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Neutrophils Beyond Acute Inflammation: Revisiting Their Role in Periapical Tissue Destruction

Opinion

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Introduction

Periapical lesions are a frequent consequence of persistent endodontic infection and represent a complex host response to microbial stimuli originating from the root canal system. Traditionally, the immunopathogenesis of periapical bone destruction has been attributed mainly to macrophages and lymphocytes, which are thought to regulate osteoclastogenesis through cytokine-mediated pathways. In contrast, polymorphonuclear neutrophils (PMNs) have long been regarded as short-lived effector cells primarily involved in acute inflammation, with little relevance in chronic periapical disease.

Accumulating experimental evidence, however, challenges this classical view and suggests that neutrophils play a sustained and functionally relevant role in both acute and chronic stages of periapical lesion development. This opinion article revisits the role of neutrophils in periapical inflammation and bone resorption, highlighting emerging data that support a paradigm shift in our understanding of periapical immunopathogenesis.

Classical Concepts and Their Limitations

Periapical lesions are widely interpreted as the outcome of a chronic inflammatory response driven by the interaction between bacterial products and host immune cells. Histological studies in humans and animal models have consistently reported macrophages and lymphocytes as prominent components of periapical inflammatory infiltrates. Consequently, most mechanistic studies have focused on lymphocyte–macrophage interactions and their ability to produce proinflammatory cytokines associated with osteoclast activation and alveolar bone loss. However, several experimental observations indicate that periapical lesion development can occur independently of lymphocyte activity, suggesting that alternative immune mechanisms may be involved. These findings raise important questions regarding the exclusive emphasis placed on adaptive immune cells and highlight the need to reconsider the contribution of innate immune populations, particularly neutrophils.

Emerging Evidence for Sustained Neutrophil Involvement

Neutrophils are classically described as the first line of defense against invading microorganisms, rapidly recruited to sites of infection where they exert antimicrobial functions through phagocytosis, degranulation, and the release of reactive oxygen species. Their role in chronic inflammatory diseases has historically been underestimated. Nevertheless, recent studies in inflammatory and autoimmune disorders have demonstrated that neutrophils can persist in tissues, actively modulate immune responses, and contribute to chronic tissue damage.

Data from our experimental studies using murine models of periapical lesions provide compelling evidence that neutrophils are not transient participants in periapical inflammation. Following pulp exposure and sustained root canal contamination, periapical lesions exhibited dense neutrophilic infiltrates at all evaluated time points, from early to advanced stages. Notably, neutrophils represented the predominant inflammatory cell population throughout lesion progression (Figure 1).

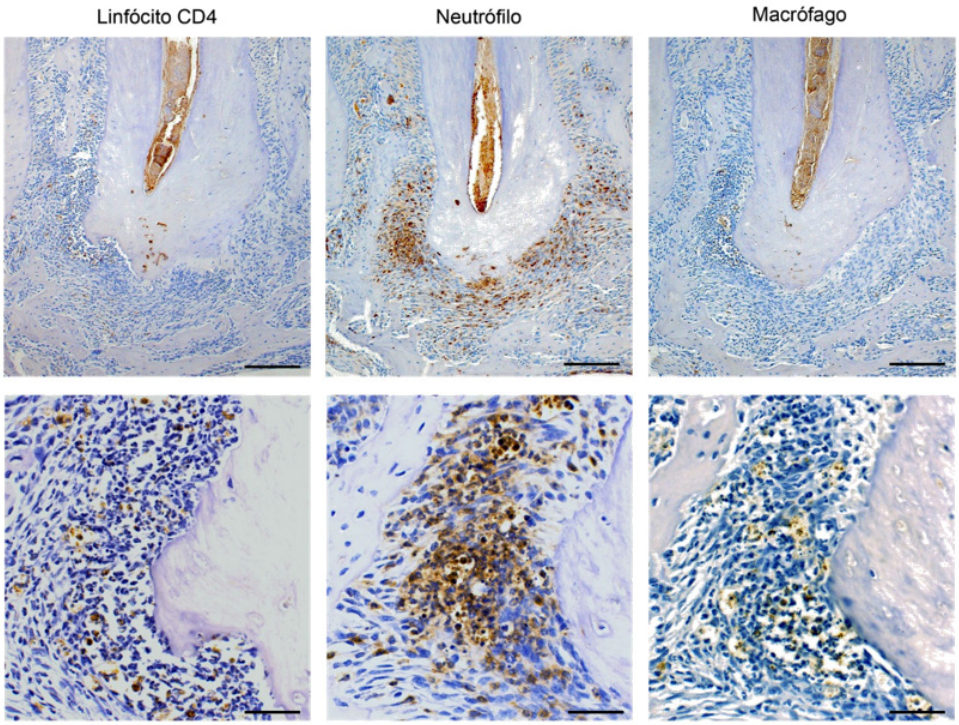

Figure 1: Representative immunohistochemical images of lymphocytes, neutrophils, and macrophages in periapical lesions of the distal root of the mandibular first molar 21 days after coronal opening and root canal contamination in wild-type mice.

Immunohistochemical analyses further demonstrated a positive correlation between neutrophil density, lesion size, and the number of osteoclasts over time. These observations suggest that neutrophils may directly or indirectly influence bone resorption dynamics in periapical tissues, positioning them as key regulators rather than passive bystanders [1-3].

Dual Roles of Neutrophils: Protection Versus Destruction

Beyond their antimicrobial activity, neutrophils are now recognized as potent sources of inflammatory mediators, including cytokines, proteases, and reactive oxygen species. In periapical lesions, neutrophil-derived mediators such as interleukin-1 may contribute to connective tissue degradation and osteoclast activation, thereby amplifying bone destruction. Interestingly, evidence from genetically modified mouse models indicates that neutrophil function in periapical lesions is highly context dependent. In several cytokine and adhesion molecule knockout models, an inverse correlation was observed between lesion size and neutrophil numbers, suggesting a protective role in controlling infection-induced bone resorption. In contrast, CCR5-deficient animals exhibited increased neutrophil accumulation associated with larger lesions, possibly due to impaired monocyte recruitment and dysregulated inflammatory responses.

These findings underscore the functional plasticity of neutrophils and support the concept that their impact on periapical tissues may range from protective antimicrobial defense to pathological tissue destruction, depending on the local immune environment.

Implications for Periapical Disease Research

Recognizing neutrophils as central players in periapical inflammation has important implications for both basic research and clinical practice. It challenges the traditional dichotomy between acute and chronic inflammation and highlights the need to investigate neutrophil phenotypes, regulatory mechanisms, and interactions with other immune and stromal cells within periapical tissues. Future studies should aim to clarify whether specific neutrophil subsets are associated with protective versus destructive outcomes and to determine how neutrophil activity is regulated during persistent endodontic infection. Such insights may open new avenues for therapeutic strategies that modulate neutrophil function to limit bone destruction while preserving host defense.

Concluding Remarks

The evidence discussed in this article supports a re-evaluation of the role of neutrophils in periapical lesion development. Rather than being confined to acute inflammation, neutrophils appear to be actively involved in both acute and chronic stages of periapical tissue destruction and may significantly influence disease progression. A deeper understanding of neutrophil biology in periapical lesions is essential for advancing our knowledge of endodontic pathology and for the development of more targeted and biologically informed therapeutic approaches.

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