ROLE OF NEUTROPHILS IN HEALTH AND DISEASE

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ABSTRACT

Neutrophils are phagocytic cells so named because of their neutral staining with Wright stain, which act primarily by engulfing and degrading bacteria, cellular debris and other particulate matter. Polymorphonuclear leukocytes or neutrophils are the cellular hallmark of an acute inflammatory response. Neutrophils are circulating leukocyte in humans and play a fundamental role in the innate immune response. Neutrophils are the most abundant leukocyte within the periodontal tissues in early and chronic periodontal lesions. The concentration of neutrophils in the periodontal tissues exceeds that of blood. Neutrophils protect against periodontal disease by modulating chronic inflammation through the release of factors perhaps identical to factors with antimicrobial roles which suppress (and augment) lymphocyte and monocyte activity. In conclusion patients with neutrophil dysfunction are more susceptible to gingival disease and to ulceration of the oral mucosa.

Key Words: Neutrophil, PMN, Leukocyte,

INTRODUCTION:

The human body has many ways to protect itself. Some are simply physical barriers like the skin is tough, outer keratin layer that shields the living cells beneath it from a hostile environment. Others are potent biochemical substances that offer relatively non-specific protection against a broad range of microorganisms. A more elaborate chemical barrier is provided by the groups of blood proteins that together make up the complement pathway, these proteins mediate a cascade of enzymatic reactions that can be triggered by molecular features on the surfaces of some microorganisms, which may ultimately lead to lysis or enhanced phagocytosis of the foreign body. But specialized cells that travel through the body to search out and destroy microorganism and other foreign substances carry out by far the most complex, dynamic and effective defense strategies. In human beings, three major groups of cells provide these types of defense.

They are the neutrophils, monocyte-macrophages and lymphocytes. Two of these the neutrophils and the monocyte-macrophage series are phagocytic cells, which act primarily by engulfing and degrading bacteria, cellular debris and other particulate matter. The third group, which comprises the lymphocytes and their relatives, has phagocytic capacity but instead participate in a host of other protective responses/reactions that are collectively known as immune responses.

Neutrophils are the most abundant circulating leukocyte in humans and play a fundamental role in the innate immune response. Neutrophil abundance, coupled with their brief (6-8h) circulating half life, mandates a basal rate of production by the bone marrow of $5 \times 10^{10} - 10 \times 10^{10}$ neutrophils/day; the advantage to the host
of this rapid turnover is uncertain. Neutrophil homeostasis is maintained by a fine balance between granulopoiesis, bone marrow storage and release, intravascular margination clearance and destruction. Neutrophils are short lived, non-mitotic cells generated in large numbers from pluripotential stem cells residing in the bone marrow. Neutrophils are so named because of their neutral staining with wright stain. They are also known as PMN or polys or microphages (neutrophils leave the blood, they always retain their small size).

Neutrophils are the most abundant leukocyte within the periodontal tissues in early and chronic periodontal lesions. The concentration of neutrophils in the periodontal tissues exceeds that of blood. In minimally inflamed gingival, $2.5 \times 10^7$ PMN/cm$^3$ infiltrate the connective tissues and $1.7 \times 10^8$ PMN/cm$^3$ are found at junctional epithelium.

Bacteria and their products interact with gingival epithelium, the first physical barrier to microbial pathogens, to induce an inflammatory response consisting of cytokines, chemokines and antimicrobial protein production and subsequent recruitment of neutrophils. Neutrophils have multiple surface receptors that enable them to bind to and phagocytize bacteria once they reach the site of infection. Serum factors called opsonins help trigger this process. Once engulfed, the bacteria are exposed to the neutrophil’s intracellular killing process.

Defects in any of the functions or a marked decrease in the number of neutrophils capable of responding to the site of infection may result in varying degrees of susceptibility to infection. These qualitative and quantitative defects may be inherited, acquired or drug induced. The oral manifestations associated with a decrease in the number of circulating neutrophils are well documented and include mucous membrane infections, gingivitis and periodontitis. Conditions like agranulocytosis, congenital or cyclic neutropenia and leukaemia result in severe break down of the oral tissues. In conclusion patients with neutrophil dysfunction or well-defined abnormalities of neutrophils are more susceptible to gingival disease and to ulceration of the oral mucosa.

**HISTORY**

As the primary circulatory phagocytic cells, neutrophils play a key role in host defense against extracellular bacteria, especially pyogenic bacteria. The importance of these cells in combating infections disease is demonstrated through the increased susceptibility to recurrent bacterial infections observed in patients with defective neutrophil production or function. The importance of neutrophil in the defense against periodontal infection has also been strongly supported by studies of Localized Aggressive Periodontitis. Neutrophil abnormalities have been demonstrated in patients with L.J.P as well as in those with rapidly progressive forms of periodontitis. Neutrophils function is a two-edged sword, although they are primarily protective, they also can act as proinflammatory cells capable of causing significant destructions.

**NEUTROPHIL DEVELOPMENT:**
In normal adults neutrophils are found in the bone marrow, blood and tissue. In the bone marrow neutrophils undergo development and proliferation from blast cells through promyelocytes to myelocytes. After the myelocytes stage the cells become metamyelocytes, “Band” cells. These cells are released from the marrow into the blood where they remain for about 10 hours. They then migrate into the tissues where they survive for only one or two days. This migration is either random or in response to specific chemical signals called chemoattractants.

**FORMATION OF POLYMORPHONUCLEAR LEUCOCYTES**

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<th>Bone marrow</th>
<th>Blood</th>
<th>Tissues</th>
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<td>Precursors</td>
<td>Proliferating</td>
<td>Mature/storage</td>
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<tr>
<td><a href="#">CFU-GEMM</a></td>
<td>myeloblast</td>
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<tr>
<td>CFU-GM</td>
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**NEUTROPHIL FUNCTION:**

The polymorphonuclear leukocyte and monocyte/macrophage constitute the main phagocytic cell system in mammalian host defense against infecting agents.

These cells of myeloid lineage perform a wide variety of functions including engulfment of micro-organisms, secretion of lytic enzymes, and release of mediators responsible for co-ordination of the inflammatory response, as well as tissue repair and remodeling. The initial recruitment of circulatory phagocytes is prompted by the expression of integrin and selectin class adhesion molecules on capillary endothelial cells. (ICAM-1, ICAM-2, and ELAM-1) for which neutrophils have specific receptors (CR3, LFA-1, and CR4). Neutrophils then progress towards a gradient of increasing levels of signaling molecules.
(Chemotaxis), which include both endogenous chemoattractants, like complement component C5a and interleukin-8 (IL-8), and exogenous elements such as bacterial protein synthesis-signaling peptides, characterized by N-formyl-l-methionyl-l-leucyl-l-phenylalanine (FMLP).

**ADHERENCE:**

This process involves Margination and attachment of the PMN to vascular endothelium via specific molecules present on the surface of the PMN and the endothelial cell. The surface of the neutrophil is coated with surface adhesions. Many cell interactions are dependent on binding of cells to each other or to a substrate. These interactions are controlled by receptors on the surface of the immune cells and ligands on other cells or on the substrate, called adhesion molecules.

There are four main groups of adhesion molecules:

1. Integrins;
2. Adhesion molecules of the immunoglobulin supergene family;
3. Lectin-like adhesion molecules;
4. The CD44, or Hermes group, which interact with ligands called addressins on vascular endothelium.\(^7\)

**CHEMOTAXIS:**

Chemotaxis is directional migration of leukocytes along a chemical gradient. The neutrophils travel to the site of microbial injury in response to specific chemical agents (chemoattractants). Typically, healthy periodontal tissues are characterized by a paucity of inflammatory cells within the connection tissues. However, polymorphonuclear leucocytes neutrophils are commonly found during the junctional epithelium and separate bacterial plaque from the tissues.

**MARGINATION:**

This process takes place most commonly in post capillary venules, small, thin-walled vessels in which blood flows relatively slowly –and results from changes not only in the neutrophil but also in the local endothelial cells.

**EMIGRATION**

Once attached, neutrophils actively line themselves along the endothelial cells to migrate out of the venule and into the adjacent tissue in a process termed *emigration*. The neutrophil then travel by ameboid motion up the concentration gradient of chemotactic factors until they arrive at the focus of the injury or infection.

**OPSONIZATION:**

Many types of particles including most species of encapsulated bacteria do not interact effectively with any cellular receptor and hence cannot be phagocytized directly. However, phagocytosis of such particle can occur when their surface are coated with certain host-derived proteins. Proteins that have this ability to enhance phagocytosis are known as **opsonins**.

**PHAGOCYTOSIS**

On arrival at an injured site, neutrophils immediately begin the process of engulfing any bacteria, cellular debris, or foreign particular matter in the area.
NEUTROPHIL DEFECTS AS RISK FACTORS FOR PERIODONTAL DISEASES:

The host response to pathogenic microorganisms involves a complex array of interaction between numerous cellular and humoral components of the immune system. Host responses operative in periodontal diseases have been reviewed by Genco et al and others studies of host response in periodontal diseases have pointed clearly to the PMN, as the key productive cell, which made normal circumstances, limits the pathology caused by periodontal organisms. The neutrophil does not act alone but operates as part of a neutrophil antibody – complement axis that exerts a protective role against Gram negative organisms, which are important in periodontal diseases.

Observations from human and animal disease states demonstrate that defective neutrophil function is associated with the presence of periodontal destruction associated with neutrophil abnormalities were reported as early as 1902. A number of naturally occurring conditions in individual with inherently depressed neutrophil function, such a Cyclic neutropenia and Chediak – higashi syndrome, have been shown to be associated with periodontal destruction.

The second line of evidence implicating the neutrophil as a major protective cell against oral bacterial pathogens is the observation that several periodontopathic bacteria have significant anti-neutrophil virulence factors. Porphyromonas
gingivalis and A. actinomycetemcomitans are leukoaggressive; i.e., they produce toxins and other factors, which either reduce neutrophil function or kill neutrophils.\(^{11,12}\)

**Leucocytes in the dentogingival area and saliva**

Leucocytes found in clinically healthy gingival sulci are predominantly neutrophils. In healthy human gingival sulci, they are found to be 91.2% to 91.5% and mononuclear cells are only 8.5 to 8.8%.

It is interesting to note that the main portal of entry of leucocytes into the oral cavity is the gingival sulcus. The majority of these cells is viable and has been found to have phagocytic and killing capacity. Therefore, they constitute a major protective mechanism against extension of plaque into the gingival sulcus.

pH changes in the periodontal environment could alter the balance between the host and bacteria, even though pH is one of the many factors, the PMNs are exposed to. Studies on pH changes are useful for giving insight into the determinants of PMN activation at diseased periodontal sites.

In addition to desquamated epithelial cells, the saliva contains all forms of leucocytes, the majority being PMNs. The number of leucocytes varies from person to person and at different times of the day. Living PMNs in saliva are sometimes referred to as 'Orogranulocytes'. The rate of their migration into the oral cavity is termed the 'Organulocytic' migratory rate. Skougoard in 1994 proposed that the rate of migration is correlated with the severity of gingival inflammation and is hence a reliable index for assessing gingivitis.\(^{13}\)

**CONCLUSION**

Several lines of evidence suggest that phagocytic cells, especially polymorphonuclear neutrophils, play an important role in maintaining the health of periodontal tissues. The intact neutrophil function is important in determining host resistance to periodontal disease. Severe periodontal disease has been reported among young patients with cyclic or "benign" neutropenia and agranulocytosis.

Neutrophils and macrophages are critical in host defense against bacterial infection. There is a strong relationship between altered PMN activity and localized juvenile periodontitis. Neutrophils use a variety of unique mechanisms to kill microorganisms. The ability of neutrophils to reduce oxygen to superoxide, hydrogen peroxide and several other O2 reduction products. The defective host response, in terms of neutrophil function, can result from an underlying genetic defect as in LJP, or bacterial virulence factors that circumvent or modify normal neutrophil function.

Therapeutic interventions, therefore, would focus on correcting inherited defects or preventing the actions of the bacteria on the neutrophil.

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