

Expansion of CD4+ cytotoxic T lymphocytes with specific gene expression patterns may contribute to suppression of tumor immunity in oral squamous cell carcinoma: single-cell analysis and in vitro experiments

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<https://hdl.handle.net/2324/7329444>

出版情報 : Kyushu University, 2024, 博士 (歯学) , 課程博士
バージョン :
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論文名 : Expansion of CD4⁺ cytotoxic T lymphocytes with specific gene expression patterns may contribute to suppression of tumor immunity in oral squamous cell carcinoma: single-cell analysis and in vitro experiments.

(口腔扁平上皮癌において増加する CD4 陽性細胞傷害性 T 細胞は腫瘍免疫を抑制する : シングルセル解析と in vitro 実験)

区分 : 甲

論文内容の要旨

Background: Cancer immunotherapy targeting CD8⁺ T cells has made remarkable progress, even for oral squamous cell carcinoma (OSCC), a heterogeneous epithelial tumor without a substantial increase in the overall survival rate over the past decade. However, the therapeutic effects remain limited due to therapy resistance. Thus, a more comprehensive understanding of the roles of CD4⁺ T cells and B cells is crucial for more robust development of cancer immunotherapy.

Methods: In this study, we examined immune responses and effector functions of CD4⁺ T cells, CD8⁺ T cells and B cells infiltrating in OSCC lesions using single-cell RNA sequencing analysis, T cell receptor (TCR) and B cell receptor (BCR) repertoire sequencing analysis, and multi-color immunofluorescence staining. Finally, two Kaplan-Meier curves and several Cox proportional hazards models were constructed for the survival analysis.

Results: We observed expansion of CD4⁺ cytotoxic T lymphocytes (CTLs) expressing granzymes, which are reported to induce cell apoptosis, with a unique gene expression patterns. CD4⁺ CTLs also expressed CXCL13, which is a B cell chemoattractant. Cell-cell communication analysis and multi-color immunofluorescence staining demonstrated potential interactions between CD4⁺ CTLs and B cells, particularly IgD⁻ CD27⁻ double negative (DN) B cells. Expansion of CD4⁺ CTLs, DN B cells, and their contacts has been reported in T and B cell-activated diseases, including IgG4-related disease and COVID-19. Notably, we observed upregulation of several inhibitory receptor genes including CTLA-4 in CD4⁺ CTLs, which possibly dampened T and B cell activity. We next demonstrated comprehensive delineation of the potential for CD8⁺ T cell differentiation towards dysfunctional states. Furthermore, prognostic analysis revealed unfavorable outcomes of patients with a high proportion of CD4⁺ CTLs in OSCC lesions.

Conclusion: Our study provides a dynamic landscape of lymphocytes and demonstrates a systemic investigation of CD4⁺ CTL effects infiltrating into OSCC lesions, which may share some pathogenesis reported in severe T and B cell-activated diseases such as autoimmune and infectious diseases.