PAF, a potent proinflammatory mediator, looking for its role in the pathogenesis of joint damage

Cell activation is accompanied by remodelling of its membrane components producing structurally diverse intracellular and extracellular lipids that seem to be essential in signal transduction, cell-cell communication, and as mediators in inflammation and pathophysiological mechanisms. Phospholipases are pivotal enzymes in the generation of these lipids, including eicosanoids (mostly prostaglandins), platelet activating factor (PAF), diacylglycerides, and other newly discovered bioactive autacoids.

PAF signals neutrophils in a juxtacrine fashion, while remaining within the endothelial plasma membrane, but does also work in conjunction with chemokines increasing synergistically the release of arachidonic acid and the adherence and motility of neutrophils. In addition, PAF elicits IL8 gene expression in human fibroblasts and collaborates with proinflammatory cytokines. For example both PAF and tumour necrosis factor (TNF) synergistically modulate endothelial cell function and PAF also increases leucocyte extravasation caused by IL1 in vivo.

Could the synergistic effect between PAF and other mediators unmask the real contribution of PAF to the joint inflammatory reponse? As with adhesion molecules, the regulated expression of different signalling molecules (PAF and chemokines) by endothelial cells in different temporal patterns, in response to different agonists and in different vascular beds, provides a mechanism for differential activation of different leukocytes. Most of known inflammatory mediators have been found in the synovial fluid or synovial membrane, or both, in experimental and human arthritis. Recent data strongly suggest that PAF plays an important part in several phases of joint damage. Thus, PAF, participates in the recruitment of neutrophils in experimental arthritis. The administration of PAF receptor antagonist inhibited the accumulation of neutrophils in the synovial fluid in an acute arthritis rabbit model induced by urate crystals.

PAF in the cytokines and inflammatory lipids network

Cytokines exert a considerable multilevel impact, both regulating key enzymes of lipid mediator pathways and generating lipid mediators central to their action. Most of proinflammatory cytokines increase PAF synthesis by different kinds of cells. In addition, PAF can modulate inflammatory responses increasing the synthesis and release of TNF, IL1, IL2, and IL6 by different cells. In fact, there was a diminution of synovial fluid cytokine concentrations in different models of experimental arthritis in animals prophylactically treated with PAF receptor antagonists. PAF also participates in the synthesis pathway of leukotrienes and prostaglandins. Thus, PAF upregulates COX-2 expression, but not COX-1, at the transcriptional level. Consequently, the administration of...
PAF and extracellular matrix

Recent data suggest that PAF could participate in the turnover of matrix protein. In vitro studies have shown that in bovine cartilage, PAF decreases the proteoglycan chondrocyte synthesis, and activates osteoclast resorption. In cultured synovial cells, PAF decreases the synthesis of collagen and proteoglycans (Gutierrez, unpublished data). In synovial cell cultures PAF triggers collagenase expression. In addition, the administration of PAF receptor antagonists improved the loss of articular proteoglycan content. Finally, a recent study suggests that PAF may be an angiogenic factor. Therefore, a number of studies suggest that PAF could be an important mediator modifying the matrix protein turnover in chronic arthritis.

PAF and arthritis

There is, therefore, a large amount of data suggesting that PAF might play a part in inflammation. Certain information about PAF and arthritis has been afforded in recent years. Both joint resident cells, as synovial B cells, and recruited inflammatory cells (mononuclear and neutrophils), can produce PAF after cytokine stimulation. In addition, PAF can prime cells of the inflamed synovial membrane as endothelial cells, synovial B cells, and leucocytes. PAF, in its biologically active form, has been found in the joint fluid in experimental and human arthritis. Although PAF by itself exhibits moderate inflammatory activity after injection in a normal rabbit knee joint, its simultaneous injection with TNFα considerably increased the inflammatory response obtained by the cytokine alone. Finally, the administration of structurally different PAF receptor antagonists to animals with various types of arthritis significantly ameliorated morphological joint lesions. In a pilot study in rheumatoid arthritis patients receiving a PAF receptor antagonist, there was a noticeable improvement in the clinical and biochemical parameters. Taking into account the critical role of PAF in many steps of joint injury, the relevant question is why this important mediator has been relatively neglected in rheumatology research. One potential explanation is that PAF receptor released very early during the inflammatory process and therefore PAF receptor antagonists are most effective when prophylactically given in an experimental model of arthritis. It cannot be discounted that a more powerful PAF antagonist could be useful in the down regulation of the inflammatory cascade amplification elicited by PAF. A different pharmacological approach has been considered using recombinant PAF acetylhydrolase. The administration of this enzyme considerably decreased pleurisy and paw oedema, conditions pathogenetically related to arthritis.

On the whole, there is no doubt that PAF is an important biological mediator of inflammatory processes, including arthritis. However, further studies are needed to unravel whether PAF modulation effects, probably in combination with other therapeutic modalities, could have a role in the treatment of chronic joint inflammation.

G HERRERO-BEAUMONT
J EGIDO

Division of Rheumatology and Inflammation Laboratory,
Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Spain


PAF, a potent proinflammatory mediator, looking for its role in the pathogenesis of joint damage

G HERRERO-BEAUMONT and J EGIDO

Ann Rheum Dis 1997 56: 211-213
doi: 10.1136/ard.56.4.211