RHEUMATOID ARTHRITIS

PlGF's role extends beyond angiogenesis

Best-known for its role in angiogenesis, placental growth factor (PlGF) is gaining recognition for its involvement in inflammatory processes, and a report in *Arthritis and Rheumatism* now implicates this ligand in rheumatoid inflammation.

Increased levels of PlGF in the synovial fluid of patients with rheumatoid arthritis (RA) have previously been reported. Now, Seung-Ah Yoo *et al.* have demonstrated that PlGF is expressed in the layer that lines the hyperplastic synovium of RA joints. Cultured fibroblast-like synoviocytes from this layer constitutively expressed PlGF, but could be induced to produce more in response to interleukin (IL)-1 β and tumor necrosis factor (TNF). PlGF, when added to mononuclear cells from the synovial fluid and peripheral blood (PBMCs) of patients with RA, specifically increased the production of TNF and IL-6 from these cells, but not from PBMCs of healthy controls. Cyclosporin and FK-506 blocked this induction, which suggested the involvement of a calcineurin-dependent pathway.

Similar to PlGF, its receptor, vascular endothelial growth factor receptor 1 (VEGFR-1, formerly termed Flt-1), was expressed at high levels in rheumatoid synovium and in PBMCs from patients with RA; its expression in PBMCs correlated positively with disease activity. In line with this observation, IL-1 β and TNF increased VEGFR-1 expression in PBMCs from healthy patients. In view of these findings,

Yoo *et al.* investigated the effects of blocking VEGFR-1 on rheumatoid inflammation using a novel anti-VEGFR-1 hexapeptide, which inhibits the interaction between PlGF and its receptor. Treatment of PBMCs with the hexapeptide or anti-VEGFR-1 antibodies inhibited the PlGF-induced increase in IL-6 production in a dose-dependent manner.

Subcutaneous injection of this anti-VEGFR-1 peptide for 3 weeks reduced the severity of arthritis in mice with mild-to-minimal collagen-induced arthritis, and prevented the progression of arthritis in mice with established arthritis after 6 weeks' treatment. The paws and ankles of the anti-VEGFR-1-hexapeptide-treated mice showed less inflammation, synovial hyperplasia and bone destruction than control mice. Consistent with these observations, significantly lower levels of IL-6 were seen in these mice. Finally, arthritis failed to develop in response to anti-collagen II antibodies in PlGF^{-/-} mice.

These findings have implicated PlGF and VEGFR-1 as molecular components in the pathogenesis of RA, and have introduced these molecules as potential therapeutic targets.

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Original article Yoo, S.-A. *et al.* Role of placenta growth factor and its receptor Flt-1 in rheumatoid inflammation. *Arthritis Rheum.* 60, 345–354 (2009).