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COMMENTARY

Regulatory T cells in the tumour microenvironment of head and neck cancer: Emerging target in the era of immunotherapy

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Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous disease that arises from different anatomic sites of the upper aerodigestive tract and is associated with various aetiology.[1] Smoking, alcohol consumption, and human papillomavirus (HPV) infection are common etiologic factors of HNSCC. Particularly, HPV infection is a predominant cause of oropharyngeal cancer, and HPV-positive HNSCC possesses distinct characteristics, including a young age of onset, frequent lymph node involvement, heavy lymphocyte infiltration, and better prognosis after surgical resection. Currently, the overall incidence of HPV-positive HNSCC is increasing, highlighting the medical importance of understanding this disease. HPV infection accompanied by the expression of the viral oncogenes E6 and E7 inactivates the tumour-suppressor proteins p53 and Rb, promoting genomic instability and cancer development.[2] In addition, HPV interferes with immune surveillance through various mechanisms including suppression of interferon response and downregulation of major histocompatibility complex I expression.[3] Induction of T-cell exhaustion is another strategy used by HPV to evade host immune surveillance, and HPV-positive HNSCC has been considered a good candidate for immunotherapies, including programmed cell death-1 (PD-1) checkpoint inhibitors. Conversely, recent studies have revealed that the response to PD-1 blockade is not associated with HPV infection status in recurrent and/or metastatic HNSCC.[4,5] Thus, to broaden treatment options and contribute to improving treatment outcomes, it is necessary to investigate the mechanisms involved in providing intrinsic resistance to PD-1 blockade in HPV-positive HNSCC.

Among heterogeneous populations of tumour-infiltrating immune cells, some cellular subsets exert suppressive capacity to attenuate antitumor immune responses. Myeloid-derived suppressor cells, tumour-associated macrophages with M2-like phenotype, and regulatory T cells (Tregs) are representative examples

of cellular subsets involved in immune suppression. Among these, Tregs are a functionally distinct T cell subpopulation involved in the maintenance of immune homeostasis.[6] Tregs specifically express transcription factor forkhead box P3 and inhibit effector T cell populations in a direct or indirect manner. As demonstrated by numerous preclinical and clinical observations, the abundance of Tregs was associated with poor prognosis and treatment resistance via their suppressive capacity. In our recent study, we have shown that the tumour microenvironment of HPV-positive HNSCC is characterized by disproportional enrichment of Tregs compared to HPV-negative HNSCC based on the analysis of transcriptomic data and flow cytometry.[7] Tumor-infiltrating Tregs of HNSCC highly express immune checkpoint coinhibitory receptors, exerting suppressive capacity to inhibit effector T-cell proliferation. The clinical implication of balance between Tregs and effector $CD8^+$ T cells in the context of HPV infection was also highlighted in the survival analysis. Importantly, indoleamine 2,3-dioxygenase (IDO) pathways were involved in the enrichment of Tregs in the HPV-positive HNSCC, and simultaneous inhibition of IDO and PD-1 was associated with a durable response. Collectively, further investigation with IDO inhibitor and PD-1 inhibitor is warranted to improve the treatment outcome of HPV-positive HNSCC, offsetting the suppressive capacity of Tregs in the tumour microenvironment.

Targeting Tregs can be achieved in several ways. Traditionally, Tregs were regarded as a key subset to hinder immune-mediated control of tumours, making depletion of Tregs a plausible approach. Tregs in the tumour microenvironment can be characterized by the expression of several cell surface markers, including CD25, CCR4, and various coinhibitory or costimulatory molecules. Among these, CCR4, a chemokine receptor that allows Tregs to migrate to the tumours, can be regarded as an appreciable candidate to be exploited in the depletion of Tregs. This concept was realized through preclinical study and ongoing efforts with an anti-CCR4 monoclonal antibody are under investigation. Targeting Treg-relevant suppressive cytokines would be another worthwhile approach to be exploited. The indispensable relationship between immunosuppressive transforming growth factor-beta (TGF-β) and Tregs was widely acknowledged and intensively studied. Currently, inhibition of cognate receptor for TGF-β is actively explored as a therapeutic strategy to overcome immunotherapy resistance.[8] Furthermore, CD39 and CD73 overexpressed on Tregs can contribute to the production of adenosine,[9] providing a therapeutic window to target CD39/CD73 and reverse Treg-mediated metabolic reprogramming. Activation of vascular endothelial growth factor (VEGF) signalling pathway is also involved in Treg accumulation to the tumour microenvironment through interaction between VEGF and VEGF receptor 2 (VEGFR2) expressed on Tregs.[10] Thus, blockade of the VEGF/VEGFR2 axis can attenuate trafficking of Tregs to the tumour microenvironment and immune suppression. IDO has immune regulatory roles associated with tryptophan metabolism. One of the major pathways by which IDO can affect T cell immune responses is via activation of suppressive Treg cells. The implication of IDO-mediated enrichment of Tregs in HPV-positive HNSCC was highlighted by our study,[7] supporting clinical utilization of IDO inhibitor in this disease.

In conclusion, Tregs should be regarded as a therapeutic target based on their well-known suppressive function implicated in poor prognosis and therapeutic resistance. Especially, therapeutic targeting of Tregs has significant implications in HPV-positive HNSCC, evidenced by disproportional enrichment of Tregs with suppressive capacity. A deeper understanding of the development and function of Tregs in the tumour microenvironment would enable harnessing Tregs in a meticulous way. Finally, continuing efforts to exploit Tregs would enrich the treatment landscape and ultimately contribute to improving treatment outcomes.

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