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The Emerging Role of Neutrophil Extracellular Trap in Dental Implant

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Abstract: An inflammatory reaction is elicited by implants, which is critical for osseointegration. During the first phase of osseointegration, leukocyte-infiltrated blood coagulum fills the gaps surrounding implants. Reactive oxygen species are produced when polymorphonuclear neutrophils are quickly drawn to inflammatory areas and have been demonstrated to adhere to artificial implant surfaces in a matter of minutes. Neutrophils release their own DNA in response to infection and inflammation; this process is known as "neutrophil extracellular trap formation," or "NETosis." The function of neutrophil extracellular trap process in dental implants will be the main topic of this review.

Keywords: Dental Implants, Neutrophil Extracellular Trap, Polymorphonuclear Neutrophils, NETosis.

Research Paper

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INTRODUCTION

Dental implants have a long and convoluted history of being used for the restoration of missing teeth since tooth loss is so widespread and can be caused by trauma as well as the most common cause, gum disease. The idea of replacing teeth (dental implants) arose in ancient Egyptian civilization, which consisted of replacing missing teeth with carved seashells or stones embedded in the lower jaw [1]. Earlier implants composed of precious metals and designed to imitate natural roots are also known to exist. Patients who are entirely or partly edentulous can now receive excellent oral rehabilitation because to the widespread use of prosthetic restorations that depend on dental implants, which increases the range of options for therapy [2]. The prevalence of dental implants in the global population is estimated to reach up to 23% by the year 2026 [3]. Since the introduction of titanium alloys for the purpose around 1981, there has been a marked increase in the use of dental implants to replace lost teeth in patients. Care has to be taken in selecting the patient to receive an implant. There has to be enough bone in the affected part of the mandible or maxilla to secure and support the implant, and the site must also have a good supply of blood. This means that the patient must be free of circulatory disorders, and should also be a non-smoker [4]. The vast majority of white blood cells are neutrophils, which make up 95% of the granulocyte family and 50% to 70% of blood leukocytes [5]. Neutrophils, which are normally present in the oral cavity, link to endothelial cells via engaging with adhesion receptors. They escape the circulatory system and travel from the periodontal sulcus into the oral cavity via drainage [6]. While the role of neutrophils in the natural response to biomaterial implantation is recognized, there is limited knowledge about the factors that regulate their function. Hence, this review will primarily focus on the role of neutrophil extracellular traps in dental implants.

METHODOLOGY

Using keywords like "dental implants, neutrophil extracellular trap, polymorphonuclear neutrophils, NETosis" in scientific databases including Web of Science, Scopus, PubMed, and Google Scholar, pertinent publications were found for use to carry out this study.

Dental Implant

Dental implants are described as "a piece of material inserted below the soft tissue barrier on (eposteal), inside (endosteal), or within (transosteal) of the bone to hold or maintain an oral replacement" [7]. "Inert, alloplastic components inserted into the bone of the jaw for the treatment of tooth loss and to help with restoration of lost orofacial features" is another definition of dental implants provided by Pye *et al*., [8]. A dental

implant is a medical device generally made of an inert metal or metallic alloy. It is surgically placed within the jawbone tissues to replace one or more missing teeth or to anchor fixed or removable prostheses. The intention of a dental implant is to improve both the comfort and functionality of patients with either total or partial tooth loss [9].

Implant Osseointegration

In the 1950s, Braunemark observed that the drilling of a titanium fragment into a rabbit's bone resulted in its consolidation and subsequent difficulty in removal [10]. The strong correlation between the titanium implant and the bone provided sufficient resilience to withstand the transmission of forces. In other words, according to Brennemark, the titanium oxide layer of the implant and the bone form a strong connection, allowing for direct attachment between the load-bearing endosseous implant and the living bone, without the requirement of soft tissue intervention [11]. Osseointegration refers to the formation of bone directly next to the implant surface, without any infiltration of fibrous or connective tissue. The clinical definition of osseointegration is the asymptomatic and firm attachment of an implant in bone, capable of withstanding occlusal stresses [9]. Osseointegration, an intricate process that typically takes four to six months to fully occur, is an essential prerequisite for successful implant therapy [12].

Osseointegration, in a state of good health, is a complex procedure that necessitates many weeks for total redemption. Following implantation, the bone-implant contact elicits inflammatory reactions from both bone tissue and cells. Bone regeneration is a complex process that is controlled by several biological factors in the vicinity of the implant. This process takes place after the aforementioned events. Subsequently, mineralization of the bone occurs at the contact and distance sites of dental implants, leading to bone remodeling [13]. The initiation of the first phase of the acute inflammatory response occurs with the development and constriction of blood clots. The infiltration of immune cells, which is a crucial component of immune responses, has a substantial impact on the biocompatibility and functionality of dental implants, and may ultimately result in their failure. The primary injury to peri-implant tissue initiates an inflammatory reaction that is controlled by the cells of innate immunity, such as macrophages, dendritic cells, mast cells, and neutrophils [14].

Innate Immune Response to Dental Implant

Implantation of orthopedic biological material elicits an acute immunological response mostly mediated by myeloid-derived, non-specific immune cells. The initiation of this inflammatory stage is prompted by signals produced as a result of injury to the bone during implantation, as well as the potential infiltration of bacteria into a previously sterile tissue inside the body [15]. Subsequent to this stage, the immune system cells present at the location of implantation play a crucial role in determining the ultimate result of the implant, either successful integration or failure [16].

The release of signaling molecules, such as cytokines and chemokines, regulates the movement and behavior of stem and progenitor cells, as well as the movement and activation of immune cells [17]. Immune system cells have a substantial influence on the functionality of bone-dwelling implants. The macrophage is a specific kind of innate immune cell that plays a crucial role in the regeneration of osseous tissue, contributing to both the integration of implants and the total healing of bones. During the early phases of tissue injury, inflammatory macrophages secrete TNF-α, IL-1b, IL-6, and IL-12. These chemicals propagate inflammation by recruiting supplementary kinds of immune cells. Over time, when the transition occurs from irritation to recovery, macrophages become the most abundant and acquire anti-inflammatory characteristics, such as generating TGF-b, IL-10, and matrix remodeling proteins [18, 19]. Studies have shown that modifying the surface of dental and orthopedic implants naturally promotes an anti-inflammatory macrophage phenotype. This suggests that the profile of macrophages is influenced by both chemical and physical cues in the damaged region [20]. Macrophages play a crucial role in regulating both the immune response and the process of recruiting and differentiating stem cells during healing. Studies have shown that eliminating macrophages decreases the quantity of inflammatory and mesenchymal stem cells (MSCs) that go towards the site of the bone implant. Therefore, it seems that macrophage activity is essential for regulating the immune response to implants. However, macrophages are not the first responders in situations of tissue injury. Neutrophils, which have not been thoroughly studied in the context of tissue repair, play a significant role in recruiting macrophages and aiding in the healing process. After tissue damage [21], neutrophils quickly gather at the site in groups within a matter of minutes to hours. They employ various mechanisms such as degranulation, phagocytosis, enzyme release, and the formation of extensive DNA-based fibre networks to carry out antimicrobial activities [22].

Neutrophils

Each species has a distinct function within its ecosystem [23]. They differentiate into distinct subpopulations of neutrophil-killers and neutrophil-cages of stem cells inside the bone marrow. They possess a brief lifespan and exhibit exceptional mobility, enabling them to infiltrate tissue regions inaccessible to other cells or chemicals [24]. The neutrophil is a kind of

phagocyte often seen in the circulation. Neutrophils promptly and actively migrate towards the site of inflammation during the first stage of activation, in response to bacterial infection or exposure to the environment [25]. The neutrophil is one of the first inflammatory cells to migrate to the site of inflammation. Chemotaxis refers to the process by which cells move across blood arteries and interstitial space, guided by chemical signals such as IL-8. Neutrophils are characteristic indicators of acute inflammation and are attracted to the site of damage shortly after trauma. However, due to the fact that certain pathogens cannot be digested, neutrophils may need assistance from other kinds of immune cells to eliminate some infections [26, 27].

Neutrophil Extracellular Traps (NETs)

The NETs are extracellular formations consisting of decondensed chromatin fibres that are associated with neutrophil granular proteins, including neutrophil elastase, myeloperoxidase, and cathepsin G. Neutrophil extracellular traps (NETs) effectively restrict the spread of microbes prior to the arrival of an adequate number of leukocytes to the affected region. NETs may also be activated by non-infectious substances or placental microparticles, posing a potential threat to the host [28]. NETosis is strongly associated with the generation of reactive oxygen species (ROS) and the citrullination of histones, figure (1). Platelets have been identified as the catalyst for NET creation in neutrophil activation, using Toll-like receptor 4 as part of the pathway [29]. NETosis seems to have an anti-inflammatory function and plays intricate roles in the localised control and advancement of the inflammatory response [30].

During an infection, the production rate of neutrophils from bone marrow may rise by a factor of 10, indicating the strong attraction and reaction of neutrophils to inflammatory signals. Neutrophils perform three main functions: producing oxidative bursts, releasing granules, and forming NETs. The neutrophil plays a significant role in both starting and intensifying the inflammatory response. As a result, the control of neutrophil behaviour and NETosis is crucial for the effectiveness of the template. Neutrophils and NETs have the potential to either combat or contribute to sickness and destruction. It is the responsibility of researchers to comprehend this interaction between neutrophils and biomaterials in order to customise the design and make use of the regenerative capacities of neutrophils [31].

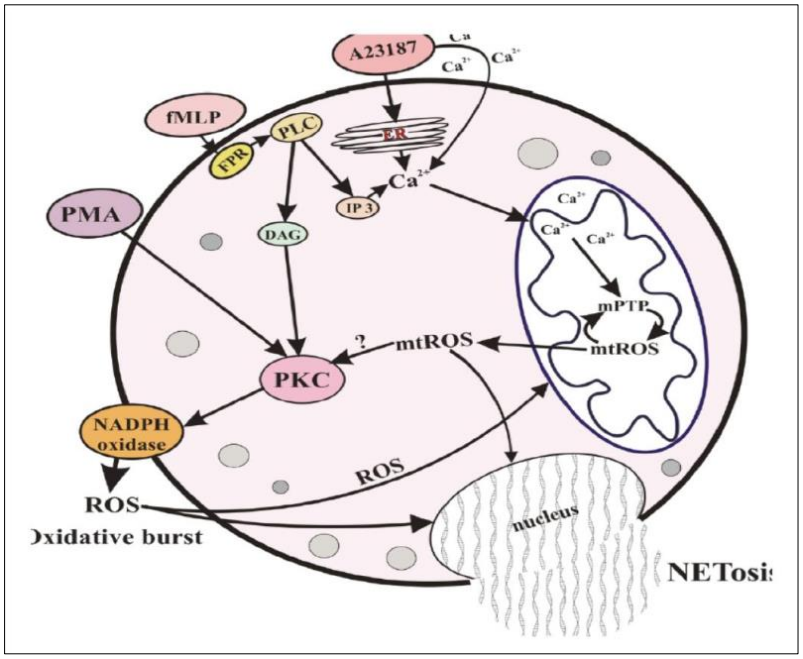

Figure 1: Mechanisms of NETosis [30]

Significance of NETs Detection

Detecting NETs may serve as a predictive tool for patients with illnesses characterised by a heightened rate of NET production, hence enabling doctors to provide tailored therapy. In order for NETs to serve as screening tools, it is necessary to conduct research that establish standardised criteria for defining normal and abnormal levels. This may include quantifying NET-related substances in the bloodstream, such as cfDNA, citH3, NE, and MPO. Circulating free DNA (cfDNA) has been measured in blood samples of individuals with colorectal and breast cancer using a simple nucleic acid-staining test [32, 33]. While evaluating cfDNA alone may be used to identify cancer, the measurement of circulating MPO/cfDNA conjugates and citH3 may provide a more specific analysis for NET

(neuroendocrine tumour) classification [34]. CitH3 has a high degree of specificity for NETosis, making it a potential instrument for comprehending discrepancies in NET levels [35]. Thalin noted that the elevated plasma levels of citH3 were a noteworthy predictor of short-term death in some cancer patients [36], and other observational studies provide information on the importance of NETs in the advancement of colorectal cancer [37].

Neutrophil Extracellular Traps in Dental Implant

Multiple studies indicate that neutrophil extracellular traps (NETs) play intricate roles in the localised control and advancement of the inflammatory response. Within the field of orthopaedic implants, macrophages play a crucial and diverse function in integration. However, it remains uncertain if this activity overlaps with that of other cell types, such as neutrophils [9-39]. Although cytokine release has been solely used as the indicator for studying the interaction between neutrophils and biomaterials, the phenomenon of NETosis has not been extensively investigated in this particular context. Neutrophils exhibit distinct activation patterns when exposed to smooth, rough, or rough-hydro Ti surfaces. This activation involves the release of inflammatory chemicals, enzymes, and the creation of NETs. Furthermore, the activation of neutrophils plays a crucial role in the polarisation of macrophages, highlighting the significance of neutrophil activation in the entire process of healing [21].

Neutrophils have been hypothesised to eliminate pathogenic organisms by engulfing them (phagocytosis), attacking them with enzymes, producing reactive oxygen species (ROS), and enhancing the initial pro-inflammatory response by producing cytokines and chemokines [40-42]. At first, NETosis was seen as a part of the neutrophils' antibacterial function, since NETs are produced when bacterial-dependent TLR or immunoglobulin-dependent Fc receptor activation occurs [43]. Nevertheless, researchers have since shown the occurrence of NETs in diverse sterile inflammatory circumstances. In the context of sterile inflammation, neutrophil extracellular traps (NETs) contribute to the pro-inflammatory response by exerting cytotoxic effects via the presence of unbound histones [44]. Additionally, NET-based enzymes facilitate the conversion of pro-IL-1β to its active form, IL-1β, and NETs themselves serve as a damage-associated molecular pattern (DAMP) signal to activate other immune cells. NETs serve as sites of attachment for bactericidal enzymes such as MPO, leukocyte proteases, and LL-37. LL-37 is a multifunctional enzyme that exhibits both chemotactic and antibacterial activities [45].

Vitkov *et al*., discovered that roughened Ti implant surfaces may trigger a NETotic response (46). The study conducted by Abaricia *et al*., [21], shows that the neutrophil response is influenced by the type of surface modification. These modifications affect the inflammatory response of neutrophils. The researchers have previously observed a similar effect in macrophages, where roughness and hydrophilicity lead to an increased anti-inflammatory profile [47]. Abaricia *et al*., discovered that when neutrophils are exposed to rough, hydrophilic surfaces, they release a reduced amount of pro-inflammatory chemicals and do not undergo NETosis. This effect may enhance osseointegration by reducing the pro-inflammatory polarisation of macrophages upon interaction with NETs. Neutrophils are not present throughout the proliferative phase of osseointegration. However, it would be intriguing to investigate the interaction between neutrophils and NET-MSCs. If neutrophils have an inhibitory influence on the osteogenic differentiation of MSCs, it becomes crucial to eliminate them from the surface of the implant prior to the healing process. Remarkably, the inhibition of NETosis by pharmaceutical agents enhanced the anti-inflammatory properties of surface alterations during the co-cultivation of macrophages and neutrophils. These findings indicate that inhibiting NETosis might potentially facilitate the body's regenerative process and promote osseointegration of titanium implants. According to the previous work, the inflammatory response to Ti biomaterials that are used in clinical settings is influenced by the activity of neutrophils. It is suggested that inhibiting NETosis, a process involving the release of neutrophil extracellular traps, might help speed up the resolution of inflammation caused by these implants [21].

CONCLUSIONS

Since the discovery of NETs, there has been significant advancement in understanding their defensive functions and their involvement in implants. Specifically, the examination of the influence of NETs on implantation has emerged as a topic of increasing interest. NETs have the potential to enhance the ability of neutrophils to fight infections by increasing their defensive activity even after cell death. This allows for maximum utilization of antimicrobial proteins. Conversely, NETs may have a negative impact on dental implants. Ensuring a proper equilibrium in NET formation is essential for maintaining optimal oral health. Further work is needed to explore the potential of NET regulation in implants as a future therapeutic approach.

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