Neutrophils, Interleukin 8, and Related Chemotactic Cytokines

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1 Introduction

Neutrophils are the most frequent immigrant cells in inflammatory lesions. They are usually present in very high numbers and are often incriminated as effectors of tissue damage because of their high contents in neutral and acid proteases and their ability to generate superoxide and other reactive oxygen derivatives.

In order to release enzymes and other products, and to generate oxygen-derived radicals, neutrophils must be activated. The circulating cells are quiescent and most neutrophils are eliminated from the circulation and substituted by new ones without becoming involved in a defense function, i.e., without apparent activation. Upon inflammation (and often independently of its course) neutrophils are recruited into the affected site, and this process involves multiple activation events.

Initially, circulating neutrophils sense chemotactic signals that are generated in the affected tissue site and diffuse into the local microvessels. The type of chemotactic molecule that initiates recruitment depend on the type of inflammatory injury. N-formylmethionyl peptides are likely to be preponderant upon infection, while C5a is the initial attractant when immune complexes are formed. In other situations, like trauma or ischemia, the initial stimulus for neutrophil mobilization is unknown.

While one must assume, as we do, that recruitment starts with the formation of a single chemotactic agonist, the process is invariably going to expand through the involvement of additional agonists that can act in concert on the same cell since they are directed to distinct receptors.

Once the neutrophils begin accumulating in the inflamed tissue, chemotactic stimulation as well as phagocytosis concur in the triggering of product release.

2 The Neutrophils

The neutrophils mature in the bone marrow for about 2 weeks before being ready for release into the blood (Bainton et al. 1971). The most striking event in maturation is the formation of the azurophil or primary granules at the promyelocyte stage and the specific or secondary granules later on, at the myelocyte stage. The process can be followed in promyelocytes by cytochemistry of myeloperoxidase which is detected in the rough endoplasmic reticulum where it is produced, in the Golgi apparatus, where

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it is packaged, and in the granules, which are its storage site (Bainton et al. 1971). It is assumed by analogy that all azurophil granule enzymes, including the neutral proteases, which are particularly important in inflammation, are formed and packaged together with the myeloperoxidase, and that specific granules arise in a similar way in myelocytes. When granule formation ceases, the rough endoplasmic reticulum is largely shed and the Golgi apparatus decreases markedly in size. From this stage on the neutrophils are unable to form new granules and gradually acquire the properties that are essential for their function: the ability to migrate in response to chemotactic stimuli, to phagocytose, and to activate the respiratory burst.

3 The Granules

The two granules are easily distinguished in electron micrographs reacted for peroxidase. The electron-dense staining of oxidized diaminobenzidine in the azurophil granules contrasts with the pale, uniform matrix of the specific granules. The biochemical properties of both types of granules were established following subcellular fractionation which also revealed the presence of subcellular storage organelles that are considerably smaller than the granules (Baggiolini 1982; Baggiolini and Dewald 1984). The azurophil granules contain a remarkable series of lytic enzymes including lysosomal hydrolases, three neutral serine proteases (elastase, cathepsin G, and proteinase 3), lysozyme, and myeloperoxidase, which is the only nonhydrolytic enzyme. Proteinase 3 was identified more than 10 years ago (Baggiolini et al. 1978, 1980), and was almost forgotten, when Kao et al. (1988) described its purification. More recently, this serine protease was found to be a major autoantigen in Wegener's granulomatosis (Goldschmeding et al. 1989). The specific granules contain type-I collagenase, lysozyme, lactoferrin, and vitamin B\textsubscript{12}-binding protein(s). Nothing more is known, and it is difficult to speculate about the role of this granule population in neutrophil function. The existence of storage organelles that are distinct from the granules was originally suggested by the subcellular distribution profiles of acid glycosidases (Bretz and Baggiolini 1974). They were later shown to contain cathepsin B, cathepsin D, and proteinase 3 (Baggiolini 1982; Baggiolini and Dewald 1984). In a subsequent study, we found that gelatinase is localized in such small storage organelles (Dewald et al. 1982).

4 Neutrophil Activation

Chemotactic agonists are the stimuli that recruit neutrophils from the blood into infected or inflamed tissues. In the tissues, the neutrophils usually experience a second process of activation induced by particles (e.g., bacteria or immune complexes) which they phagocytose. This second activation event is directed against the offending agent to be eliminated and is considerably more extensive.