1. Unveiling the Tumour Microenvironment in Canine Pulmonary Adenocarcinoma Through Single-Cell RNA Sequencing

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Primary pulmonary carcinoma, a prevalent malignancy in humans, is relatively rare in dogs. When possible, surgical resection is the treatment of choice, but the prognosis remains poor in advanced stages. Deciphering the complex tumour microenvironment is pivotal as it may reveal targets for adjuvant therapies. This study aimed to investigate specific cancer-associated cell types and gene expression profiles in canine pulmonary adenocarcinoma (PAC), the most common histologic subtype of canine primary pulmonary carcinoma.

Fresh leftover biopsy samples from three histologically confirmed primary PAC cases, surgically excised via curative-intent lobectomy, were obtained. Tissues were dissociated into single-cell suspensions and droplet-based single-cell RNA sequencing (10x Genomics) was conducted. The data from PAC samples were integrated with previously analysed datasets of four healthy lung samples for downstream analysis. Cell subpopulations were identified based on their gene expression and their relative abundances in both conditions were statistically compared. Differentially expressed genes between PAC and healthy samples were calculated and gene set enrichment analyses were conducted to better characterise cancer-related heterogeneity within cell types.

In PAC samples, four main cell compartments were observed, as in healthy lungs: mesenchymal, immune, epithelial, and endothelial. Most cell subpopulations identified in healthy lungs were also present in tumours. PAC samples exhibited a higher relative proportion of mature dendritic cells and lymphoid cells, particularly regulatory T lymphocytes, B lymphocytes, and plasma cells. Additional immune cell subtypes were even exclusively found in PAC samples. As expected, PAC epithelial cells were dominated by multiple clusters identified as cancer cell clusters, each exhibiting a particular gene expression signature. Differential gene expression analyses revealed distinct gene expression profiles between PAC and healthy lung tissues. For instance, cancer-associated fibroblasts (CAFs) overexpressed genes associated with contractility, inflammation, matrix remodelling, and collagen synthesis. Additionally, gene set enrichment analysis of CAFs revealed significant enrichment of pathways associated with epithelial-to-mesenchymal transition.

This study expands our understanding of the cellular and molecular heterogeneity of the canine pulmonary adenocarcinoma microenvironment, identifying molecular signatures of cancer-associated cell types. The gained insights carry significant implications for the development of new strategies for the treatment of this condition, especially in advanced stages or unresectable cancers.

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