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Opinion Article

Role of T-Cells in the Improvement of Anti-Tumor Immunity

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DESCRIPTION

T-cells are the main agents of antitumor immunity. However, in the Tumour Micro Environment (TME), T-cells degenerate and acquire their expected effectiveness for tumour immunity, showing lower proliferative capacity, decreased effector functions, and overexpressed inhibitory receptors. T- cell fatigue is a sign of T-cell malfunction in the TME, and T-cells produce a variety of inhibitory receptors, including lymphocyte activation gene 3 protein, CTLA-4 (Cytotoxic T-Lymphocyte-associated Antigen-4), T-cell immunoglobulin domain and mucin domain protein 3, and Programmed cell Death protein 1 (PD-1) Lymphocyte Activation Gene 3 (LAG-3). Targeting PD-1, PD-L1, and/or CTLA-4, immune checkpoint blockade therapy is intended to enhance T-cell function and has been effectively used to increase antitumor T-cell activity in a variety of malignancies. The success rates of the current checkpoint blockade therapy, however, marginally better than 40% overall in several cancer types. The current checkpoint blockade immunotherapy situation clearly demonstrates the existence of several potential pathways other than exhaustion that could result in tumour immunotherapy resistance in the TME. Recently, it has also been discovered that cellular senescence in Tumor-Infiltrating T-cells (TILs) is a significant T-cell dysfunctional state generated by diverse malignant tumours. Tumour cells and tumor-associated regulatory T (Treg) cells are both significant inducers of the development of mortality in effector T-cells.

Senescent T-cells differ significantly from exhausted T-cells in that they exhibit distinct phenotypes such as expression of Senescence-Associated-galactosidase (SA-gal), loss of the costimulatory molecules CD27 and CD28, upregulation of the cell cycle molecules P16, P53 and P21, secretion of proinflammatory and inhibitory cytokines, and strong suppressive activity.

Senescent T-cells can actively impact other immune cells within the TME, causing adaptive T_{reg} cells and performing direct inhibition on DC's and effector T-cells, in addition to having impaired anticancer activities. This current evidence strongly implies that immunological suppression in the TME is amplified and crucially mediate by senescent T-cells. Therefore, preventing the senescence of effector T-cells may also be a crucial checkpoint and an effective technique for tumour immunotherapy and antitumor immunity. Responder T-cells can become senescent T-cells when contacted to human T_{reg} cells or tumour cells. It is crucial for preclinical studies and translational research to know whether the molecular mechanisms of T-cell senescence also occur in the mouse immune system given the potential immune system differences between humans and mice. Mouse T_{reg} cells and tumour cells can both cause the senescence of responder T-cells. Furthermore, discovered that mouse T_{reg} cells and tumour cells plays a role in the establishment of T-cell senescence that is mediated by DNA damage and MAPK (Mitogen-Activated Protein Kinase) signalling pathways.

In adoptive T-cell transfer therapy for melanoma models, *in vivo* investigations showed that inhibiting DNA damage and/or MAPK P38 signalling can prevent effector T-cell senescence and malfunction as well as improve antitumor immunity and immunotherapy. Additionally, adoptive T-cell transfer therapy of melanoma models can be improved by combining checkpoint blockade immunotherapy with an anti-PD-L1 antibody to prevent T-cell senescence by inhibiting DNA damage or P38 signalling. Cancer immunotherapy can be effectively improved by simultaneously targeting effector T-cell senescence and exhaustion.

CONCLUSION

T-cells degenerate and develop their predicted efficiency for tumour immunity in the Tumour Micro Environment (TME). T-cell dysfunction in the TME is indicated by T-cell depletion. T-cell activity has been effectively increased in a number of cancers *via* immune checkpoint blockade therapy. It is crucial for preclinical studies and translational research to know whether the molecular mechanisms of T-cell senescence also occur in the mouse immune system.

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