Identification of suitable immune checkpoints as targets for cancer immunotherapy

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Anti-PD-1 and anti-CTLA-4 antibodies have dramatically improved the overall survival of melanoma patients. However, further developments are required, particularly in enhancing the anti-tumor effect and preventing autoimmunity. Targeting immune checkpoints selectively upregulated in the tumor environment may help to achieve this. Therefore, we attempted to identify the T-cell-suppressive molecules upregulated on melanoma cells by IFNγ stimulation and their receptors upregulated on cytotoxic T lymphocytes (CTLs) activated by tumor stimulation. First, we found that some melanoma cell lines become less sensitive to CTL recognition when they are pretreated with IFNγ. We expected that IFNγ-inducible, T-cell-suppressive molecules are preferentially upregulated on such melanoma cells. Using DNA microarray analysis, we identified candidate molecules. Among them, we first focused on CD155, which is a costimulatory molecule expressed on melanoma cells. The CD226 (stimulatory) and TIGIT (inhibitory) receptors control T-cell function through mechanisms analogous to those associated with interactions between CD28/CTLA-4 and CD80/CD86. We found that CD155 was highly expressed on melanoma tissues. In addition, TIGIT was upregulated and CD226 was downregulated on CTLs by tumor stimulation. The overexpression of CD155 suppressed cytokine release from melanoma-specific CTLs via the interaction with TIGIT. These findings suggested that antimelanoma CTL responses are controlled by an imbalance in CD226 and TIGIT expression on T cells and also by the expression levels of CD155 on melanoma cells. Further, we focused on MHC class II molecules among the candidates. Finally, we found that PD-L1, CD155, and MHC class II acted synergistically to suppress the CTLs in the effector phase. Our data address the important issues concerning the enhancement of antitumor effect and prevention of autoimmunity in treatments using immune checkpoint inhibitors.