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Inflammatory responses of a platelet-activating factor

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SUMMARY

Platelet-activating factor (PAF) has a wide spectrum of biological activity and is associated with a number of disease states in relation to inflammatory responses. The actions of PAF are abolished by a specific PAF acetylhydrolase (PAF-AH) through hydrolysis of the acetyl residue. The authors of this study have cloned the PAH-AH gene from monocyte-derived macrophage cDNA library by PCR. Oligonucleotide PCR primers were designed based on the amino acid sequence of PAF-AH purified from human low-density lipoprotein particles. The PAF-AH cDNA was cloned and expressed in mammalian cells and *Escherichia coli.* The recombinant PAF-AH (rPAF-AH) thus obtained exhibited the same substrate selectivity as the native enzyme, i.e. it hydrolysed a phospholipid with a short residue at the sn-2 position. The authors have also reported a tissue-specific expression of the PAF-AH gene, for example, cultured macrophages, differentiated monocytes and tissues containing a large number of macrophages such as the thymus and tonsils express large amounts of PAF-AH, while tissues like the heart, kidney, liver and cerebral cortex show no expression.

As PAF is a potent stimulant of vascular permeability and inflammation, the authors tested the anti-inflammatory activity of rPAF-AH in both *in vitro* and *in vivo* systems. In an *in vitro* system, PAF pre-incubated with rPAF-AH, lost its ability to activate polarization and spreading of neutrophils—a characteristic feature of the immune response. In a rat footpaw oedema model, rPAF-AH blocked PAF-induced oedema formation by >85% and in a pleurisy model it brought about a >80% reduction of vascular leakage produced by PAF. The authors conclude that supplemental PAF may reverse the pathological response in diseases such as asthma, systemic lupus erythematosus and septic shock where plasma PAH-AH has been reported to be low.

COMMENT

Although a number of PAF antagonists are known and are under clinical trial for various diseases,[1,2] the authors of this paper have done an interesting study in which they have cloned and expressed the PAF-AH gene and substantiated their results by demonstrating its biological activity. Besides PAF, which is a potent pro-inflammatory phospholipid, a number of other autacoids like histamine, leukotrienes, bradykinin and prostaglandins play an important role in mediating the inflammatory response. Chemical and immune stimulation of various cell types, namely neutrophils, eosinophils, macrophages, mast cells and vascular endothelial cells not only release PAF but also release other mediators of inflammation.

In this study the authors have demonstrated tissue-specific expression and the *in vitro* and *in vivo* anti-inflammatory activity of rPAF-AH against PAF. Since this is an experimental study where actions of only one of the mediators of inflammation, i.e. PAF have been blocked, the outcome of the study holds promise only towards PAF-mediated pathological responses. Diseases such as asthma, systemic lupus erythematosus and septic shock are multifactorial. It would be interesting to know the clinical effectiveness of PAF-AH therapy.

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