Editorial

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.[12] 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]

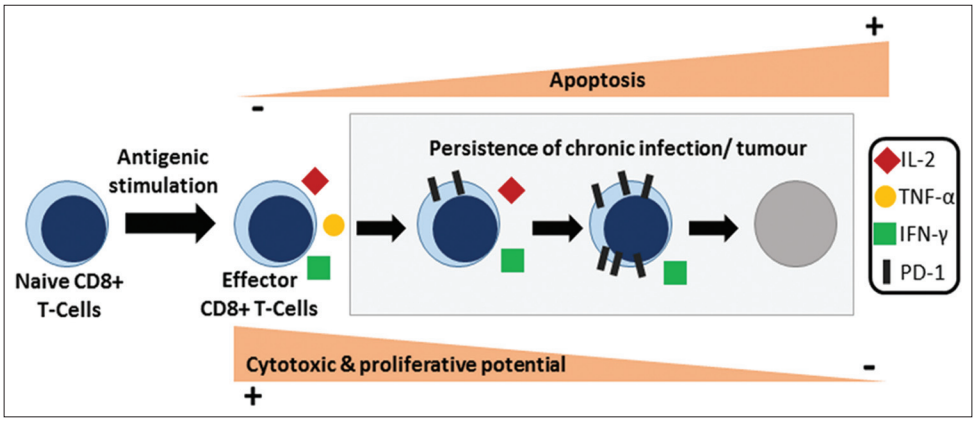

Figure 1: Stepwise development of T-cell exhaustion, IL-2: Interleukin-2, TNF-α: tumor necrosis factor-α, IFN-γ: Interferon-γ, PD-1: Programmed cell death.

Quite a few studies have linked the PD-1 pathway and T-cell exhaustion in cancerous conditions. These includes 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.[14-18] Furthermore, increased expression of PD-L1 is supposed to be strongly associated with poor prognosis.[14] 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.[19,20]

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.[13]

References

1. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.
2. Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006;6(10):715-27.
3. Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest 2007;117(5):1137-46.
4. O'Connell J, O'Sullivan GC, Collins JK, Shanahan F. The Fas counterattack: Fas-mediated T cell killing by colon cancer cells expressing Fas ligand. J Exp Med 1996;184(3):1075-82.
5. Strand S, Hofmann WJ, Hug H, Müller M, Otto G, Strand D, *et al.* Lymphocyte apoptosis induced by CD95 (APO-1/Fas) ligand-expressing tumor cells – a mechanism of immune evasion? Nat Med 1996;2(12):1361-6.
6. Hahne M, Rimoldi D, Schröter M, Romero P, Schreier M, French LE, *et al.* Melanoma cell expression of Fas(Apo-1/CD95) ligand: implications for tumor immune escape. Science 1996;274(5291):1363-6.
7. Ranges GE, Figari IS, Espevik T, Palladino MA Jr. Inhibition of cytotoxic T cell development by transforming growth factor beta and reversal by recombinant tumor necrosis factor alpha. J Exp Med 1987;166(4):991-8.
8. Torre-Amione G, Beauchamp RD, Koeppen H, Park BH, Schreiber H, Moses HL, *et al.* A highly immunogenic tumor transfected with a murine transforming growth factor type beta 1 cDNA escapes immune surveillance. Proc Natl Acad Sci U S A 1990;87(4):1486-90.
9. Cousins SW, McCabe MM, Danielpour D, Streilein JW. Identification of transforming growth factor-beta as an immunosuppressive factor in aqueous humor. Invest Ophthalmol Vis Sci 1991;32(8):2201-11.
10. Singh S, Ross SR, Acena M, Rowley DA, Schreiber H. Stroma is critical for preventing or permitting immunological destruction of antigenic cancer cells. J Exp Med 1992;175(1):139-46.
11. Wherry EJ. T cell exhaustion. Nat Immunol 2011;12:492-9.
12. Yi JS, Cox MA, Zajac AJ. T-cell exhaustion: characteristics, causes and conversion. Immunology 2010;129(4):474-81.
13. Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56(5):739-45.
14. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, *et al.* PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Cancer Res 2007;13(6):1757-61.
15. Gehring AJ, Ho ZZ, Tan AT, Aung MO, Lee KH, Tan KC, *et al.* Profile of tumor antigen-specific CD8 T cells in patients with hepatitis B virus-related hepatocellular carcinoma. Gastroenterology 2009;137(2):682-90.
16. Yamamoto R, Nishikori M, Kitawaki T, Sakai T, Hishizawa M, Tashima M, *et al.* PD-1-PD-1 ligand interaction contributes to immunosuppressive microenvironment of Hodgkin lymphoma. Blood 2008;111(6):3220-4.
17. Mumprecht S, Schürch C, Schwaller J, Solenthaler M, Ochsenbein AF. Programmed death 1 signaling on chronic myeloid leukemia-specific T cells results in T-cell exhaustion and disease progression. Blood 2009;114(8):1528-36.
18. Zhang L, Gajewski TF, Kline J. PD-1/PD-L1 interactions inhibit antitumor immune responses in a murine acute myeloid leukemia model. Blood 2009;114(8):1545-52.
19. Sakuishi K, Apetoh L, Sullivan JM, Blazar BR, Kuchroo VK, Anderson AC. Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. J Exp Med 2010;207(10):2187-94.
20. Jin HT, Anderson AC, Tan WG, West EE, Ha SJ, Araki K, *et al.* Cooperation of Tim-3 and PD-1 in CD8 T-cell exhaustion during chronic viral infection. Proc Natl Acad Sci U S A 2010;107(33):14733-8.