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Opinion Article

An Aging-Related Signature Predicts Favorable Outcome and Immunogenicity

Xiaoan Wang*

Department of Clinical Microbiology, National Institute of Respiratory Diseases (INER), Mexico City, Mexico

ABOUT THE STUDY

In 2018, Electron Spectroscopy for Chemical Analysis (ESCA) was the sixth leading cause of death among all cancers, accounting for 5% of all cancer-related deaths. Esophageal squamous cell cancer and adenocarcinoma are the two types of ESCA. After diagnosis, approximately half of ESCA patients present with unresectable or metastatic disease. Better therapy efficacies and clinical benefits for ESCA patients have been observed in recent years as a result of advancements in multidisciplinary treatment. The survival outcome of unresectable or metastatic ESCA, on the other hand, was still poor, with a median survival of less than one year. Several molecular indicators have recently been identified to predict ESCA prognosis outcomes; however, they are sometimes ineffective. As a result, more robust biomarkers are required to reliably assess the survival status of ESCA patients.

Immune Checkpoint Inhibitor (ICI) therapy has significantly improved the prognosis of several advanced cancers, including melanoma, renal cancer, Non-Small Cell Lung Cancer (NSCLC), and Essential Shared Care Agreements (ESCA). Furthermore, ICI therapy, along with surgery, chemotherapy, and targeted therapy, has become a main clinical practice for Lung Adenocarcinoma (LUAD). Blocking the immune checkpoints of Programmed Cell Death Protein 1 (PD-1) or its Programmed Death Ligand-1 (PD-L1) is the best-described immunotherapy approach to date, and it is quickly becoming the standard first-line treatment strategy for NSCLC. Although clinical trials and real-world data show that ICI treatment has a significant therapeutic advantage, a major limitation is that only a subset of patients responds to clinical treatment. As a result, new effective determinants for selecting ESCA patients for immunotherapy are urgently needed.

Age is a significant risk factor for the majority of diseases, including human tumors. Aside from age, its relevant molecular traits have also been linked to disease prognosis. Recent research has linked specific genes (e.g., *APOE* and *FOXO3*), genomic regions (e.g., 5q33.3), and numerous single-nucleotide polymorphisms to longevity. Because of the complex interactions between ageing and numerous factors in the genome, environment, and age-related diseases, it is difficult to decompose and investigate ageing. Peters et al. conducted a large-scale transcriptomic exploration to better understand the ageing transcriptome landscape and identified aging-relevant genes.

In order to establish and confirm an aging-relevant risk signature, we collected 351 ESCA samples from three independent datasets based on publicly available sources. Multi-level immunologic analysis was performed to investigate the possible molecular functions underlying the determined risk signature, and the results revealed that this risk signature has a strong capacity for assessing immune microenvironment. Furthermore, the discovered ageing signature may be able to predict ICI therapy response and outcome. The findings of this study may be useful in predicting ESCA patients' survival and immunogenicity.

We formed and validated an aging-relevant risk signature for prognosis evaluation, immunogenicity, and ICI response prediction using gene expression profiles and clinical data from several ESCA datasets. Future prospective studies are required, but our findings suggest that the ageing risk signature may play a role in ESCA clinical prognosis and immunotherapeutic efficacy surveillance.

Endogenous and exogenous factors that indicate specific mutational patterns are manifested as mutational signatures. Among these, the aging-relevant mutational signature 1 was found to be associated with a poor tumour microenvironment and prognosis in triple-negative breast cancer, implying that it may play a role in immune treatment efficacy. Following that, a recent study integrated somatic mutational profiles of melanoma and NSCLC samples that received ICI therapy and discovered that both tumours with an ageing signature had a poorer survival outcome. In contrast to mutation-level biomarkers, an aging-relevant risk signature was constructed at the transcriptomic level in our study, and we discovered that this signature has the ability to predict prognosis outcome and immunogenicity in ESCA.

Correspondence to: Xiaoan Wang, Department of Clinical Microbiology, National Institute of Respiratory Diseases (INER), Mexico City, Mexico, E-mail: xiaoanwang@gmail.com

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Six of the 22 identified ageing genes (*ANXA5, MEOX1, PCSK5, HLA-DOB, SREBF1,* and *KLRB1*) were also linked to tumour immunity. *ANXA5* has been linked to antigen-presenting cell infiltration in gliomas and has recently been identified as a novel immune checkpoint inhibitor. In breast cancer, a molecular signature containing *MEOX1* was created to predict survival and immune immunologic status. *PCSK5* has been linked to cancer alternative splicing events, which contribute to carcinogenesis and the immune microenvironment in squamous cell carcinoma of the head and neck. An immune-related prognostic model including HLA-DOB was found to be associated with prognosis and immunity in ovarian cancer. Increased *SREBF1* transcription promoted invariant natural killer T cell activity, increasing lipid biosynthesis while inhibiting anti-tumour effect. A recent study found that *KLRB1* deficiency increased T cell-mediated toxicity and anti-tumour function in glioma. The evidence presented above supports the potential implications of a known risk signature in immune infiltration and immunotherapy efficacy.

Given the limited of ESCA datasets containing both gene expression profiles and ICI treatment data, we used an urothelial cancer immunogenomic dataset, which is currently the largest immunotherapy dataset, to investigate the relationship between the ageing risk signature and ICI treatment efficacy. The results showed that patients in the low-risk group had a better ICI prognosis and response status (i.e., CR and PR). Taking into account cancer homogeneity in specific situations (e.g., therapy outcome assessment), we conclude that the aging-relevant signature predicts ICI efficacy not only in urothelial cancer but also in ESCA and other tumour subtypes.

Our study has limitations. First, the gene expression profiles of ESCA samples were obtained from publicly available datasets, which may have resulted in differences in the analysis procedure of different cohorts. Second, only The Cancer Genome Atlas Esophageal Carcinoma (TCGA-ESCA) dataset was used to calculate relevant results from the genomic mutational profile; no additional mutational data was used for validation. Finally, there is a lack of experimental verification for multiple associations.

In summary, we developed a risk prediction model using ageing gene expression data from ESCA samples to assess prognosis, immunogenicity, and immunotherapy response. The newly discovered signature could be used as an indicator for ESCA clinical monitoring and treatment.