T-cell Exhaustion and Cancer Immunotherapy

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The failure of our immune system to destroy the antigenic malignant cells is one of the challenging query and research arenas in cancer immunology. The chief immune cells of interest include the CD 8+, CD 4+ and the memory T-cells. The theory of cancer immune surveillance was proposed to elucidate the significance of the immune cells in defence against the cancer cells. The theory postulated that both the innate and adaptive immunity can respond, recognize and destroy the malignant cells. In response, to escape the immune system, the tumor produces an immunosuppressive state in the host.1-3 Few examples of such immunosuppression mechanism include T-cell exhaustion, T-cell apoptosis induced by Fas ligand expressed on the tumor cells, decreased T-cell (especially naive T-cells) stimulation by transforming growth factor produced in tumor microenvironment, highly proliferative tumor cells/infectious agents outnumbering the T-cells and even the non-malignant host stroma may prevent an immune response to be elicited.4-10

T-cell exhaustion is characterized by deprived effector function, sustained expression of inhibitory receptors and a distinct transcriptional state.11 It is reported in numerous chronic infections, such as lymphocytic choriomeningitis virus, human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and adenovirus, as well as in certain malignant neoplasms.15 The dysfunctional T-cells are incompetent in controlling the infection and the tumor cells.11 This loss of functional and phenotypic features occur in a stepwise method (Figure 1).11,12 The function of production of interleukin-2 (IL-2) is affected first, followed by tumor necrosis factor-α and interferon-γ (more resistant). Lastly, the T-cells might undergo apoptosis due to apoptotic factor expression and failure to respond to IL-7 and IL-15 (regulators of T-cell homeostasis).12

From the therapeutic point of view, it is essential to recognize the pathways and molecular signatures governing the T-cell exhaustion, to restore the anti-tumor immunity. Few molecules identified include CD28, CTLA-4, PD-1, ICOS, BTLA, and B7-H4. Among these molecules programmed death-1 (PD-1) and B7-H4 are thought to be the prime inhibitors of T-cells.13 The PD-1 receptor was first described in 1992 as a member of the CD28 family. They are the modulators of T-cell antigen-specific receptor signaling and govern the T-cell activation, inactivation and survival.14

![Figure 1: Stepwise development of T-cell exhaustion, IL-2: Interleukin-2, TNF-α: tumor necrosis factor-α, IFN-γ: Interferon-γ, PD-1: Programmed cell death.](image-url)
Quite a few studies have linked the PD-1 pathway and T-cell exhaustion in cancerous conditions. These include expression of PD-1 on the tumor-infiltrating CD8+ T-cells in solid tumors like renal cell carcinoma, hepatocellular carcinoma, melanoma and on antigen-specific T-cells in non-solid tumors like Hodgkin’s lymphoma and chronic myeloid leukaemia. Furthermore, increased expression of PD-L1 is supposed to be strongly associated with poor prognosis. Further, it is noted that blockade of PD-1 signaling, either through antibody or PD-1 deficiency, re-establishes the functional T-cell responses in several cancers. However, few studies have shown that targeting PD-1 alone does not reverse the T-cell exhaustion. These other molecules identified include T-cell immunoglobulin mucin 3 and LAG-3. Thus, the most effective method to reverse T-cell functions would be to target multiple pathways.

The cancer immunotherapy mainly focuses on vaccinations and adoptive cell therapies. Vaccinations are based on tumor-associated antigens whereas adoptive cell therapies deal with tumor-associated antigen specific T-cells. Targeted immunotherapies using molecular pathways like PD-1 and B7-H4 can serve as a potential role in improving prognosis and survival of the cancer patients. The role of T-cell exhaustion is yet to be explored with respect to the oral squamous cell carcinoma and in the times ahead, cancer immunotherapy could be the possible alternative solution to the conventional cancer therapies (resection, chemotherapy, and radiotherapy) and its related morbidity.

References