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Phagocytosis in mucosal defence

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The recognition that wandering cells play a major role in the protection against infections was established a century ago by Metchnikoff. It was demonstrated that humoral factors like antibodies cooperate with phagocytes to form a defence system of great biological value.

The phagocytic cells in host defence include the neutrophilic and eosinophilic polymorphonuclear leucocytes and the mononuclear phagocyte system. The latter includes the blood monocytes, tissue macrophages etc.

This is a summary of the current state of understanding of the role of polymorphonuclear neutrophilic cells (PMN) in defence of the host against microbes.

PRODUCTION AND DELIVERY OF THE CELLS

The bone marrow is the site of production of the PMN. The most striking feature of the production is its enormous turnover potential. Studies have demonstrated that the average daily output of neutrophils is approximately 10^{11} cells rising by a factor of 5 during bacterial infection. The granulocytes of the blood are distributed between freely circulating cells and marginal pools. These pools are in constant exchange and equilibrate rapidly.

EMIGRATION AND CHEMOTAXIS

The emigration and chemotaxis of neutrophils into inflamed or injured tissues is one of the most fundamental events in the inflammatory response. Emigration includes adherance of the blood PMN to the vascular endothelium especially in the post-capillary venules and subsequently passage through the capillary intercellular spaces.

Once in the extracellular space the movement of cells is directed a process called chemotaxis. The cells are attracted by several substances called chemotactic factors (Table 1). The interaction between microorganisms and host tissues leads to generation of chemotactic factors by several mechanisms. Microbes may generate chemotactic factors directly or indirectly through activation of lymphocytes of leucocytes. By activating either the classical or alternate complement pathways generation of the chemotactic complement products C3A, C5A and C567 occurs.

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Table 1. Chemotactic factors

1. Bacterial products
2. Leucocyte and lymphocyte products
3. Products of the complement, kallikrein and plasmin systems

Especially C5A is strongly chemotactic and attractive to the neutrophil. Also products of the kallikrein and plasmin systems are strongly chemotactic agents.

Chemotactic agents are soluble substances that act on cells from a distance like hormons and interact with the plasma membrane of the cells. Specific receptors on the cells are believed to play an important role in receiving the chemotactic signals. A gradient of chemotactic molecules induces phagocytes to crawl toward sites of infection or injury. Phagocytes move by extending a flattened protrusion called a lamellipodium, with the cell rising above and back of the lammellipodium. Then the cell contents of cytoplasmic granules, vacuoles and nuclei flow into and fill the lamellipodium. This leads again to a protrusion and the entire process is repeated.

In the sinus the phagocytes are in the first line of the host defence. This was elegantly demonstrated by using fluorescens microscopy by Lundberg et al. Early in an infection before the microbial invasion of the sinus mucosa occurs granulocytes start swarming out through the epithelial layer and emerge into the secretion. This means that during a clinical infection in the retained sinus secretion the neutrophil host defence is established before the bacteria have invaded the mucosa.

PHAGOCYTOSIS

Many bacteria, especially nonencapsulated are easily recognized and ingested by neutrophils. However, encapsulated bacteria, for example pneumococci, must be opsonized by specific antibodies and serum complement before phagocytosis. Opsonization make the bacteria aptizing to the phagocytic cell. On the surface of neutrophils are located special receptors for complement (C3b) and the Fc-part of immunoglobulin G.

The molecular process leading to phagocytosis involves actin and myosin. Particle contact with the plasma membrane produces a configuration change in the membrane-associated actin-binding protein. This promotes polymerization and crosslinking of monomeric actin, causing gelation of the actin. Finally myosin binds. The overall effect is the extension of a peripheral pseudopod and invagination of the cell membrane around the microbe resulting in formation of a phagocytic vacuole. ATP provides the metabolic energy for these mechanical events.

MICROBIAL KILLING

Several mechanisms both oxygen-independent and oxygen-dependent lead to the final destruction of the ingested organism (Table II). These mechanisms involve delivery of the lysosomal digestive enzymes into the phagocytic vacuole. Through a coordinated series of metabolic events termed the "respiratory burst" highly reactive oxygen radicals are formed and the killing of the microbe can take place. The killing of certain ingested organisms requires oxygen for production of bactericidal substances like hydrogen peroxide, superoxide anion, hydroxyl radicals and singlet oxygen.

Table 2. Antimicrobial systems of the PMN

oxygen-independent antimicrobial systems:	acid, pH 4
	lysozyme
	lactoferrin
	granular cationic proteins
oxygen-dependent antimicrobial systems:	myeleperoxidase
	H_2O_2
	superoxide anion (02)
	hydroxyl radical (04)
	singlet oxygen

The pO_2 in sinus secretion during purulent sinusitis is low. As O_2 is important for killing it can be concluded that during purulent sinusitis killing of bacteria is significantly impaired. Thus, it seems reasonable to argue that drainage and aeration of the sinus cavity is to be regarded as an important complement to the antibiotic therapy. Reduced pO_2 is one reason for reduced killing, virus is another. Infection with virus reduces both chemotaxis and bacterial killing.

TISSUE DAMAGE

The polymorphonuclear neutrophils are an important part of the host defence. However, the neutrophils can also be destructive. During phagocytosis and so-called frustrated phagocytosis of immunocomplexes, proteases and cationic proteins are liberated-secreted into the tissue. This might cause damage to the tissue.

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