A037 · Aging-associated Mechanisms of Aggressiveness in HPV(-) Head and Neck Cancer

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Session: Day 2 · Fri Oct 2, 2026 · 2:15–4:15 PM

Aging represents a fundamental driver of cancer risk and progression, yet the mechanisms by which aging reshapes the tumor microenvironment remain incompletely understood. To interrogate how aging alters cellular and microenvironmental organization in cancer, we developed an integrated single-cell atlas of HPV-negative head and neck squamous cell carcinoma (HNSCC) encompassing 73 patients aged 18–91 years. Using a multi-layered computational framework combining NMF-based module discovery and partial correlation network analysis, we reveal that age-associated differences in tumor composition are driven primarily by selective shifts in cell type abundance and organization rather than widespread age-dependent transcriptional rewiring. We identify an age-enriched cellular community centered on basal-like squamous epithelial states linked to epithelial-mesenchymal transition, matrix-associated myofibroblast-like CAFs, and FOLR2+ macrophages, which together associate with poor prognosis and reduced immune infiltration. Cross-dataset in-silico validation via TCGA transcriptomes, spatial transcriptomics, and mouse tumor models confirms the correlation of these cell types across patients, specific ligand-receptor usage, and increased proportions of epithelial and stromal cells in aged mouse models. Among epithelial cell-intrinsic age-associated transcriptional changes, midkine (MDK) emerges as a rare but robust tumor-derived signal linked to stromal remodeling, immunosuppression, and invasive epithelial programs. These findings reveal conserved mechanisms of age-dependent cellular reorganization in the tumor microenvironment and identify MDK and associated stromal-remodeling pathways as potential intervention points for age-stratified cancer therapy.

Aging-associated Mechanisms of Aggressiveness in HPV(-) Head and Neck Cancer

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