

A New Turn in Aeon Duration of Periodontal Disease Neutrophil Priming

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Abstract: Periodontal disease is a complex infectious disease resulting from interplay of bacterial infection and host response to bacterial challenge and the disease is modified by environmental, acquired risk factors and genetic susceptibility.

Neutrophil priming is a relatively new concept, and its role in the pathophysiology of different forms of periodontal diseases is still unclear. With advances in our understanding of neutrophil biology, various intracellular signaling pathways and mechanisms of tissue destruction, greater insights into the periodontal pathogenesis can be gained.

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I. Introduction:

Periodontitis is defined as an inflammatory disease of supporting tissues of teeth caused by specific microorganisms or group of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar with periodontal pocket formation, gingival recession or both.¹

Periodontal disease is a complex infectious disease resulting from interplay of bacterial infection and host response to bacterial challenge and the disease is modified by environmental, acquired risk factors and genetic susceptibility.²

Bacteria grow in complex polymicrobial associations known as biofilms attached to biotic or abiotic surfaces. As a surface becomes colonized with individual cells, the bacteria form microcolonies, which then secrete a sticky extracellular polymeric substance that helps the bacteria adhere to the surface, and to each other. Upon secretion of the extracellular polymeric substance, the biofilm matures by becoming larger and taking on a distinctive architecture.³ Usually, this structure includes separate regions of fast- and slow-growing cells, water channels that circulate metabolites, and the establishment of nutrient gradients. Such complex structural organization allows the biofilm to exhibit functional heterogeneity which allows biofilm to demonstrate tremendous metabolic and phenotypic flexibility. This confers several new characteristics and advantages of the biofilm.

NEUTROPHIL HOMEOSTASIS : NETOSIS:

Neutrophils are an essential component of the innate immune response and a major contributor to inflammation. Consequently, neutrophil number in the blood is tightly regulated. Accumulating evidence shows that stromal derived factor-1 (CXCL12) through interaction with its major receptor CXCR4 provides a key retention signal for neutrophils in the bone marrow. Granulocyte colony-stimulating factor induces neutrophil release from the bone marrow, in major part, by disrupting stromal derived factor-1/CXCR4 signaling. Granulocyte colony-stimulating factor expression is regulated by a novel feedback loop that senses neutrophil emigration into tissues. Specifically, engulfment of apoptotic neutrophils by tissue phagocytes initiates a cytokine cascade that includes interleukin-23, interleukin-17, and ultimately granulocyte colony-stimulating factor.⁴ Granulocyte colony-stimulating factor plays a central role in the dynamic regulation of neutrophil production and release from the bone marrow in response to environmental stresses. Recent studies have begun to elucidate both the pathways linking neutrophil clearance to granulocyte colony-stimulating factor expression and the mechanisms by which the factor induces neutrophil release from the bone marrow.

Neutrophils are short-lived granulocytes that play a pivotal role in the initial defence against invading pathogens in mammals. Neutrophils, recruited to the site of infection, effectively kill microorganisms by phagocytosis, degranulation, and generation of reactive oxygen species (ROS).⁵ In certain conditions, neutrophils enhance their antimicrobial properties by releasing neutrophil extracellular traps (NETs), composed of extracellular chromatin decorated with histones and numerous granular proteins. Many of these granular components like myeloperoxidase (MPO), α -defensins, elastase (NE), cathepin G, and lactoferrin, have bactericidal activities capable of eliminating microorganisms and/or their virulence factors. Uncontrolled inflammatory response during sepsis is the proposed underlying cause of excessive NET formation.⁶ Increasing

experimental and clinical evidence indicates that overzealous NET formation during sepsis can lead to the development of multiple organ dysfunction highlighting the pathophysiological role of NETs in sepsis. This review aims to summarize the recent knowledge on the underlying mechanisms of NET formation in varied species, as well as, the beneficial and detrimental effects of NETs found in various septic animal models.

As sentinel cells of innate immunity, neutrophils can respond to many pathogens or their associated molecular patterns by releasing NETs. "NETosis" is the term commonly used to describe the sequence of cellular events leading up to the active release of NETs. Similar to other forms of cell death such as apoptosis or programmed cell death and necroptosis, a regulated form of necrosis, NETosis is a highly regulated process.⁷ Dysregulation of NETosis found in many disease states like sepsis, can result in collateral damage to the host. The cellular mechanisms mediating the release of NETs, however, remain poorly understood. Brinkmann et al. and Fuchs et al. first documented *in vitro* NETosis in human neutrophils using the potent protein kinase C activator, phorbol 12-myristate 13-acetate (PMA). Following PMA stimulation, human neutrophils undergo morphological changes including chromatin decondensation, loss of nuclear envelope, mixing of nuclear contents and cytoplasmic granular proteins, loss of membrane integrity and, ultimately, release of cell free DNA (cfDNA) (18). A recent *ex vivo* study by the authors documented similar morphological changes in PMA-activated canine neutrophils indicating that dog neutrophils may undergo suicidal NETosis.⁸

PRIMING CAUSES AND EFFECTS:

Neutrophil priming was described by McPhail *et al.* in the early 1980s, as "the ability of a primary agonist, typically at substimulatory concentration, to influence/enhance superoxide production triggered by a secondary stimulus." A priming agent is a substance that by prior exposure enhances the response of a neutrophil to an activating stimulus. In a resting normal circulating neutrophil, the microbicidal capacity is very low when exposed to activating agents. Once exposed to specific priming agents, this capacity is enhanced several folds. These agents do not express the priming function on their own and have to be in contact with the cell for specific period to prime it.⁹

Two separate mechanisms have been proposed for priming. Rapid priming occurs within minutes of being stimulated. The short duration of response is as a result of transfer and release of preexisting intracellular granules with preformed receptors to the plasma membrane. In this type of priming, there is no active synthesis of proteins, just an increase in the number and affinity of cell surface receptors. Delayed priming takes more time as compared to rapid priming. Here, the priming agent causes an activation of transcription factors which results in the active synthesis of new protein molecules (including receptors and cytokines).¹⁰

NEUTROPHIL PRIMING AND PERIODONTITIS:

Periodontitis is a chronic inflammatory condition affecting the structures surrounding the tooth. As it progresses, neutrophil extravasation and accumulation at the site of inflammation is seen. The knowledge of central role which the neutrophil plays in the host response fuelled the idea that it may play a crucial role in the progress from periodontal health to disease. The initial reports in this regards reported that conditions such as Chediak-Higashi Syndrome and Lazy leukocyte syndrome were associated with early and severe periodontal infection, bone loss, tooth mobility, and tooth loss.¹¹ These are disorders with primary neutrophil deficiency. Other conditions associated with secondary neutrophil impairment such as Down's syndrome, Papillon-Lefevre syndrome, and inflammatory bowel disease also demonstrate an increased risk and significant amount of periodontal destruction. Furthermore, disorders directly involving the functioning of neutrophils such as leukocyte adhesion deficiency type I and II demonstrate severe tissue destruction. It has been observed that induced neutropenia and primary neutrophil abnormalities may lead to rapid periodontal infection. These observations highlighted the importance that altered neutrophil function may play in the pathogenesis of periodontal diseases.¹²

The increase in the amount of oxidative burst products produced and released from both resting and stimulated cells is the hallmark of a primed neutrophil. Such products include superoxide, hydroxyl radicals, and hydrogen peroxide. These parameters have been studied in the several studies. In a study, no significant difference between the priming between healthy and chronic periodontitis was observed. Another study demonstrated increased Fc gammaR-mediated chemiluminescence of peripheral neutrophils in chronic periodontitis patients as compared to controls. This study found that unstimulated chemiluminescence by neutrophils is more in aggressive periodontitis patients compared to chronic periodontitis patients. Another study reported that neutrophils from chronic periodontitis patients release more reactive oxygen species as compared to controls in both stimulated and unstimulated scenario. Neutrophils exposed to *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* neutrophils from chronic periodontitis patients released significantly more reactive oxygen species when compared patients with aggressive periodontitis. Poor glycemic control has also been shown to enhance the production of superoxide radical suggesting an underlying priming

response. Conflicting results have been obtained stating no change or decrease in oxidative burst products in both chronic and aggressive forms of periodontitis are present.¹³

II. Conclusion:

Priming of neutrophils is one of the vital processes which regulate the intensity of response of neutrophils at the site of inflammation. It can also modulate and enhance the neutrophil response at an inflamed site. Neutrophil priming is a relatively new concept, and its role in the pathophysiology of different forms of periodontal diseases is still unclear. With advances in our understanding of neutrophil biology, various intracellular signaling pathways and mechanisms of tissue destruction, greater insights into the periodontal pathogenesis can be gained.

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