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Dual nature of NETosis in oral squamous cell carcinoma: Promoting tumor progression and modulating immune responses

Letter to editor

Neutrophil extracellular traps (NETs) play a crucial role in both physiological and pathological processes, serving as both protectors and triggers. Although they are essential in the defense against pathogens, an excessive amount of NETs may lead to inflammation and tissue damage in conditions like rheumatoid arthritis and autoimmune diseases. In oral squamous cell carcinoma (OSCC), NETs are responsible for tumor progression and metastasis, shaping the microenvironment and evading immune surveillance. The diverse functions performed by neutrophil extracellular traps (NETs) make them promising targets for therapeutic intervention in oral squamous cell carcinoma (OSCC), providing a ray of hope amidst the processes of tumorigenesis. Therefore, understanding the dynamics of NETosis across diverse diseases is imperative for developing targeted therapeutic strategies that harness their protective functions while mitigating their detrimental effects. This approach would pave the way for precision medicine in the realm of immune modulation and disease intervention.

1. NETosis in tumour progression

Oral squamous cell carcinoma (OSCC) is a complex disease characterized by the interplay of various molecular components, including neutrophil extracellular traps (NETs). NETs play a dual role in OSCC as both agents and regulators, orchestrating a symphony of molecular intricacies that shape the tumor microenvironment [1]. In response to tumor-derived factors, neutrophils undergo NETosis, a transformation that involves the release of chromatin, histones, and granular proteins into the extracellular space. This process is guided by the toll-like receptor (TLR) signaling pathway, which triggers the production of reactive oxygen species (ROS) through the NOX2 enzyme [1,2].

The involvement of the protein kinase C (PKC) pathway is significant in this process, as it plays a crucial role in influencing the chromatin landscape, thereby aiding in the formation of neutrophil extracellular traps (NETs). Concurrently, the enzymatic activity of peptidyl arginine deiminase 4 (PAD4) is essential in orchestrating histone citrullination, a process that profoundly affects chromatin architecture. However, understanding the precise interplay between PKC and PAD4 in chromatin remodeling remains a puzzle, complicating our comprehension of their respective roles [3,4]. Nevertheless, the nuanced intricacies of PAD4's involvement in histone citrullination highlight its importance as a master regulator in the complex organization of chromatin structures. In the context of oral squamous cell carcinoma (OSCC), the dual nature of NETs presents a perplexing paradox, as they simultaneously signal malignancy and influence the tumor microenvironment. This complex interaction among molecular components creates a web of intricacies, obscuring our understanding of the fundamental mechanisms underlying tumorigenesis.

2. Therapeutic strategy in NETosis

In the therapeutic approach to oral squamous cell carcinoma (OSCC), targeting neutrophil extracellular traps (NETs) involves inhibiting their formation or function to impede tumor progression. This strategy encompasses inhibiting peptidyl arginine deiminase 4 (PAD4), a crucial enzyme involved in chromatin decondensation during NETosis, thereby reducing histone citrullination and NET release. Additionally, interventions may target upstream signaling pathways like toll-like receptor (TLR) signaling or reactive oxygen species (ROS) production to prevent NETosis initiation. Disrupting existing NET structures through enzymatic degradation or blocking their interaction with OSCC cells further inhibits tumor-promoting effects. Importantly, these therapies selectively target pathological NETosis while preserving normal neutrophil function, aiming to mitigate NET-mediated pro-tumorigenic effects and enhance OSCC treatment outcomes [5].

3. Histopathological insights on OSCC NET's

Histopathological examination of tissues from patients with oral squamous cell carcinoma (OSCC) provides valuable insights into the potential involvement of neutrophil extracellular traps (NETs) within the tumor microenvironment. While traditional staining techniques may not directly visualize NETs, characteristic features indicative of NETosis can be observed. Notably, increased neutrophil infiltration, accompanied by morphological changes such as altered nuclear morphology and the presence of eosinophilic material suggestive of extracellular DNA, points towards potential NETosis activity. Additionally, signs of acute inflammation, including vascular congestion and inflammatory cell infiltration, further support the involvement of NETosis in OSCC progression [6].

4. IHC detection of NET markers in OSCC

Immunohistochemistry (IHC) detects Neutrophil Elastase (NE), Myeloperoxidase (MPO), citrullinated histone H3 (Cit-H3), Peptidyl Arginine Deiminase 4 (PAD4), and DNA/histone complexes in oral squamous cell carcinoma (OSCC). These proteins are indicative of neutrophil extracellular trap (NET) formation. Additionally, interleukins (IL-1β, IL-8), tumor necrosis factor-alpha (TNF-α), and high-

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mobility group box 1 protein (HMGB1) highlight the inflammatory response linked to NETosis in OSCC. IHC integration aids in understanding NETosis presence, localization, and extent within OSCC tissue, facilitating targeted therapeutic strategies for OSCC management [6].

In summary, the intricate role of neutrophil extracellular traps (NETs) in oral squamous cell carcinoma (OSCC) underscores their dual nature as contributors to tumor progression and potential targets for therapeutic intervention. A comprehensive understanding of NETosis across various diseases is crucial for devising precise treatment strategies that harness their protective functions while mitigating their harmful effects. Targeted therapeutic approaches, such as inhibiting peptidyl arginine deiminase 4 (PAD4) or disrupting upstream signaling pathways, offer promising avenues for impeding OSCC progression. By selectively targeting pathological NETosis while preserving normal neutrophil function, these interventions hold significant potential to enhance treatment outcomes and advance the field of precision medicine in immune modulation and disease management. As research continues to unravel the complexities of NET-mediated processes in tumorigenesis, integrating these findings into clinical practice can lead to meaningful advancements in OSCC treatment and other NET-related conditions.

CRediT authorship contribution statement

Nitya Krishnsamy: Conceptualization, Data curation, Methodology, Project administration, Resources, Writing – original draft. **Kochli Channappa Niranjan:** Conceptualization, Supervision, Validation, Writing – review & editing. **Vikram S. Amberkar:** Conceptualization, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

Nil.

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