Tumor-Associated Neutrophils

Tumor-Associated Neutrophils (TANs) in Glioma

Tumor-associated neutrophils (TANs) are a subset of neutrophils that infiltrate the tumor microenvironment (TME) and play a **dual role** in tumor progression. Their functions can be **pro-tumorigenic (N2 phenotype) or anti-tumorigenic (N1 phenotype)**, depending on the signals they receive from the TME.

Roles of TANs in Glioma

Gliomas are highly heterogeneous brain tumors, and the tumor microenvironment (TME) significantly influences their progression. TANs contribute to glioma growth through several mechanisms:

1. Immunosuppressive Effects (Pro-Tumorigenic N2 Phenotype) - **Secrete immunosuppressive cytokines** (e.g., TGF-β, IL-10) that inhibit T-cell function. - Promote the **recruitment of regulatory T cells (Tregs)** and myeloid-derived suppressor cells (MDSCs). - Suppress antigen-presenting cell (APC) activity, reducing anti-tumor immune responses.

2. Enhancement of Glioma Growth & Invasion - Release **matrix metalloproteinases (MMPs)** that degrade the extracellular matrix (ECM), facilitating tumor invasion. - **Promote angiogenesis** via VEGF secretion, supporting glioma vascularization. - Increase **glioma cell proliferation** by releasing growth factors such as HGF and G-CSF.

3. Drug Resistance and Therapeutic Implications - TANs contribute to **resistance to chemotherapy**, including temozolomide (TMZ), by supporting glioma cell survival. - They interact with glioma stem-like cells (GSCs), promoting tumor recurrence and resistance to therapy.

4. Potential Anti-Tumorigenic Functions (N1 Phenotype) - In the presence of **IFN-β or type I interferons**, TANs may shift toward an **N1 phenotype**, which enhances cytotoxicity against glioma cells. - **Produce reactive oxygen species (ROS) and TNF-α**, which can trigger glioma cell death.

Experimental research studies

Wang et al. aimed to investigate the heterogeneity and role of TANs in glioma and to develop a prognostic model.

Analysis of scRNA-seq data identified cellular subpopulations and differentially expressed neutrophil-related genes (DE-NRGs). Bulk RNA-seq was obtained from four independent datasets. Molecular subtypes of glioma samples were determined by consensus clustering. WGCNA was conducted to elucidate the association between gene modules and subtypes. We developed a risk score model. Expression of selected genes was confirmed using immunohistochemistry (IHC). In vitro experiments were also performed for functional verification, including CCK8, EdU, Transwell, and TUNEL assays.

A total of 108 DE-NRGs for TANs were identified based on scRNA-seq data. Two molecular subtypes were characterized, showing significant differences in prognosis and clinical features. Immune-related analyses demonstrated varied immunological characteristics between subtypes. The risk score model was constructed with 7 genes, including AEBP1, CAVIN1, DCTD, DEPP1, DUSP6, FKBP9, and UGCG. It showed significant prognostic value and was validated across three external datasets. The mutation landscape highlighted higher IDH mutation prevalence in low-risk groups. Drug sensitivity analysis indicated TMZ resistance in high-risk groups. In vitro experiments showed that UGCG could promote glioma cell proliferation, migration, and invasion, while decreasing apoptosis.

This study explored the heterogeneity of TANs and developed a prognostic model, providing insights for prognostic prediction and guiding personalized treatment strategies in glioma. Declaration of Generative AI in Scientific Writing: The authors declare nonuse of generative AI and AI-assisted technologies in the writing process [1)].

Key Findings from the Study (Cancer Med. 2025) - **108 differentially expressed neutrophil-related genes (DE-NRGs) identified.** - **Two glioma molecular subtypes based on TAN profiles.** - **High-risk group showed temozolomide (TMZ) resistance.** - **Gene UGCG was found to promote glioma proliferation, migration, and invasion.**

Clinical Implications - **TAN-targeted therapies** (e.g., blocking TGF-β signaling to prevent pro-tumorigenic transformation). - **Immunotherapy strategies** to reprogram TANs toward an anti-tumorigenic phenotype. - **TAN-based biomarkers** for glioma prognosis and treatment resistance prediction.

This study highlights the complexity of TANs in glioma and their potential as therapeutic targets for improving treatment outcomes.

1)

Wang W, Li J, He Q, Liu C, Wang S, Zheng Z, Zhang B, Mou S, Sun W, Zhao J. Integrated Analysis to Reveal Heterogeneity of Tumor-Associated Neutrophils in Glioma. Cancer Med. 2025 Mar;14(5):e70745. doi: 10.1002/cam4.70745. PMID: 40052358.