMP-3, MMP-9, and tumour necrosis factor (TNF)-α were significantly increased by enforcing HIF-1α expression in RA (4-6). Further, hypoxia-induced MMP-3 and IL-33 expression was remarkably attenuated by knock-down of HIF-1α (4, 5), whereas hypoxia-induced IL-8 or MMP-1 expression was not apparently repressed by HIF-1α siRNA (4). It is well accepted that the inflammatory cytokines play a dual role in the pathogenesis of RA, which can promote inflammation and destruction of bone. Interestingly, Hu *et al*. have measured that HIF-1α overexpression enhanced RASF-mediated expansion of inflammatory T helper (Th)1 and Th17 cells, leading to proinflammatory interferon-γ and IL-17 production (6). Above all, this is so clear that HIF-1α may contribute to the persistent expression of proinflammatory cytokines and accelerate inflammation and destruction of bone in RA. By the way, Hy *et al*. have investigated IL-33 in turn could induce more HIF-1α expression in RASF (5). On the other hand, it has indicated that IL-17A activated HIF-1α via the nuclear factor-kappaB pathway in hypoxia (7). What is more, Wang *et al*. agreed that the expression of VEGF and HIF-1α decreased more after CD147 inhibition than after infliximab treatment in the engrafted tissues in SCID-HuRAg mice. Taken together, we agree with this comment that HIF-1α may be a potent driving force behind RA, owing to contribute the expression of inflammatory cytokines, MMPs and angiogenesis.

In summary, it is therefore entirely possible that the HIF-1a was significantly associated with RA. Although we agree that these findings provide additional useful information for clinical practice, to ascertain the exact mechanisms of action of HIF-1α, further studies will be required to comprehensively explore the role of HIF-1α, and the development of therapeutic agents targeting HIF-1a might result in important new, innovative therapies for RA.

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