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Commentary

Age-Specific Prognostic Role of *NLRC4* in HNSCC Therapy

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DESCRIPTION

Head and Neck Squamous Cell Carcinoma (HNSCC) is a complex and aggressive cancer, made more challenging by the growing proportion of elderly patients in its demographic. With approximately one-third of HNSCC cases occurring in individuals aged 70 or older, tailoring treatment strategies to this subgroup is no longer optional it is essential. Unfortunately, standard therapeutic protocols often fail to account for the biological and clinical heterogeneity that aging brings. The use of radiotherapy, chemotherapy, and immunotherapy in older patients remains controversial, with limited benefit seen compared to younger cohorts. This discrepancy underscores a deeper issue the lack of effective, predictive biomarkers that consider how aging alters tumor biology.

The missing piece in geriatric oncology

Our recent multi-omics, multicenter study sheds light on this very question, revealing that not only does gene expression matter in predicting survival, but the interaction between specific genes and age might be even more critical. Among the thousands of genes analyzed, *NLRC4* stood out as the only gene whose prognostic impact was consistently modified by age across multiple datasets. This finding offers a compelling new perspective on how we should approach personalized treatment in HNSCC.

In younger patients, higher *NLRC4* expression correlated with better survival outcomes an indication of a protective role. In contrast, in elderly patients, the same expression pattern was associated with worse outcomes. This flip in prognostic direction suggests a complex, age-modified biological function of NLRC4, one likely tied to immune system dynamics that change over time. For clinicians, this means that a "One-size-fits-all" interpretation of gene expression levels is not just inadequate it could be misleading.

NLRC4, the immune microenvironment and a new era of prognostic modeling To truly grasp the prognostic significance of *NLRC4* in HNSCC, one must look beyond simple gene-age correlations and consider the broader cellular context. Our immune landscape analysis revealed that *NLRC4* expression is predominantly high in monocytes and macrophages, cell types that play dual roles in tumor progression depending on their polarization state (M1 *vs.* M2). This observation is particularly relevant in aging individuals, immune cell function and plasticity undergo significant alterations.

In elderly patients, the tumor microenvironment may tip toward an immune-suppressive state, making *NLRC4's* role more aligned with pro-tumor activities. In younger individuals, a more active and responsive immune system may allow *NLRC4* to participate in anti-tumor immunity. This biological insight aligns well with our observed data: *NLRC4* is not inherently good or bad it is context-dependent, and that context is heavily influenced by age.

But the implications of this discovery go even further. Through three-way interaction analysis involving *NLRC4*, age, and extracellular matrix related genes particularly those from the collagen family we demonstrated that high-order interactions provide superior prognostic accuracy compared to conventional two-way models. In other words, understanding multiple factors interact can drastically enhance our ability to predict outcomes and personalize treatment, especially in complex cancers like HNSCC.

This leap in predictive modeling has practical applications. For example, by stratifying patients into subgroups based on *NLRC4* expression and age, oncologists could make more informed decisions regarding aggressive treatments versus supportive care. Additionally, *NLRC4* could become a target for age-specific therapies perhaps modulating its activity in older patients to counteract its pro-tumor role.

Moreover, drug discovery pipelines may benefit from this finding. Our bioinformatic analyses identified several immunity-related drugs that target pathways associated with *NLRC4*, opening avenues for repurposing existing medications or developing new agents tailored to gene-age profiles. The

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convergence of transcriptomics, immunology, and clinical oncology presents a fertile ground for innovation.

CONCLUSION

The discovery of *NLRC4* as an age-modified prognostic marker in HNSCC represents a pivotal step toward precision oncology that respects biological age as a defining factor. As the population ages and cancer treatment grows more sophisticated, the blunt instrument of chronological age must be replaced with molecularly informed decision-making. Genes like *NLRC4* exemplify the potential of this paradigm shift. The implementation of high-dimensional models in clinical settings requires validation, regulatory approval, and infrastructure that can handle complex data inputs. However, the direction is clear the future of cancer treatment lies not just in finding new drugs, but in understanding known factors interact within the rich tapestry of human biology.

For HNSCC patients and particularly the elderly this could mean more accurate prognoses, better-targeted therapies, and ultimately, improved survival and quality of life. The age of age-informed oncology has arrived, and *NLRC4* may well be one of its heralds.