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New Fangled Avatar of Neutrophils and its Role in Periodontitis

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Abstract: ***Periodontitis is associated with several factors, such as smoking, diabetes, age, and immune deficiency. Current studies support that periodontitis is initiated by periodontal bacteria, and neutrophils are the primary immune cells recruited to exert an antibacterial effect. There is a reciprocal interaction between the microbiota and the immune system which breeds a feed forward loop wherein each entity fortifies each other. The inflammation caused due to the microbiota creates a nutrient rich ambience for the microbes and the thriving microbe amplifies the inflammation causing progressive damage to the tissues. Neutrophils are myeloid leukocyte cells forming the initial fire wall between the microorganisms and the cells acting as executive phagocytes. Neutrophils were thought to be a part of acute conditions only, recent studies have started to reveal that they also play pivotal role in regulating adaptive immunity and perform other functions such as reverse transmigration, immunoregulation, angiogenesis and fibrogenesis. Therefore, preventing bacterial evasion might be a potential preventive action and opens up new therapeutic modalities for treatment of periodontitis This article elaborates on recruitment of neutrophils and its homeostasis, the antimicrobial mechanisms, evasion strategies of microbes against neutrophils and new developments related to it and its relation to periodontitis.***

Keywords: neutrophils, periodontitis, transmigration, immunity, phagocytosis

1. Introduction

A glitch in the pathways of communication between the molecules of innate and acquired immunity caused due to a transition in the periodontal microbiota from symbiotic state to a more dysbiotic condition results in periodontal inflammation and destruction. There is a reciprocal interaction between the microbiota and the immune system which breeds a feed forward loop wherein each entity fortifies each other. The inflammation caused due to the microbiota creates a nutrient rich ambience for the microbes and the thriving microbes amplify the inflammation causing progressive damage to the tissues.

Some of the major cells involved in periodontal inflammation include the neutrophils, complement system, Tcells and macrophages. Neutrophils are myeloid leukocyte cells forming the initial fire wall between the microorganisms and the cells acting as executive phagocytes. They are an integral part of the innate system that initially strive to create a mutualistic relationship between the microorganisms until they attain a dysbiotic state, after which the neutrophils become hyperactive and start causing collateral damage to the tissues.

Neutrophils were thought to be a part of acute conditions only, recent studies have started to reveal that they also play pivotal role in regulating adaptive immunity and perform other functions such as reverse transmigration, immunoregulation, angiogenesis and fibrogenesis. There have been developments in the etiology of leukocyte adhesion deficiency, inhibitors of leukocyte adhesion receptors, genetic characteristics of neutrophils and how neutrophils are dysregulated due to metabolic dysfunctions. This article elaborates on recruitment of neutrophils and its homeostasis, the antimicrobial mechanisms, evasion strategies of microbes against neutrophils and new developments related to it and its relation to periodontitis.

Recruitment of Neutrophils

Neutrophil recruitment entails the following steps

- Tethering and rolling
- Adhesion
- Crawling
- Transmigration

Tethering and rolling

Microbial insult results in release of inflammatory mediators and pattern recognition receptors which result in activation of surface adhesion molecules by the endothelial cells which in turn commences the recruitment process.[1] Blood neutrophils are tethered to the surface of vascular endothelial cells by the binding of E- and P-selectin to their receptor P-selectin glycoprotein ligand 1 (PSGL1), which then causes the cells to roll down the vessel wall.[2]

Adhesion and Crawling

Neutrophils can more easily interact with chemokines deposited on the endothelium when rolling along the channel. When oral pathogens come into touch with the junctional epithelium surrounding the teeth, they produce a chemotactic interleukin-8 (IL-8) gradient.[3]CXCR1 and CXCR2 are two receptors expressed by neutrophils for IL-8. The binding of IL-8 to CXCR1 is associated with chemotaxis and bond with CXCR2 results in neutrophil activation and adhesion to endothelium. Once the adhesion is finished, neutrophils crawl along the endothelium to search for an appropriate exit. The crawling of neutrophils is directional and controlled by an intravascular chemokine gradient.[4]

Transmigration

Before transmigration of neutrophils commence, the vessels prepare themselves to prevent vascular leakage that can occur during the process. There is formation of endothelial actin structure initiated by RhoA surrounds the neutrophils that contain intercellular adhesion molecule 1 (ICAM1)

clusters which help exit the neutrophils through the endothelial layer without causing any vascular leakage.

The neutrophils after passing through the endothelial layer encounter the pericytes and vascular basement membrane, and they release proteases to migrate this layer.[5]Then, neutrophils move towards the pathogens following the chemoattractant gradients, such as IL-8, N-formyl-methionyl-leucyl phenylalanine (fMLP), C5a, and leukotriene B4 (LTB4).[6]

Reverse transmigration, or the movement of transmigrated neutrophils from one area of the body to another, is an intriguing possibility that may allow these cells to re-enter circulation. This mechanism is believed to play a role in the spread of systemic inflammation.

Neutrophil Homeostasis

A system known as a "neutrostat" or neutrophil rheostat assesses the recruitment and clearance of neutrophils in peripheral tissues and, in mice at least, controls granulopoiesis through a negative-feedback loop involving a cascade of cytokines, specifically the IL-23–IL-17 G-CSF axis.[7] In particular, anti-inflammatory signals are triggered when tissue phagocytes phagocytose apoptotic neutrophils, which restricts their ability to produce IL-23, a crucial cytokine that innate and adaptive immune cells use to induce IL-17. Cells such as fibroblasts produce less G-CSF as a result of the suppression of IL-17 production that follows.

Until recently, nothing was known about locally produced, negative regulators of this inflammatory process, in contrast to the abundance of adhesion molecules that have been identified as supporting the various steps of neutrophil extravasation.[8]

Newly identified, endogenous inhibitors of the leukocyte adhesion cascade include
Del-1,
pentraxin 3,
growth-differentiation factor 15

Developmental Endothelial Locus-1: homeostatic regulation of neutrophil production and recruitment
Del-1 (also known as epidermal growth factor-like repeats and discoidin I-like domain 3) is an endothelial, cell-secreted, 52-kDa glycoprotein that acts as an antagonistic ligand of the LFA-1 and Mac-1 integrins.[9]

Indeed, Del-1 inhibits neutrophils' LFA-1-dependent endothelium adherence, in contrast to ICAM-1, which combines with LFA-1 to enhance neutrophil extravasation. Crucially, Del-1 outcompetes ICAM-1 for binding to LFA-1 at equimolar concentrations.

Leukocyte Adhesion Deficiency
Leukocyte adhesion deficiency type 1 is an autosomal recessive immunodeficiency disorder caused by mutations in the ITGB2 gene that encodes CD18, the common beta2 integrin subunit.Because beta2 integrins are necessary for strong neutrophil attachment to the vascular endothelium and subsequent transmigration to infected or inflammatory sites, individuals with this condition have reduced or absent CD18 expression, which leaves few or no neutrophils in the periodontium or other peripheral tissues. Individuals with leukocyte adhesion deficit type 1 frequently experience severe periodontitis, which can result in the early loss of all teeth, and recurring bacterial infections, mostly in the skin and mucosal surfaces.[10]

It has long been believed that decreased neutrophil defense against bacterial infection in the periodontium causes leukocyte adhesion deficiency type 1–associated periodontitis. Recent research has connected dysregulated overactivation of the interleukin-23/interleukin-17 inflammatory axis in the periodontium to impaired neutrophil recruitment. This is based on mechanistic experiments in relevant mouse models and clinical and laboratory studies using tissues and immune cells from patients with leukocyte adhesion deficiency type 1.[11]

In mice with a phenotype similar to leukocyte adhesion deficit type 1, local antibody-mediated neutralization of interleukin-17 or interleukin-23 prevented periodontal inflammation and bone loss while also reducing the microbial load.

In a patient with human leukocyte adhesion deficiency type 1, systemic administration of an antibody (ustekinumab) that blocks the common p40 subunit of interleukin–23 and interleukin–12 resulted in resolution of inflammatory periodontal lesions and healing of a severe sacral wound, which also featured elevated expression of interleukin–17. Elevated levels of IL-17 contribute to inflammatory periodontal bone lossby stimulating osteoblast expression of RANKL, a major osteoclastogenesis factor and thought to have direct stimulatory effects on osteoclastogenesis. Moreover, neutrophils release tissue-degrading enzymes, such as collagenase, which is involved in the initiation of bone resorption.TLR-activated neutrophils express membrane-bound RANKL and can stimulate osteoclastogenesis.[12]

Antimicrobial Mechanisms
- Phagocytosis
- Degranulation
- Oxidative burst
- Netosis

Phagocytosis
PMNs are the first line of defense against pathogenetic microorganisms that are external, and they react quickly to bacterial stimuli. Oral neutrophils from patients with late-onset periodontitis create higher ROS and have more phagosomes.[13] Pathogens opsonized by complement and/or IgG and non-opsonized pathogens are phagocytosed by PMNs, which are regulated by cytokines, chemokines, and cellular adhesion molecules (CAMs) as they pass through the vascular endothelium following adhesion and chemotactic effect.

The opsonization of bacteria with complement or antibodies can greatly increase the phagocytic function. Neutrophils take up bacteria and produce phagosomes, which are intracellular vacuoles. Subsequently, ROS and granule-

stored antimicrobial compounds trigger the intracellular antimicrobial response. [14]

Oxidative burst Response

The oxidative burst response, which activates the NADPH oxidase complex and results in increased oxygen consumption and ROS production, is a useful tactic for eliminating infections.[15]The NADPH oxidase enzyme system is made up of many proteins, including the flavocytochrome b588 protein, the cytosolic components p40PHOX, p47PHOX, and p67PHOX, and the small GTPase(s) Rac 1 or Rac 2. The NADPH oxidase complex is disassembled and inactive in neutrophils that are at rest. The individual parts of the enzyme complex with a catalytic activity are translocated to the membrane upon.[16]

The produced ROS NADPH oxidase complexes assemble on the plasma membrane in response to soluble stimuli, releasing generated ROS into the extracellular space; on the other hand, in response to particulate stimuli, like pathogens, the complexes assemble on the membrane of the phagosome, which contains particles, releasing generated ROS into the phagosome.[16] ROS can directly inflict oxidative damage on microorganisms by oxidizing methionine residues, lipid peroxidation, base oxidation and deamination, and breaking DNA strands.[17]

Degranulation

Increased levels of degranulation markers have been found in patients with periodontitis, confirming degranulation in the disease. Mature PMN granules include a variety of proteins, both peroxidase-positive and peroxidase-negative in histochemical classification, that serve as the host's antimicrobial defense. Both integral membrane proteins and matrix contents can be used to functionally differentiate granules.[18] Granules come in four varieties that can either undergo exocytosis to release matrix contents or assemble in phagosomes that contain bacteria. Secretory vesicles are the most easily exocytosed, and they are followed in order by gelatinase granules, particular granules, and azurophil granules. hCAP-18, lysozyme, metalloproteases (MMPs), myeloperoxidase (MPO), proteinase-3, cathepsin G, and elastase are only a few of the antimicrobial peptides found in granules.[19]

Neutrophil extracellular traps (NETs) in periodontal pockets

The granule proteins (elastase, cathepsin G, myeloperoxidase, bactericidal/permeability-inducing protein [BPI], lactoferrin, peptidoglycan recognition proteins, and MMP-9) that bind and kill bacteria and other pathogens as well as destroy microbial virulence factors, presumably through proteolytic means, are combined with extracellular, neutrophil-derived chromatin fibers to form NETs.[20]

It has long been recognized that a number of oral infections release substances that can compromise the immune system. The identification of NETs offers an avenue for innate cells to "fight back," or to disrupt extracellular bacterial virulence factors.

NETosis, a different method of eukaryotic cell death, is another way that NETs may regulate the lifespan of innate cells. In periodontal pockets, a large number of NETs with trapped bacteria are visible (pocket surface, GCF and pus).[21]

The significance of neural epithelial cells (NETs) in modifying the interactions between pathogens and hosts is still being investigated, as is their potential to prevent periodontal disorders. NETs, on the other hand, are evidently present in periodontal crevices, and it has also been suggested that bacteria that make DNAses that can break down the chromatin NET backbone would be more pathogenic than those that do not.

Furthermore, bacteria that produce DNAase may aid in the development of a pathogenic plaque biofilm. It is anticipated that the upcoming years may yield intriguing new information on the function of NETs in maintaining periodontal health and the potential evolution of tactics by periodontal pathogens to thwart NET-mediated bacterial death.

Evasion of Neutrophil-Mediated Destruction by Periodontal Pathogens

- Inhibition of recruitment
- Preventing phagocytosis
- Uncoupling killing from inflammation
- Resistance to ROS mediated killing
- Resistance to granule mediated killing
- Evasion of killing by nets

Inhibition of recruitment

P.gingivalis is known for its ability to evade the immune response. The main evasion strategy is by inhibiting the recruiting of neutrophils.When P. gingivalis invades epithelial cells, it secretes SerB, which prevents NF-κBfrom activating and reduces the generation of IL-8. P. gingivalis secretes gingipains that have the ability to degrade IL-8.[22] P. gingivalis LPS has the ability to suppress E-selectin expression, which is required for neutrophil-endothelium contact.

P. gingivalis and F. nucleatum bind nonchemotactic bacterial peptides to fMLP receptors, hence inhibiting fMLP-induced chemotaxis. T. denticola is one of the organisms that can both degrade and decrease the synthesis of IL-8. Actin rearrangement can be inhibited by T. denticola's main outer sheath protein (Msp), which stops neutrophil recruitment.[23]

Porphyromonas peptidylarginine deiminase (PPAD), arginine-specific gingipain (Rgp), capsule, exopolysaccharides (EPS), and Msp contribute to periodontal pathogen evasion from neutrophilic phagocytosis.[3]

Uncoupling inflammation from killing:

P. gingivalis coactivates the C5a receptor (C5aR) and TLR2/1 complex, which releases TGF-β1, which in turn causes E3 ubiquitin ligase Smurf1 to ubiquitinate Myeloid Differentiation Primary Response Protein 88 (MyD88) in preparation for degradation.[24]Furthermore, TLR2/1 and C5aR co-activation activates PI3K, which inhibits small GTPase RhoA to prevent phagocytosis and trigger an inflammatory response. P. gingivalis stimulates intracellular

Ca2+ signaling and C5a receptor-1 in macrophages, which together strengthen the toll-like receptor-2 activation alone's weaker cAMP responses. As a result, nuclear factor-kappaB and glycogen synthase kinase-3beta are inhibited, which suppresses inducible nitric oxide synthase-dependent pathogen death. This is achieved by activating the cAMP-dependent protein kinase A.

Resistance to ROS-mediated killing

By producing rubrerythrin and upregulating the expression of the genes PG1777, PG_RS02100, PG1660, and P. gingivalis redox-sensing protein (PgRsp), P. gingivalis evades ROS-mediated death. Superoxide dismutase (SOD), which catalyzes the conversion of superoxides into hydrogen peroxide and molecular oxygen, is expressed by P. gingivalis and F. nucleatum. F. alocis also prevents the generation of ROS.[25]

Resistance to granule-mediated killing

T. forsythia is capable of degrading serine proteases (elastase and cathepsin G) via proteolysis and LL-37 by karilysin, mirolase, and mirolysin.[26] Bacterial resistance to LL-37 can be enhanced by P. gingivalis outer membrane protein A-like proteins (OmpALPs), which can decrease LL-37 accumulation on the bacterial surface. Metalloproteases (MMPs) are degraded by the gingipains that P. gingivalis secretes. Granule recruitment to bacteria-containing phagosomes can be inhibited by F. alocis.[27]

Evasion of killing by NETs

Numerous periodontal bacterial species can secrete DNase to damage the DNA backbone of NETs. In addition, *P. gingivalis* can inactivate antimicrobial components (neutrophil elastase, cathepsin G, and LL-37) of NETs by expressing gingipain. *P. gingivalis* also expresses PPAD to citrullinate histone H3.[28]

Gene Activity in Neutrophils

Neutrophils are both transcriptionally and translationally active while they are in the bone marrow. Neutrophils are equipped with a vast arsenal of pre-formed signaling and anti-microbial chemicals, kept in granules, during this "differentiation program". Every day, somewhere between 5 and 10 × 1010 new neutrophils are created. After roughly 14 days of differentiation, neutrophils—which are generally thought of as transcriptionally inactive cells—enter the circulation as mature, virtually terminally differentiated cells.[29]

But according to new research, neutrophils go through a second surge of transcriptional activity when they leave the vasculature toward inflammatory or infected regions, like the periodontium. This process is known as the "immune response program."[20]The main translational products of the immune response program are cytokines and chemokines, which are chemicals that control inflammation resolution and aid in healing. The immune response program makes periodontal neutrophils capable of de novo manufacture of several components that may influence disease progression, even if the significance of neutrophil gene activity in the periodontal tissues has not yet been determined. Stated differently, periodontal neutrophils do not, as previously believed, rely exclusively on the contents of their granules for their functional needs.

2. Conclusion

A number of variables, including age, immunological deficiencies, diabetes, and smoking, are linked to periodontitis. According to recent research, periodontal bacteria cause periodontitis, and the main immune cell that is brought in to fight germs is the neutrophil. Neutrophils have been shown to exhibit a number of antimicrobial patterns, such as phagocytosis, degranulation, respiratory burst response, and NET formation. But periodontal bacteria have developed defense mechanisms against neutrophil-mediated apoptosis, which keeps inflammation alive. Both the inflammatory and antibacterial components have the potential to cause significant tissue damage when the inflammation worsens. Consequently, blocking bacterial evasion presents novel therapeutic options for the management of periodontitis and may be a useful preventive measure.

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