TFEB ACTIVATION IN MEDIASTINAL LYMPH NODES: A POTENTIAL MODULATOR OF IMMUNE RESPONSE IN NSCLC

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Background Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths worldwide. Despite the promise shown by immune checkpoint inhibitors (ICIs) in enhancing survival and tumor control for a subset of patients, a significant portion remains non-responsive, which may be attributed to a deficiency in CD8 T-cell tumor infiltration. The presence of pre-existing tumor-reactive T-cell infiltration is, in fact, a crucial determinant of ICI efficacy. Interestingly, despite NSCLC tumors with KRAS and TP53 mutations showing pronounced T-cell infiltration, ICI response rates stand at about 35%, pointing to varied tumor-reactive T-cell functionalities. This inconsistency suggests that the functional states of tumor-reactive T-cells vary considerably among patients. Central to these challenges is the immunosuppressive milieu of the lung tumor microenvironment that can be attributed to impaired peptide presentation in the tumor-draining lymph nodes together with a persistent IFN-γ activation signature.

Methods and Results In this study, we spotlight the role of transcription factor EB (TFEB), crucial for autophagy and MHC-II peptide presentation. Specifically, TFEB exhibited consistent overexpression in lung tissue-draining mediastinal lymph nodes, contrasting other lymphatic regions. Notably, overexpressing TFEB in CD11c+ dendritic cells augmented tumor-specific CD4 T-cell responses, yet reduced CD8 T-cell activities, suggesting a potential shift towards a tolerogenic immune environment in NSCLC.

Conclusions Conclusively, our insights into TFEB’s function in NSCLC highlight the complex relationship between tissue-specific elements and tumor immunogenicity, offering avenues for refining immunotherapeutic strategies.

REFERENCES

Ethics Approval The mouse protocol has been approved by Weill Cornell Medicine committee: 2020-0017

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