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Evolution of TETs and human T-cell development

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DESCRIPTION

The biology of human Thymic Epithelial Tumors (TETs), which are frequently found in the anterior mediastinum, is poorly understood. Here, they demonstrate using single-cell immune landscape analysis that there are three different subtypes of TETs based on the developmental pattern of intra-humoral T-cells. In the context of the various epithelial tumor cell types, they describe the developmental changes and TCR repertoires of tumor-infiltrating T cells. They show that a subset of tumor cells with KRT14/GNB3 expression and the medullary thymic epithelial cell phenotype accumulate in type 1 TETs while T-cell positive selection is suppressed. Type 2 TETs are dominated by CCL25+ cortical TEC-like cells that appear to promote T-cell positive selection. Interestingly, the CHI3L1+ medullary TEC-like cells that are the characteristic feature of type 3 TETs don't seem to support T-cell development; however, they may induce a tissue-resident CD8+ T cell response.

In summary, our work suggests that the molecular subtype of epithelial tumor cells in TETs determines their tumor immune microenvironment, and thus GNB3 and CHI3L1 might predict the immunological behaviour and hence the prognosis of these tumors. The most common primary tumors in the human anterior mediastinum are thymic epithelial tumors, including thymomas and thymic carcinomas. The aetiology and biology of TETs are still poorly understood due to a lack of pertinent cell lines and animal models. Because clinically aggressive malignant behaviour can be seen in previously classified benign tumors, the most recent clinical guidelines7 state that all TETs are potentially malignant. This implies that more research is required to fully understand the biological traits of these diverse malignancies. TETs are typically thought to have evolved from thymic epithelial cells, which are essential for the development of T cells in mammals. According to the epithelial origins of human TETs, there are two main subtypes of TECs that can be distinguished: cortical TECs and medullary TECs, which are primarily found in the cortex and medulla structures of the thymus, respectively. In contrast to mTECs, which are primarily involved in negative selection to establish central self-tolerance, it has been convincingly shown that cTECs are necessary for the positive selection of T cells during T-cell development in the thymus.

Compared to patients with type A and type C thymomas, patients with type B thymomas which may be caused by mTECs have a higher incidence of autoimmune diseases. This data suggests that tumour cells may affect T-cell development differently in human TETs. Emerging molecular classifications have recently offered insight into the molecular-level stratification of prognosis and treatment for patients with TETs. Here, they conduct a thorough investigation to unravel the epithelial origins of human TETs and their influence on immune cell composition using mass cytometry, single-cell sequencing, TCR repertoires, histological analysis, FCM detection, and immunofluorescence testing. They identify three main types of human TETs and uncover potential mechanisms that may contribute to the divergent T-cell development in each tumor type based on the phenotype of tumor cells, the immune landscape of tumors, intra-tumoral T-cell development pattern, and TCR repertoire.

They carried out a comprehensive investigation of the immune environment of human TETs using various methods. First, they were able to use CyTOF to determine the cell composition of human thymus and TETs using a panel of more than 40 markers, and they discovered a significant difference between the two tissues. The immune landscape appeared to differ among samples of human TETs whose canonical classifications were not perfectly aligned. They divided the human TET sample data into three types based on how similar their cellular make-up was. It's interesting that they discovered that our alternative classification's immune landscape did not fully align with the WHO classification and Masaoka stage.