Abstract

Treatment options for salivary gland carcinomas (SGC), especially advanced ones, are limited. Immunotherapy, particularly therapy with immune checkpoint inhibitors (ICI), has brought significant progress and change in the treatment of malignant tumors. The effect and response to immunotherapy using ICI are largely driven by the characteristics of immune cells in the tumor tissue and, as it turns out, also in the peritumoral tissue. We conducted an immunohistochemical analysis of the expression of the immune checkpoint protein PD-1 and its ligand PD-L1 on the surface of tumor cells as well as tumor-infiltrating immune cells (TIIC) in samples of salivary carcinomas, separately in their centre and at their periphery. In addition to the above, an increasing amount of evidence suggests that resistance to ICI therapy is modulated by the interaction of the Fas receptor (CD95) and Fas ligand (FasL, CD178) between tumor cells and immune cells. We therefore decided to explore the expression and interaction of Fas-FasL between tumor cells and tumor-infiltrating immune cells in the centre of the tumor and in the peritumoral area of salivary carcinoma samples. Differential evaluation of the tumor centre and tumor periphery across various histological subtypes of SGC revealed the role of peripheral TIICs and tumor cells in understanding the factors that determine the severity of the disease. Expression of PD-1 in peripheral TIICs of SGC confirmed the potential of immunotherapy using checkpoint inhibitors in patients with salivary gland carcinomas. Expression of PD-L1 in peripheral tumor cells of SGC showed a significant correlation with disease severity. Our findings suggest that the periphery of SGC tumors might represent a suitable biomarker area for assessing the severity of SGC and a suitable area for studying the mutual interactions between the tumor and the immune system. Furthermore, the analysis of the expression of the Fas receptor and Fas ligand shows that the Fas-FasL interaction on the periphery of salivary gland carcinomas presents as a useful new predictor of disease severity and response to immunotherapy. The acquired data further suggests that salivary gland carcinoma cells are resistant to apoptosis triggered by the immune cell's Fas ligand and, in higher stage tumors, may instead utilize the Fas ligand to eliminate immune cells, contributing to tumor evasion of immune response and further mediating resistance to immunotherapy.