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Human Macrophages Secrete Platelet-Activating Factor Acetylhydrolase*

A Mechanism for Resolution of Pulmonary Inflammation

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Monocytes and macrophages secrete bioactive molecules that mediate inflammatory and immunologic responses in the lung and elsewhere. The regulated production of these mediators is important, since unregulated production could result in pathological effects. Platelet-activating factor (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine, PAF) is a phospholipid autacoid that is synthesized following stimulation of monocytes or other inflammatory cells. PAF has been implicated as a mediator of lung diseases such as immune complex-induced alveolitis, asthma, and lung injury in endotoxemia. Pulmonary inflammation is associated with the accumulation of peripheral blood monocytes, followed by their maturation in situ to become macrophages. It has been suggested that the changes that occur as monocytes mature to become macrophages are important for the resolution of inflammatory lung injury.

We observed that the amount of PAF produced after cell activation was reduced by 90% when human monocytes matured to become macrophages in vitro. Decreased PAF accumulation was the result of a 250-fold increase in the intracellular activity of the enzyme that degrades PAF, PAF acetylhydrolase (PAF-AH). Increased PAF-AH activity was due to the net increase in synthesis of a new enzyme (i.e., one not present in the precursor monocytes). These studies demonstrated a novel mechanism by which an increase in activity of the degradative enzyme regulates the accumulation of PAF.

Our recent studies demonstrated that macrophages secrete PAF-AH. This enzyme is biochemically and immunologically identical to the human plasma PAF-AH. The PAF-AH secreted by macrophages and the PAF-AH in human plasma are sensitive to the same active site-directed inhibitors, are associated with the same lipoprotein particles, and transfer between low-density lipoprotein and high-density lipoprotein in a pH-dependent manner. In addition, the plasma and secreted activities hydrolyze both PAF and structurally related, oxidatively fragmented phospholipids. The latter substrates are important because they are toxic and may accumulate at sites of inflammation.

The changes that occur as monocytes mature to become macrophages (Fig 1) may limit acute inflammatory responses by the following mechanisms. First, maturation is associated with increased levels of intracellular PAF-AH, which in turn reduce the stimulated production and release of PAF. Decreased PAF production may limit the local activation of cells that respond to the lipid, such as neutrophils, monocytes, and platelets. Second, as monocytes mature to become macrophages they acquire the ability to secrete large amounts of PAF-AH. Since secreted PAF-AH degrades both PAF and oxidized phospholipids, it may regulate their accumulation in the inflammatory milieu. Finally, the secreted enzyme appears to be identical to the plasma PAF-AH. PAF-AH released from macrophages may be transported to the blood, where it limits the half-life of PAF in plasma. Thus, the maturation of monocytes to macrophages is associated with changes in the metabolism of PAF that may promote the resolution of inflammatory responses.

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