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Commentary

Interaction between intratumoral microbiota and neutrophils influences tumor progression

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Abstract: In recent years, complex interactions between intratumoral bacteria and neutrophils have been identified as significant factors in tumor occurrence and development. This commentary synthesizes findings from the past five years to explore these interactions. It is observed that during tumor progression, intratumoral bacteria promote neutrophil infiltration and the formation of neutrophil extracellular traps (NETs), which in turn drive tumor development and metastasis. Conversely, infiltrating neutrophils are also capable of slowing tumor progression by limiting the number of intratumoral bacteria. This dual role underscores a potential avenue for improving cancer treatment outcomes.

Keywords: Intratumoral microbiota, neutrophils, tumor progression

Introduction

Recent research reveals a complex interplay between microorganisms and cancer progression, highlighting that while few directly cause malignancies, many collaborate with the host immune system to promote tumor growth [1]. Notably, neutrophils - the most abundant myeloid cells in human blood - are emerging as key regulators within this dynamic [2]. This paper synthesizes findings from the last five years, demonstrating how intratumoral bacteria can attract neutrophils, leading to enhanced infiltration and the formation of neutrophil extracellular traps (NETs), which facilitate tumor initiation and metastasis. Conversely, neutrophils can also reshape the bacterial landscape in tumors, potentially slowing progression. By delving into these interactions, this commentary illuminates promising therapeutic avenues that target both microbial and immune factors, offering new hope for cancer treatment strategies (**Figure 1A**, **1B**).

Mechanisms of interaction between intratumoral microbiota and neutrophils

Recent studies highlight the intricate relationship between intratumoral bacteria and neutrophils in cancer progression, revealing how bacteria can attract neutrophils to tumor sites and induce a pro-inflammatory microenvironment that accelerates tumor growth. For instance, the Harris team demonstrated that administering A. temperans to K-ras and Tp53-mutant animal models resulted in neutrophils adopting a pro-tumor phenotype [3]. Similarly, Tan et al. found that Porphyromonas gingivalis exacerbated tumor development in mouse models of prostate cancer, fostering a pro-inflammatory environment characterized by neutrophil dominance. Mechanistically, this bacterium enhances the secretion of neutrophil chemokines and elastase, further driving cancer progression [4].

Moreover, intratumoral bacteria promote the formation of neutrophil extracellular traps (NETs), which, while aiding in bacterial clearance, can also facilitate tumor invasion. Liu et al. demonstrated that chronic alcohol consumption activates bacterial products, leading to NET formation that contributes to hepatocellular carcinoma. Antibiotic treatment reducing gut bacteria correlated with decreased NET markers and inflammatory cytokines, suggesting a link between microbial presence and tumorigenesis [5]. In addition, translocated bac-

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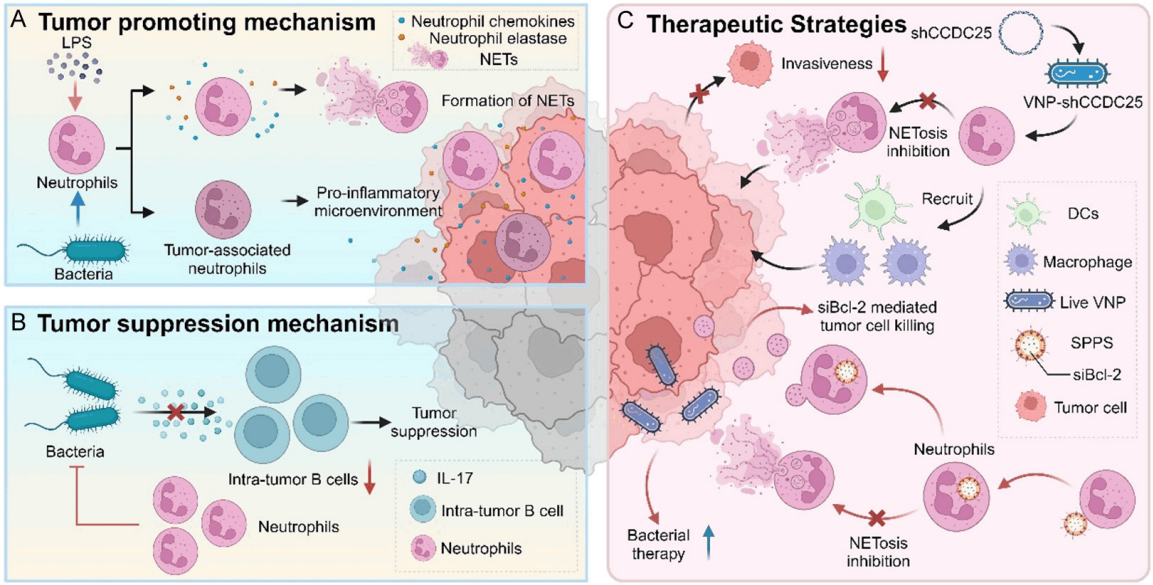

Figure 1. The mechanism and treatment strategy of the interaction between intratumoral microbiota and neutrophils affecting tumor progression. A. Bacteria and products promote tumor progression by inducing the formation of neutrophil extracellular traps (NETs) and creating a pro-inflammatory microenvironment. B. Neutrophils inhibit tumor progression by modulating bacterial function. C. Two therapeutic strategies targeting the interaction between intratumoral bacteria and neutrophils.

teria induce a large recruitment of NETs through the portal vein system, forming a fibrous network composed of DNA, histones, and antimicrobial proteins, which plays a role in bacterial clearance and affects intercellular adhesion between liver cells, further enhancing the invasive ability of tumor cells [6].

Conversely, neutrophils can also regulate the intratumoral microbiota, inhibiting tumor growth. Triner et al. noted significant differences in microbiota composition between neutrophil-deficient and control mice, where neutrophils were found to reduce bacterial abundance and associated inflammation, ultimately slowing colorectal tumor progression [7]. These findings underscore the dual and complex roles that intratumoral bacteria and neutrophils play in shaping cancer biology, presenting potential avenues for therapeutic intervention.

Therapeutic strategies based on the interaction between intratumoral microbiota and neutrophils

Recent advancements in cancer treatments are increasingly targeting the interaction between intratumoral bacteria and neutrophils, particularly focusing on reducing the formation of neutrophil extracellular traps (NETs). For instance, Liu et al. engineered the transmembrane protein CCDC25, which selectively binds to NET-DNA, into the oncolytic bacteria VNP20009, creating VNP-shCCDC25. This approach effectively inhibits pro-metastatic signaling pathways associated with CCDC25 at tumor sites, reduces NET formation, and enhances the recruitment of neutrophils and macrophages to the tumor core, significantly suppressing metastasis in lung cancer models [8]. Similarly, Zhao et al. developed a neutrophil-hitchhiking nanoparticle (SPPS) designed to inhibit NET formation, thereby enhancing bacteria-mediated tumor therapy. SPPS reprograms NETosis by clearing intracellular reactive oxygen species (ROS), which markedly decreases NET levels and improves bacterial viability in the tumor microenvironment. Notably, the encapsulated gene drug (siBcl-2) can be repackaged within apoptotic bodies by inducing apoptosis in neutrophils undergoing NETosis, enabling targeted delivery to tumor cells and improving antitumor efficacy through a synergistic effect [9]. These innovative strategies illustrate the potential of manipulating neutrophil and bacterial interactions in cancer treatment, paving the way for future research to

explore novel therapeutic approaches (**Figure 1C**).

Conclusion

In summary, intratumoral bacteria play a dual role in cancer dynamics by attracting neutrophils, which promote their infiltration and facilitate the formation of NETs, ultimately aiding in tumor development and metastasis. Conversely, neutrophils can limit the abundance and growth of these bacteria, thereby slowing tumor progression. Current cancer therapies are increasingly focusing on reducing NET formation as a key intervention strategy.

As research advances, a deeper exploration of the interactions between intratumoral bacteria and neutrophils is expected to provide valuable insights into their complex relationship. Understanding these mechanisms could lead to innovative therapeutic approaches that harness this interplay, paving the way for novel clinical applications in cancer treatment.

Disclosure of conflict of interest

None.

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