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Differential expression of PD-1 and Tim-3 marks activation versus exhaustion status of T cells in the tumor microenvironment

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Programmed Death 1 (PD-1) and T cell Ig and mucin domain-3 protein (Tim-3) are two immune checkpoint receptors (ICR) highly co-expressed on tumor infiltrating T lymphocytes (TIL). PD-1 has been shown to inhibit T cell activation and type 1 T cell responses, while Tim-3 has been proposed as a further marker of exhaustion on TIL [1,2], leading us to investigate the phenotypic and functional characteristics of TIL with differential PD-1 and Tim-3 expression from head and neck cancer (HNC) patients. Our data showed that PD-1^{+}Tim-3^{+} CD8^{+} and Foxp3^{-} CD4^{+} TILs manifested high phosphorylated signal transducers and activators of transcription 1 (p-STAT1) and the associated Th1 transcription factor T-bet, which might correlate with T cell exhaustion, both at baseline and upon TCR stimulation. Moreover, the sorted PD-1^{+}Tim-3^{+} CD8^{+} TILs expressed the lowest IFN-γ and TNF-α transcripts and the least amount of secreted IFN-γ upon TCR stimulation, indicating they are the most dysfunctional T cells in the tumor microenvironment (TME). Among CD4^{+}CD25$^{lo/-}$ TIL subsets, PD-1^{hi}Tim-3^{-} cells are more defective in terms of IFN-γ expression. Sorted PD-1^{int}Tim-3^{-} CD8^{+} and CD4^{+}CD25$^{lo/-}$ TILs showed higher TCR-stimulated expression of IFN-γ and TNF-α transcripts and secretion of IFN-γ, suggesting they are the most activated subsets. In addition, sorted PD-1^{+}Tim-3^{+} and PD-1^{hi}Tim-3^{-} TIL were less proliferative than other subsets, concomitant with lower expression of phosphorylated S6 (p-S6), while PD-1^{int}Tim-3^{-}, PD-1^{-}Tim-3^{+} and PD-1^{-}Tim-3^{-} TIL retained p-S6 activation or proliferation, suggesting that high expression of PD-1 on T cells interferes with TCR or Tim-3 signaling and associated cellular activation status. Taken together, PD-1^{+}Tim-3^{+} and PD-1^{hi}Tim-3^{-} TIL are most dysfunctional, while PD-1^{int}Tim-3^{-} TIL are more activated in terms of both Th1 cytokine production and proliferation. These results provide a better understanding of the functional status of TIL subsets and roles of PD-1 and Tim-3 in regulating anti-tumor T cell response, as targets for cancer immunotherapy.

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References

1. Jin HT, Anderson AC, Tan WG, *et al*: **Cooperation of Tim-3 and PD-1 in CD8 T-cell exhaustion during chronic viral infection.** *Proceedings of the National Academy of Sciences of the United States of America* 2010, **107**:14733-8.
2. Fourcade J, Sun Z, Benallaoua M, *et al*: **Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific CD8+ T cell dysfunction in melanoma patients.** *The Journal of experimental medicine* 2010, **207**:2175-86.

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