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Perspective

Neutrophil Polarization and Immune Regulation: Toward Immune-Bioadaptive Dental Implants

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Abstract: Neutrophils are the most abundant leukocytes and primary immune defenders in humans. Emerging evidence pinpoints that neutrophils possess a functional spectrum, mirroring macrophage polarization, spanning pro-inflammatory (N1) to anti-inflammatory/reparative (N2) phenotypes, contributing pivotally to host defense and immune modulation. In this Perspective, we first summarize the classification criteria, defining markers, and functional relevance of neutrophil polarization, highlighting their dynamic crosstalk with macrophages in shaping local immune microenvironments. Merging latest advances in immunology and biomaterials science, we move on to discuss how neutrophil-directed immunomodulation is informing the design of bioadaptive dental implants that feature tailored surface properties (chemistry, topography, wettability, etc.) to spatiotemporally steer neutrophil responses, aiming at alleviating foreign body reaction, controlling inflammation, and expediting osseointegration. The ultimate goal here is to provide guidance for designing bioadaptive implants with active immunoregulation targeting neutrophil–material interplays for tackling compromised osseointegration in dental implantation.

Keywords: neutrophil polarization; immunmodulation; bioadaptive biomaterials; dental implants

1. Introduction

Dental implant therapy has been widely implemented for tooth loss rehabilitation, but its success is often jeopardized by peri-implant infections and slow or unreliable osseointegration, especially concerning patients with compromised healing conditions (e.g., periodontitis, diabetics) [1]. Recent studies indicate that the long-term outcome of such implantation surgeries is largely dictated by the host's immune response to the implants; whether integration succeeds or fails is crucially shaped by the evolving immune microenvironment around the implants [2]. Conventional strategies focusing on enhancing antibacterial or osteogenic activity solely have shown limitations, as they overlook the pivotal need to actively regulate this immune landscape.

Over the past few years, a paradigm shift has emerged with the development of bioadaptive dental biomaterials, referring to a class of bioactive implants designed not for passive tolerance, but to actively engage with and modulate the host immune system [3]. The core philosophy lies in shifting from traditional biocompatibility ("inert and non-harmful") toward dynamic bioadaptivity ("actively instructive"). This could be accomplished through (i) the meticulous engineering of material properties such as bulk composition, micro- and nano-scale topography, surface energy, wettability, and the controlled delivery of bioactive therapeutics [4,5], and (ii) the integration of stimuli-responsive systems that enable real-time modulation of materials characteristics in response to external cues (e.g., acoustic, optical, electromagnetic) or changes in the local microenvironment (e.g.,

pH, ion concentrations, enzymatic activity) [6,7]. With such multifaceted design rationales, one can precisely orchestrate a pro-regenerative, anti-inflammatory immune milieu, thereby allaying unintended immune rejection, accelerating bone formation for granting the long-term implantation success.

While macrophages are among the most studied immune cells in dental research, relying merely on their regulation is insufficient for bioadaptive implant design, given the challenge of ensuring both infection control and biointegration within the naturally infectious oral niches. Regardless of their known antibacterial role, macrophages are recruited too slowly and have a finite ability to eradicate established biofilms [8]. By contrast, neutrophils, or polymorphonuclear leukocytes (PMNs), are the most abundant leukocyte population in human circulation and constitute primary and immediate defenders at the implantation sites [9]. As the first wave of immune cells to infiltrate injury or implantation sites, neutrophils not only execute potent antimicrobial functions through phagocytosis, degranulation, and neutrophil extracellular trap (NET) formation, they also exert profound immunomodulatory effects that could shape subsequent inflammatory and regenerative phases [10]. Despite their nontrivial role, research on neutrophil biology, especially as dental implantation is concerned, has historically lagged behind the well-mapped polarization mechanisms of macrophages. Factoring in the dynamic interplays between the microbiota and host immunity in periodontal and peri-implant sites, a crucial task is to decode and modulate temporal dynamics of neutrophil polarization, so as to achieve concurrent infection control and stable implant integration.

In this Perspective, we outline the phenotypes and polarization mechanisms of neutrophils and their functional interplays with macrophages, emphasizing the potential of leveraging these interactions in advancing the design of bioadaptive dental implants. By refocusing immunomodulatory strategies on neutrophil-centered responses, we aim to inform new biomaterial-based approaches that can dynamically regulate host immunity to ensure effective infection fighting and foster a pro-regenerative microenvironment for stable osseointegration, especially in challenging clinical settings such as diabetic or periodontally-compromised patients.

2. The Polarization of Neutrophils

2.1. Overview of Neutrophils

Macrophage plasticity is classically defined by the M1/M2 paradigm, which encompasses pro-inflammatory/anti-tumor and anti-inflammatory/pro-tumor/reparative states [11]. Building on this framework, researchers sought to unravel neutrophil functional heterogeneity. In 2009, Fridlender et al. demonstrated that TGF-β polarizes tumor-associated neutrophils (TANs) into anti-tumor (N1) and pro-tumor (N2) states, establishing an N1/N2 classification that parallels the M1/M2 framework in macrophages [12]. Following its introduction, the N1/N2 classification was rapidly extended to other fields of research. Throughout this work, this classification will serve as a model for analyzing differential neutrophil-centered immune responses to biomedical implants.

Notably, however, neutrophils are terminally-differentiated, short-lived cells that respond to inflammation in a rapid, dynamic, and reversible manner; consequently, their functional states form a spectrum rather than discrete subsets. Studies by Fine et al. and Xie et al. demonstrated that neutrophils would traverse a functional spectrum from pro-inflammatory to pro-repair/anti-inflammatory states during the shift from a healthy oral state to periodontitis, as well as when comparing homeostasis to infection [13,14]. Moreover, their position on this spectrum is not fixed but can flexibly shift in response to microenvironmental cues such as G-CSF, TGF-β, TNF-α, and IFN-γ [15]. It is this functional plasticity that enables neutrophils to adaptively respond to diverse contexts, from acute infection to chronic inflammation and tissue repair.

Unlike the clearly demarcated subtypes of macrophages, neutrophil N1 and N2 states are less precisely defined by specific surface markers. While in practice mature neutrophils can be identified by classic signatures (e.g., $CD45^+CD11b^+Ly\text{-}6G^+$ in mice or $CD45^+CD11b^+CD15^+CD16^+$ in human [16,17]), defining their subtypes remains challenging, and researchers often rely on operational definitions, such as classifying $Ly\text{-}6G^+CD206^-$ cells as N1 and $Ly\text{-}6G^+CD206^+$ cells as N2 [16]. It is crucial to note, however, markers like CD206 lack the specificity and general applicability requisite for definitive classification.

Within the context of immune regulation, the N1 phenotype is broadly associated with pro-inflammatory responses, in contrast to the anti-inflammatory functions linked to the N2 state. By functionality, the N1 phenotype is characterized by high expression of pro-inflammatory factors such as TNF-α, IL-1β, IL-12, and iNOS, coupled with enhanced reactive oxygen species (ROS) generation [18–22]. Contrastingly, cells inclined toward the N2 state typically overexpress CD206, ARG1, CD163, CD182, while actively secreting immunoregulatory and pro-repair factors such as IL-10, TGF-β, PGE2, and G-CSF [18,21,23,24]. These molecules, together with the aforementioned microenvironmental signals, form a molecular network that dynamically regulates the functional states of neutrophils, as summarily illustrated in Figure 1.

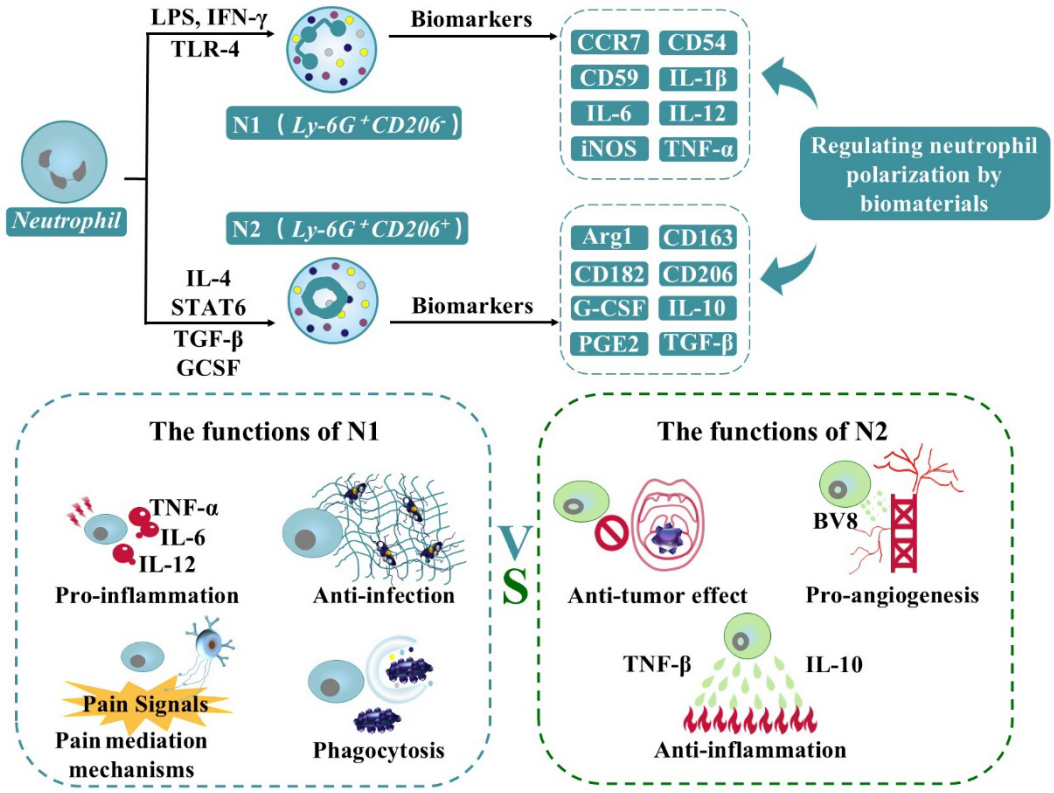

Figure 1. Classification, surface markers, and related functions of neutrophils. The N1 phenotype is characterized by pro-inflammatory, antimicrobial, and pain-signaling functions, alongside bacterial phagocytosis. In contrast, the N2 phenotype is associated with anti-inflammatory responses, angiogenesis promotion, and suppression of oral cancer. Abbreviations: Arg1 for Arginase-1; BV8 for Bombina Variegata Peptide 8; CCR7 for C-C Chemokine Receptor Type 7; CD54 for Intercellular Adhesion Molecule-1; CD59 for CD59 Glycoprotein; CD163 for Hemoglobin Scavenger Receptor; CD182 for C-X-C Chemokine Receptor Type 2; CD206 for Macrophage Mannose Receptor; G-CSF for Granulocyte Colony-Stimulating Factor; IFN-γ for Interferon-gamma; IL-6, 8, 10, 12, 1α, 1β for Interleukin-6, 8, 10, 12, 1 Alpha, 1 Beta; iNOS for Inducible Nitric Oxide Synthase; LPS for Lipopolysaccharide; PGE2 for Prostaglandin E2; STAT6 for Signal Transducer and Activator of Transcription 6; TGF-β for Transforming Growth Factor-Beta; TLR4 for Toll-like receptor 4; TNF-α for Tumor Necrosis Factor-Alpha.

2.2. Polarization of Neutrophils

A fundamental approach in immunology is the strategic polarization of neutrophils into N1 or N2 states with specific stimuli, thus elucidating their distinct functions in host defense and tissue repair. The N1 pro-inflammatory phenotype is typically triggered by pathogen- or damage-associated molecular patterns (PAMPs/DAMPs). For instance, Ma et al. demonstrated, in a murine model of myocardial infarction, that DAMP-activated TLR-4 signaling promoted N1 polarization, whereas TGF-β suppressed it [16]. Mareike et al. reported that TGF-β and granulocyte colony-stimulating factor (GCSF) could induce N2 polarization in vitro, while a combination of lipopolysaccharide (LPS) and interferon-γ (IFN-γ) is commonly used to induce the N1 phenotype [18]. Similarly, Mihaila et al. successfully polarized neutrophils into N1 and N2 types using IFN-γ and interleukin-4 (IL-4), respectively [19]. Beyond soluble factors, Yang et al. identified a cell-mediated mechanism in which exosomes from human umbilical cord mesenchymal stem cells (HucMSC-Exo) promoted N2 polarization via STAT6 signaling [24], highlighting paracrine communication as a physiologically relevant pathway guiding neutrophil polarization.

2.3. The Functions of Neutrophil Subtypes

The N1/N2 balance is a key determinant of inflammatory direction and implant integration, with pro-inflammatory N1 neutrophils driving bone destruction and anti-inflammatory N2 neutrophils promoting repair. For instance, Mihaila et al. showed that inhibiting S100A9 downregulated inflammatory mediators (CCL2–5, MPO, MMP-9), whereas N1 polarization upregulated key genes (TNF-α, IL-1β, IL-12) and chemokines (CCL3–5, CXCL1–3, CXCL10) [19]. In rheumatoid arthritis, Huang et al. linked localized joint neutrophil accumulation to N1 polarization and arthralgia and found that geranyl hydroquinone alleviated such pain [25]. In the pathological

process of periodontitis, neutrophils participate in the initiation of inflammation and bone destruction through multiple mechanisms. On the one hand, LPS from periodontal pathogens such as *Porphyromonas gingivalis* binds to Toll-like receptors, driving neutrophil polarization toward the N1 phenotype and triggering a robust release of pro-inflammatory mediators including IL-1β, TNF-α, and IL-6 [26]. Concurrently, neutrophils are to blame for liberating neutrophil extracellular traps (NETs) and proteases, such as elastase and MMP-8, to sustain local inflammation, degrade collagen, and cause periodontal attachment loss, creating a pathological vicious cycle. Analogous mechanisms have been documented in the inflammatory pathogenesis of osteoarthritis [26,27].

By comparison, N2 neutrophils exert anti-inflammatory and pro-repair functions that profit tissue healing and angiogenesis, suggesting their potential role in enhancing osseointegration. Supporting this, Ma et al. identified a reparative N2 neutrophil population in a myocardial infarction model, characterized by expression of Arg1, CD206, IL-10, TGF-β1, and Ym1 [16]. In the tumor microenvironment, a similar pro-tumoral neutrophil phenotype is frequently observed, being correlated with upregulated expression of immunosuppressive and pro-angiogenic mediators, such as iNOS, CD184, VEGF, and IL-8 [28,29]. In periodontitis, studies have found that implanting xenogeneic dental follicle stem cells can recruit host neutrophils and induce their polarization toward the N2 phenotype, secreting IL-10, BV8, and TGF-β, thereby promoting angiogenesis and periodontal tissue regeneration [28]. Yang et al. demonstrated that exosomes from human umbilical cord mesenchymal stem cells (HucMSC-Exo) induced N2 polarization, which in turn stimulated angiogenesis through BV8 secretion [24], aligning with the observations of Antuamwine et al. [29]. Conversely, He et al. reported that N2 polarization can be therapeutically targeted to curb oral cancer progression through the inhibition of aldehyde dehydrogenase 3A1 (ALDH3A1) [30]. These effects are summarized in Figure 1.

Remarkably, the N1/N2 polarization of neutrophils is closely linked to a diverse array of systemic diseases, including tumors, myocardial infarction, arthritis, periodontitis, amongst others [31]. This Perspective will focus specifically on their immunomodulatory roles in oral and bone inflammatory disorders, underlining distinct functions of each subtype. Nevertheless, within the complex oral microenvironment, the full range of neutrophil functions and underlying mechanisms remain to be further elucidated.

3. Interplays Between Neutrophils and Macrophages

Inflammation and immunoregulation form a vast, intricately balanced system. Rather than acting in isolation, neutrophils engage in sophisticated bidirectional crosstalk with macrophages, forming a dynamic immunoregulatory axis. This delicate equilibrium ultimately dictates pathological outcomes: propelling the immune response either toward chronic tissue destruction or toward resolution and repair (Figure 2).

3.1. The N1–M1 Positive Feedback Loop

During early inflammation, extensive neutrophil recruitment and polarization toward the N1 phenotype occur. Research in bone defect models reveals that N1 neutrophils secrete chemokines such as macrophage inflammatory protein (MIP) and monocyte chemoattractant protein (MCP), which not only attract additional immune cells but also directly promote macrophage polarization toward the M1 phenotype [32]. This process acts as a universal inflammatory amplifier, wherein N1 cells further enhance M1 polarization through the release of IL-12, IFN-γ, and TNF-α [33]. In turn, activated M1 macrophages produce cytokines including IL-17, stimulating epithelial cells to further recruit and activate neutrophils [32]. The presence of numerous neutrophils within the spatial domain of M1 macrophages in periodontitis tissues provides morphological proof of their intensified crosstalk, thereby substantiating the N1–M1 feedback loop [34]. Together, these interactions form a self-reinforcing N1–M1 positive feedback loop that rapidly escalates the inflammatory response to clear pathogens.

3.2. NETs as a Driver of M1/M2 Imbalance

In diabetic periodontitis, the hyperglycemic microenvironment is known to disrupt the balance between the formation and clearance of NETs [35]. A recent research by Yao et al. reveals that excessive NETs have the activity to suppress the critical Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway in macrophages, consequently inducing a polarization imbalance through favoring the pro-inflammatory M1 phenotype over the anti-inflammatory/reparative M2 state [36]. This disruption of immune homeostasis could exacerbate the destruction of periodontal tissues and accelerate bone resorption.

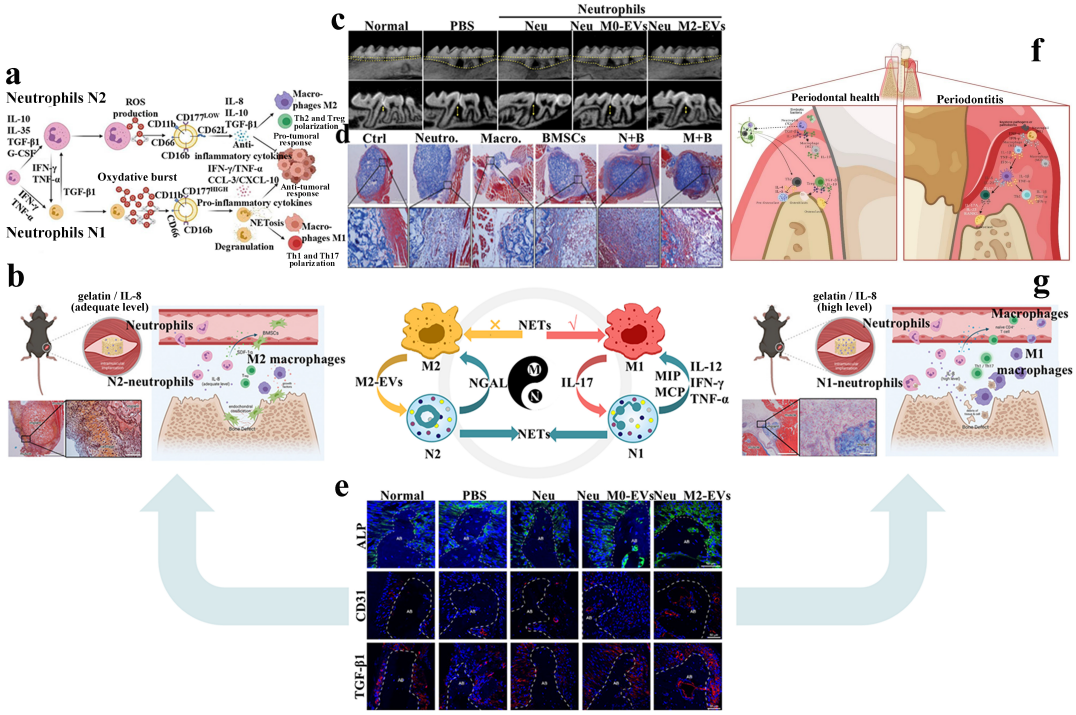

Figure 2. Neutrophil–macrophage crosstalk in immune regulation. (**a**) N1 and N2 neutrophils communicate with macrophages and orchestrate their polarization via NETs release and cytokine signaling. (**b**,**g**) Neutrophils facilitate macrophage recruitment and IL-8-mediated polarization during bone regeneration, jointly promoting fracture healing. (**c**) Interaction mechanisms between N1/N2 neutrophils and M1/M2 macrophages in periodontal health and diseases. (**d**) Micro-CT and 3D reconstruction of alveolar bone loss in ligature-induced periodontitis after stimulation with M2-EVs. (**e**) Masson's trichrome staining of neutrophils, macrophages, and MSCs during murine osteogenesis. (**f**) Immunofluorescence staining of neutrophil markers in periodontitis mice treated with M2-EVs. Images (**a**,**c**) reproduced with permission from Ref. [14] @ Springer Nature 2022. Images (**b**,**e**,**g**) reproduced with permission from Ref. [32] @Elsevier 2021. Images (**d**,**f**) reproduced with permission from Ref. [36] @Elsevier 2025.

3.3. N2–M2 Synergy and Efferocytosis

The timely resolution of neutrophil/macrophage-mediated inflammation relies on an N2–M2 negative feedback loop. In models of myocardial infarction and stroke, N2-polarized neutrophils were showed to guide macrophages toward a reparative M2 phenotype via secretion of neutrophil gelatinase-associated lipocalin (NGAL), thereby facilitating tissue repair [37,38]. Similarly, in a periodontitis bone resorption model, M2 macrophages were found to release extracellular vesicles (M2-EVs) that promoted neutrophil N2 polarization, fostering a coordinated pro-regenerative microenvironment [36]. On the other hand, efferocytosis, i.e., the clearance of apoptotic neutrophils by macrophages, serves a central event in inflammation resolution. This process actively triggers M2 polarization in macrophages and acts as a critical signal transitioning the tissue microenvironment from inflammation to repair. Dysregulation of efferocytosis has been intimately linked to the pathogenesis of multiple chronic inflammatory diseases [39,40].

3.4. Functional Dichotomy: Neutrophils vs. Macrophages

Although both neutrophils and macrophages are phagocytic immune cells, they exhibit fundamental functional differences. Neutrophils act as the first responders in acute inflammation. With a short lifespan (hours to days) [13,15], they are rapidly recruited from the bone marrow and eliminate pathogens through potent microbicidal mechanisms such as degranulation and the release of NETs [39]. However, their aggressive response can exacerbate tissue injury. In contrast, macrophages serve as versatile regulators in later inflammatory phases. They derive mainly from monocyte differentiation and possess a considerably longer (months to years) [41]. The functional repertoire of macrophages is more complex and integrative: in addition to phagocytosing pathogens and apoptotic neutrophils, they play central roles in antigen presentation to initiate adaptive immunity, as well as in cytokine-mediated immune regulation and tissue repair [42].

These findings together hint on an intricate connection between neutrophils and macrophages, such that resolving their collective dynamics within a shared microenvironment is key to affording effective immune

regulation. This reciprocal interplay highlights the need to target both cell types synergistically in the design of immunomodulatory biomaterials. Importantly, despite their close association, distinct functional differences persist between them, and thus a balanced perspective acknowledging both their interconnectedness and individual characteristics is essential for a comprehensive understanding of their roles in inflammation and immune regulation.

4. Neutrophil-Targeted Engineering of Immunomodulatory Bioadaptive Biomaterials for Dental Implants

The host reaction to implanted medical devices, formally known as the foreign body reaction (FBR), involves neutrophils as crucial early responders. Within hours post-implantation, these cells infiltrate the site and shape the initial immune landscape through rapid reactions to inflammatory cues [43,44]. Their pivotal role makes them a central target in biomaterial design. A key challenge in current research lies in whether advanced material strategies can actively steer neutrophil polarization to build an immune niche conducive to osseointegration, rather than one leading to fibrosis or chronic inflammation.

Motivated by this goal, the design philosophy for next-generation dental implants is shifting from "passive compatibility" to "active immunomodulation". In the initial phase (24–72 h post-implantation), the material should guide neutrophils to effectively clear pathogens and undergo controlled N1 polarization to contain infection. During the critical 3- to 7-day window, the implant must then allow a transition toward the N2 phenotype, thereby initiating inflammation resolution and tissue repair programs [45,46]. To achieve long-term stable integration, material strategies should further incorporate temporal regulation mechanisms (e.g., controlled-release systems or smart responsive interfaces) to dynamically tune the immune microenvironment throughout the entire osseointegration process, hence adapting to the evolving stages of bone and periodontal tissue healing.

Upon entering the oral environment, biomaterials rapidly acquire a "protein corona", a layer of adsorbed proteins that mediates all subsequent biological interactions. It is this dynamic interface, rather than the material per se, that engages with both microbes and host cells, with its composition dictating the ensuing immune and tissue responses [33]. During corona formation, adhesive proteins compete for surface binding sites. For example, vitronectin typically outcompetes fibronectin in plasma, causing its preferential adsorption. Although both proteins contain RGD sequences that bind integrin receptors [47], they activate distinct downstream pathways: vitronectin primarily signals through integrin αvβ3 to regulate cell migration and angiogenesis [48], while fibronectin preferentially engages α5β1 integrin to support osteodifferentiation [49]. These specific protein–integrin interactions subsequently trigger protease cascade systems, including coagulation, complement, and kallikrein-kinin pathways, and promote the adhesion and activation of platelets and neutrophils [33]. Ultimately, this sequence of molecular events directs the host response toward divergent biological outcomes.

In light of the above, through rational design of implant surface properties (e.g., topography, chemistry, wettability), neutrophil function can be modulated by engineering the adsorbed protein corona, which steers their subsequent recognition, activation, and immune responses (Figure 3). Current evidence strongly supports the feasibility of such immunomodulatory approaches. Hydrophobic surfaces tend to initiate destructive inflammation by adsorbing proteins such as fibrinogen, which activates neutrophil integrins and Toll-like receptors, leading to NF-κB and NLRP3 inflammasome activation, NETosis, and cytokine release [50–52]. Conversely, hydrophilic surfaces promote the formation of a hydration layer and facilitate the functional adsorption of vitronectin and fibronectin, establishing a pro-resolution milieu conducive to tissue repair [53]. Surface roughness and stiffness provide critical mechanical cues that influence neutrophil behavior. Rough surfaces enhance integrin-dependent neutrophil adhesion and spreading, activating the FAK/Src signaling axis and driving polarization toward the pro-inflammatory N1 phenotype [54]. Stiffness, on the other hand, activates the JAK1/STAT3 pathway, stimulating N2 phenotype formation, reducing inflammatory factors and ROS, and enhancing pro-angiogenic capacity [55]. Nanoscale surface topography is also known to modulate protein adsorption and cellular behaviors, but the key design parameters of such nanotopographic cues for optimizing neutrophil responses remain to be fully elucidated [56]. Beyond these factors, the micro-nano landscape of dental implant surfaces plays a decisive role in determining their eventual fate between infection and successful osseointegration. While microporous structures possess inherent osseointegration potential (e.g., through mechanical interlocking effects) [57], they paradoxically act as ideal niches for pathogenic bacterial adhesion and colonization [58,59]. This bacterial colonization could initiate a robust neutrophil-mediated inflammatory response: through LPS binding to Toll-like receptor 4 (TLR4), these bacteria activate the MyD88 pathway, initiating NF-κB signaling and triggering substantial release of inflammatory cytokines such as TNF-α and IL-1β for propelling periodontal inflammation and tissue destruction [60,61], potentially compromising osseointegration efficiency if the inflammation persists. Aside from physical properties, the chemical composition of an implant also constitutes a critical determinant of its immunomodulatory outcome. For examples, titanium ions (commonly released from corroded Ti-based implants) have been found to activate

the complement system and generate C3a, subsequently triggering downstream pro-inflammatory pathways [62]. By contrast, magnesium ions are documented to suppress NLRP3 inflammasome activation by modulating extracellular ATP and mitochondrial function, offering anti-inflammatory benefits [63], signifying the promise of developing Mg-containing biomaterial implants.

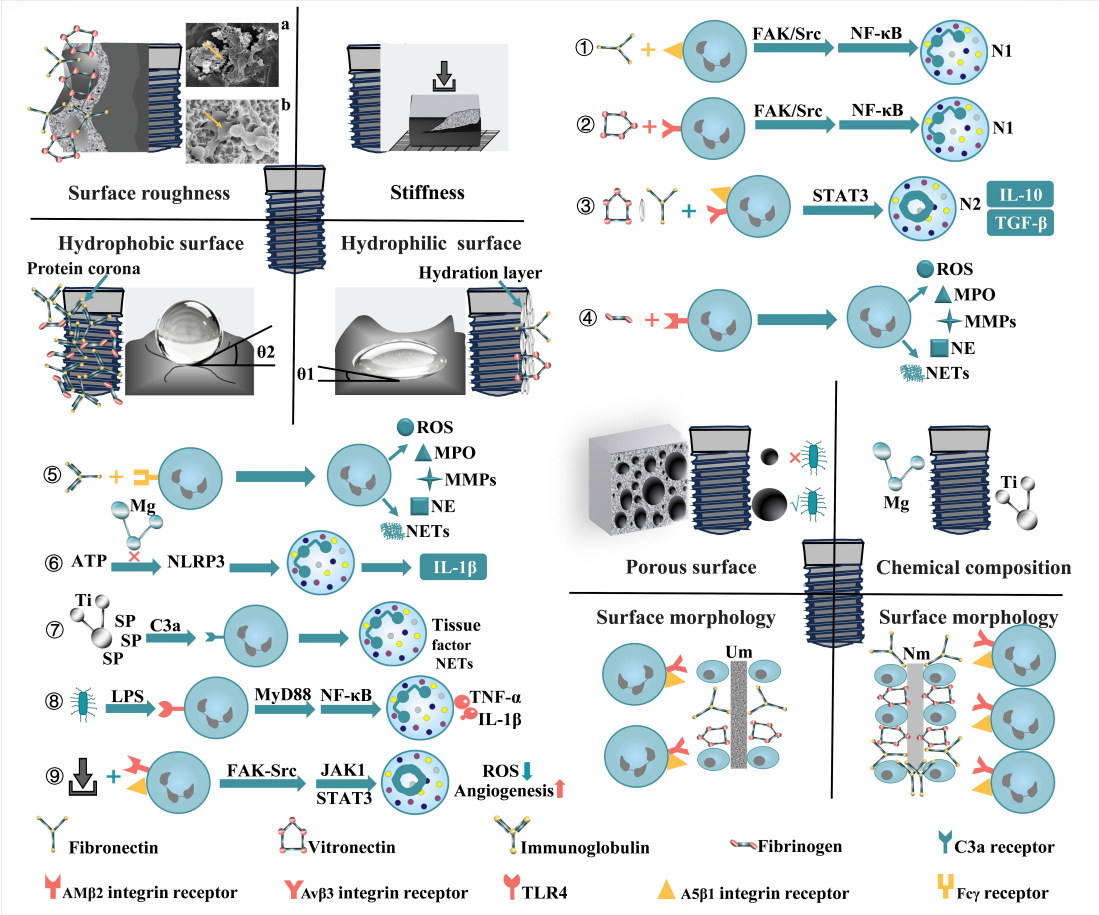

Figure 3. Common strategies for engineering dental implants targeting neutrophil-mediated osteo-immunomodulation. ① Fibronectin binding to integrins; ② Vitronectin binding to integrins; ③ Hydrophilic surface-mediated signaling; ④ Fibrinogen binding to integrins; ⑤ Immunoglobulin-mediated neutrophil polarization; ⑥ Magnesium ion-mediated neutrophil polarization mechanism; ⑦ Titanium ion-mediated neutrophil polarization mechanism; ⑧ Bacterial-induced neutrophil inflammatory signaling. ⑨ Stiffness-mediated neutrophil polarization on implants. Yellow arrows in SEM images (upper left) indicate neutrophils; These cells in (a) and (b) are located on smooth and rough titanium surface, respectively. SEM images reproduced with permission from Ref. [53] Elsevier 2020.

For clarity, the above mechanisms are summarized as follows: (i) The physicochemical properties of an implant surface serve as the primary interface that shapes the host immune response by governing the adsorption of proteins and microorganisms; (ii) This adsorbed "biomolecular layer" is recognized by receptors on immune cells such as neutrophils, triggering distinct intracellular signaling pathways; (iii) These cascades ultimately lead to the secretion of specific cytokines and enzymes, molding the immune microenvironment toward either a pro-inflammatory or anti-inflammatory phenotype and eventually dictating the healing outcome. It should be noted, however, that the specific response mechanisms of neutrophils in this context remain insufficiently investigated, with current understanding largely extrapolated from macrophage polarization pathways. This gap implies the great potential of "bio-adaptive" implants in precisely regulating neutrophil function, an area that calls for growing attention in future research.

5. Conclusions and Future Perspectives

In this *Perspective*, we harness latest knowledge in neutrophil biology to reframe the design principles for immune-bioadaptive dental implants. By focusing on and elucidating the N1-to-N2 spectrum of neutrophil polarization, we clarify how these pioneer immune cells dictate the critical early stages of host-implant integration.

The discussion further extends to the dynamic reciprocity between neutrophil subsets and macrophage populations, delineating how their temporal crosstalk orchestrates the transition from inflammatory initiation to regenerative resolution. With these mechanistic insights in mind, we propose innovative biomaterial engineering strategies that leverage surface topographical cues, biochemical functionalization, and stimuli-responsive material systems to precisely guide neutrophil recruitment and polarization behaviors, thus spatiotemporally reshaping pathological microenvironments associated with compromised healing conditions.

To move ahead in this nascent yet burgeoning field, several key aspects demand focused in-depth research endowers. First and foremost, a deeper mechanistic understanding of neutrophil heterogeneity and their space/time-dependent, multivalent communications with macrophages within peri-implant tissues will be essential and instrumental to identify novel therapeutic targets. This should be ideally coupled with the development of smart biomaterials capable of stimuli-responsive immunomodulation, such as systems that can dynamically adapt their surface properties in response to local inflammatory cues for spatiotemporally-controlled regulation of neutrophil activity. Second, the creation of advanced on-chip models that better simulate human immune cell interactions would likely prove a powerful platform for evaluating these novel strategies [64,65], while standardized characterization protocols for neutrophil subtypes in human clinical samples will enable smoother translation from preclinical findings to bedside applications. Particular emphasis needs to be placed on accomplishing prolonged immunomodulatory effects through sustained biofactor delivery systems, or alternatively, surface modification features that maintain their bioactivity throughout the critical healing periods. Furthermore, albeit for promise in current studies, heroic efforts must be devoted to addressing translational hurdles, including but not limited to, material stability in complex oral environments, patient-specific customization per immune profiles, and the feasibility of scaled-up manufacturing [1,66]. The fusion of neutrophil-targeted strategies with macrophage-centered approaches will be fruitful for creating adaptive immunomodulatory therapies that effectively span the entire healing process.

The future of dental implantology, as accumulating evidence will show, lies in the development of intelligent implants that can dynamically alter their immunomodulatory properties and actively foster a sequentially infection-fighting, pro-healing microenvironment, rather than passively resisting infection or immune challenges. By integrating artificial intelligence with personalized immunoprofile analysis [67,68], such implantable devices are anticipated to achieve precisely-defined immunoregulation to ensure rapid yet predictable osseointegration, especially benefitting patients with compromised healing capacity. As multidisciplinary research continues to unravel the mystery of neutrophil biology and material–immune interactions, we would be increasingly capable of advancing toward the realization of personalized, immune-adaptive implants capable of dynamically responding to patient-specific regenerative demands.

Author Contributions

J.Z.: writing—original draft, writing—review & editing, visualization, software, formal analysis, data collection and curation; F.Y. and Z.J.: conceptualization, writing—review & editing, methodology, supervision, resources, project administration, funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

Not applicable.

Data Availability Statement

No new data were generated in this study.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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