



Beyond immune suppression: the intrinsic function of PD-L1 in ovarian cancer and melanoma

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Accumulating evidences have revealed that the immune response in cancer microenvironment plays important roles in tumor progression and treatment. Tumor infiltrating immune cells include effector T cells subsets (1), regulatory T cells (Tregs) (2), antigen presenting cells (APCs) (3) and myeloid-derived suppressor cells (MDSCs) (4). The interaction between tumor cells and these immune cells regulates tumor dissemination, relapse and metastasis (5). Tumor cells have developed multiple different mechanisms to evade host immune surveillance, including programmed cell death 1 ligand (PD-L1, B7-H1, CD274) and programmed cell death receptor 1 (PD-1, CD279) pathway, also known as PD pathway. PD-L1 is a functional ligand of PD1 on effector T cells, upon engagement, the PD pathway can inhibit the function of effector T cells, affect the survival and proliferation of activated T cells and lead to T cells exhaustion (6,7). PD-L1 is seldom expressed on normal human tissues, however, PD-L1 protein is found to be overexpressed in many human cancers. The interaction of PD-L1 on tumor cells with PD1 suppresses T cells function and help tumor cells to escape anti-tumor immune response (8,9).

Based on the dominant role of PD pathway in regulating cancer immune response, blockade therapy targeting PD pathway has been developed for cancer treatment. Therapeutic antibodies against PD1 or PD-L1 have been approved by FDA for advanced cancer treatment (4,10). Because of the promising results of anti-PD1 and anti-PD-L1 immunotherapy, most of researches about PD pathway have focused on the role of interaction between PD1 and PD-L1 in regulating anti-tumor immunity, the intrinsic function of PD-L1 or PD1 remains largely

unknown. Kleffel and colleagues has demonstrated that PD1 expression in melanoma cells promotes tumorigenesis in immune deficient mice, indicating that PD pathway has intrinsic function in cancer beyond immune suppression (11).

More recently, Clark and colleagues reported that tumor intrinsic PD-L1 function in cell growth and pathogenesis of ovarian cancer and melanoma (12). In the study, they knocked down PD-L1 expression in murine ovarian cell line ID8agg and melanoma cell line B16 using RNAi methodology and then evaluated cell proliferation and tumor growth. Both PD-L1 low ovarian cancer cells and melanoma cells showed attenuated proliferation and tumor growth *in vitro* and *in vivo*. This phenotype was observed in both WT mice and NSG mice, indicating that PD-L1 function on tumor growth is independent of anti-tumor immunity. Moreover, anti-PD-L1 antibody retard PD-L1 expressing melanoma tumor growth in NSG mice, anti-PD-L1 therapy also decreased metastases and improved overall survival of tumor challenged NSG mice. These results suggested important intrinsic function of PD-L1 signaling on tumor progression independent of anti-tumor immunity.

In addition, Clark *et al.* explored the mechanism whereby PD-L1 could regulate tumor growth and linked PD-L1 expression to autophagy and mTOR signaling pathway. By analyzing RNA-seq results in PDL-L1 low and control cells, Clark *et al.* showed that PD-L1 signaling can regulate the expression of genes that are involved in autophagy and mTOR pathway. These findings are consistent with recent research showing PD-1 and PD-L1 can regulate mTOR pathway in tumor cells (13). It's worth to notice that although PD-L1 expression showed similar function in both

ovarian cancer cells and melanoma cells *in vitro*, distinct function was observed *in vivo*, indicating that PD-L1 function is cell specific and depends on tissue types.

These results have revealed the important intrinsic function of PD-L1 in ovarian cancer and melanoma. The regulation of PD-L1 on autophagy and mTOR signaling in tumor cells is distinct from its function in tumor immunology, indicating that intrinsic function of PD-L1 can also be targeted for cancer treatment. These findings together with other researches suggest that anti-PD-L1 therapy may have a dual effect on limiting tumor progression, by both suppressing tumor growth and boosting anti-tumor immunity.

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