

## **Abstract**

Tumor immunology is a progressively developing, multidisciplinary branch of biology. Results of basic research have already been successfully translated to clinical practice. The immediate success of new immunotherapeutic drugs, especially immune checkpoint inhibitors, has further supported the expansion of basic and clinical research in this field. In the case of head and neck squamous cell carcinoma (HNSCC), some immune system elements, such as CD8<sup>+</sup> T cells, were shown to play an important role in the progression of the disease. Importantly, HNSCC is a diverse group of diseases, and a significant number of the tumors are induced by high-risk strains of human papillomavirus (HPV). HPV-associated tumors (HPV<sup>+</sup>) respond better to standard therapy, and the immune system was shown to be one of the crucial factors in this phenomenon. We focused on the analysis of phenotype, function, and prognostic value in tumor-infiltrating immune cells in HNSCC patients regarding the HPV status of the tumor. We were able to detect CD8<sup>+</sup> tumor-infiltrating T cells reacting to HPV16 antigens in the majority of HPV<sup>+</sup> oropharyngeal cancers. Moreover, activity of these T cells was enhanced after blockade of both PD-1 and TIM-3 immune-checkpoint pathways, supporting a concept of combined immunotherapy. In our immunohistochemical analysis, we identified a strong prognostic role of tumor-infiltrating B lymphocytes (TIL-Bs) in oropharyngeal cancer patients. Furthermore, visible cell-to-cell interactions between TIL-Bs and CD8<sup>+</sup> T cells were a superior prognostic marker. Finally, we analyzed the functional capacity of tumor-infiltrating plasmacytoid dendritic cells (pDCs) in HNSCC, a subset of DCs that is essential for antiviral immunity. We showed that, compared with HPV<sup>+</sup> HNSCC, the cytokine milieu of HPV<sup>-</sup> tumors significantly impacted production of IFN $\alpha$  by pDCs and favored induction of regulatory T cells in the tumor microenvironment. We significantly contributed to the knowledge of the HNSCC immunological diversity and described B cells as an important new biomarker with translational potential.

**Key words:** head and neck squamous cell carcinoma, human papillomavirus, tumor immunology, tumor-infiltrating lymphocytes, plasmacytoid dendritic cells