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INSIGHTS

β-Catenin regulates tumor-derived PD-L1

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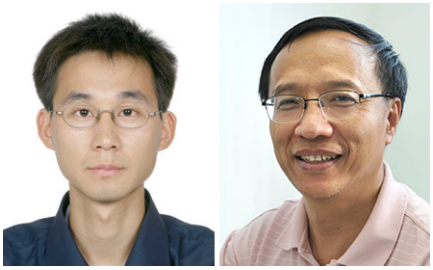
In this issue of *JEM*, Du et al. (https://doi.org/10.1084/jem.20191115) report that enhancement of the β-catenin signaling by Wnt or EGF treatment increases the expression of PD-L1 in an AKT and β-catenin–dependent manner, and blocking the AKT pathway synergizes with anti–PD-1 in a glioblastoma model.

Recently, programmed cell death protein 1 (PD-1)/PD-L1 blockade has become an increasingly appealing therapeutic strategy for cancer patients (Zou et al., 2016). However, only a small portion of patients benefit from PD-1/PD-L1 blockade. Thus, it is urgent to develop novel strategies to improve the therapeutic effect of PD-1/PD-L1 blockade. Wnt/β-catenin pathway, involving in many vital cellular functions, is aberrantly activated in multiple kinds of malignancies and contributes to tumor recurrence. Notably, activation of β-catenin was reported to lead to T cell exclusion and to resist PD-L1 blockade by reducing chemokine-mediated recruitment of $CD103^+$ dendritic cells in an inducible autochthonous melanoma mouse model (Spranger et al., 2015). However, the molecular mechanism of how tumor-intrinsic β-catenin regulates PD-L1–mediated immunosuppression is unknown. In this issue of *JEM*, Du et al. (2020) observed that glioblastoma samples show higher active β-catenin and expression of PD-L1 positively related to the histological grade of cancer, but negatively correlate to the $CD8^+$ T cells infiltration. Impressively, Wnt3A treatment, stimuli of β-catenin signaling, markedly increases the transcription of PD-L1. Depleting β-catenin reduces the expression of PD-L1, while overexpressing a constitutively active β-catenin mutation enhances the PD-L1 expression, suggesting the critical role of β-catenin in regulating PD-L1 expression. Epidermal growth factor receptor (EGFR) signaling, which is frequently amplified in glioblastomas, also enhances β-catenin signaling. Thus, Du et al. (2020) also validate the effect of EGFR on the expression of PD-L1. Indeed, enhancement of EGFR signaling increases the expression of PD-L1 in a protein kinase B (PKB, also known as AKT) and β-catenin–dependent manner. As the central mediator of Wnt/β-catenin pathway, β-catenin could translocate to the nucleus and form a complex with the T cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors to initiate gene transcription (Cadigan and Waterman, 2012). Du et al. (2020) observe that EGF or Wnt3A treatment or overexpression of constitutive β-catenin significantly increases the transcription activity of *CD274* promoter, while blocking AKT reduces the transcription activity of *CD274* promoter. Consistently, EGF or Wnt3A treatment increases the binding efficacy of β-catenin and LEF1 in *CD274* promoter region in an AKT-dependent manner. Furthermore, depleting phosphatase and tensin homologue (PTEN) or overexpressing constitutive β-catenin significantly limits the $CD8^+$ T cells' activation and promotes tumor growth, while depleting β-catenin reduces the expression of PD-L1, releases the brake for the infiltrated $CD8^+$ T cells, and thus prolongs mouse survival in vivo. Impressively, blocking AKT with a small molecular MK2206 limits tumor growth and synergizes with anti–PD-1 to prolong mice survival in a $CD8^+$ T cell–dependent manner. Mechanistically, MK2206 treatment reduces the expression of PD-L1 in tumor tissue, and combined treatment further increases the number of infiltrated $CD8^+$ T cell. They also observe the correlation of PTEN, AKT, or β-catenin with expression of PD-L1 and the infiltration of $CD8^+$ T cells based on clinical samples.



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Taken together, Du et al. (2020) identify the novel role of tumor-intrinsic AKT–β-catenin axis in PD-L1 transcription. They also provide primary evidence to support the combination of AKT blocking and anti–PD-1 for clinical treatment of glioblastoma. Notably, besides activation of AKT, EGF treatment will also trigger the activation of Ras/mitogen-activated protein kinase pathway that is reported to be involved in regulating PD-L1 mRNA stability and translation (Coelho et al., 2017). This suggests EGF treatment might also regulate PD-L1 mRNA stability or translation. Glycogen synthase kinase (GSK) is one of the major negative regulator of β-catenin. Wnt stimulation limits the function of GSK that leads to the activation of β-catenin. Moreover,

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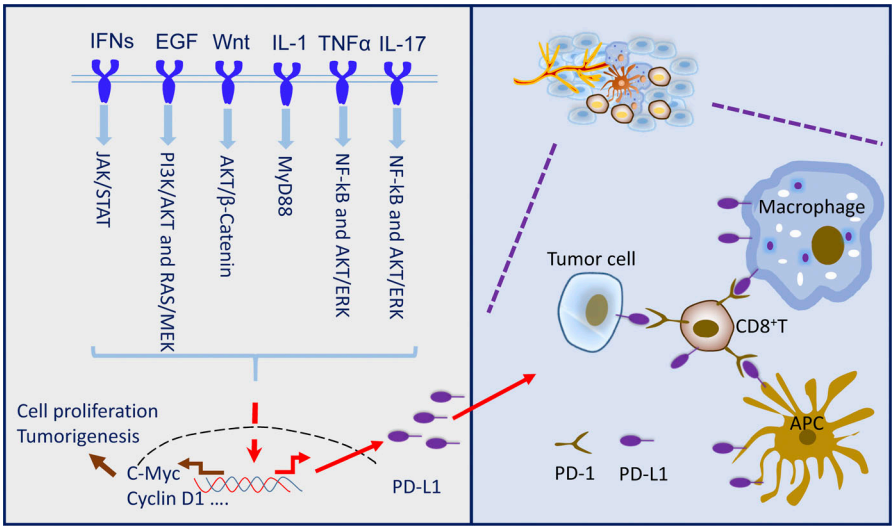

Extracellular signals regulate the expression of PD-L1 in TME. Many cytokines were reported to regulate the expression of PD-L1 in TME; especially, macrophages, dendritic cells, and CD8⁺ T cells in TME express higher PD-L1 than tumor cells. Thus, the role of AKT–β-catenin axis to the expression of PD-L1 in immune cells is also worth further exploration.

Wnt can also promote the expression and function of c-Myc that is also reported to provoke the transcription of PD-L1 (Casey et al., 2016). Thus, the effect of GSK and c-Myc in PD-L1 regulation is also worth studying.

Currently, many cytokines have been reported to be involved in regulating the expression of PD-L1. Among them, type I and II IFN are the most potent cytokines to up-regulate PD-L1 on tumor cells and induce the adaptive immune resistance (Mühlbauer et al., 2006; Tumeh et al., 2014). Notably, IFNγ is mainly produced by activated CD8⁺ T cell in tumor microenvironment (TME). Anti–PD-1 treatment will release the brake and activate CD8⁺ T cells for producing IFNγ, which is expected to enhance the PD-L1 level in TME. However, the AKT inhibitor and anti–PD-1 combination treatment promotes CD8⁺ T cell infiltration but reduces the PD-L1 level in tumor tissue. Additionally, TNFα and IL-17 were also reported to promote the expression of PD-L1 in tumor cells, and blocking NF-κB and AKT pathway diminishes the effect of TNFα and IL-17 on the expression of PD-L1 (Wang et al., 2017). This suggests that AKT–β-catenin axis could play a fundamental role in regulating PD-L1 expression in TME. The study by Du et al. (2020) also helps highlight the role of infiltrated immune cell–derived PD-L1 on antitumor immunity. Up to now, several cytokines, including TNFα (Hartley et al., 2017) and IL-1β (Su et al., 2018), were reported to increase the PD-L1 level in monocytes and macrophages respectively. Interestingly, compared with tumor cells, macrophages and dendritic cells usually express higher levels of PD-L1; loss of PD-L1 on myeloid cells, but not tumor cells, significantly reduces the tumor growth in vivo (Tang et al., 2018). This indicates the critical role of myeloid cell–derived PD-L1 in establishing immunosuppressive TME. More evidence is also emerging to indicate the vital role of PD-L1 in APC. PD-L1 in APCs also binds to costimulatory factors to limit the full activation of T cells (Zhao et al., 2019) and the therapeutic effect of anti–PD-L1 treatment (Mayoux et al., 2020). Interestingly, MK2206 treatment markedly reduces the expression of PD-L1 in whole tumor tissue, but could synergize with anti–PD-1. It raises the possibility that down-regulation of PD-L1 or blocking PD-1 might not simply reduce the interaction of PD-L1 and PD-1. The reduced PD-L1 could free more B7-1/2, while PD-1 blockade increases more CD28, which further strengthens B7-mediated T cell reactivation. Another possibility could be that blocking AKT might also limit β-catenin–mediated down-regulation of chemokines in tumor tissue that promotes dendritic cells infiltration. A recent study suggests one more possibility: tumor-infiltrated CD8⁺ T cells are also observed to highly express PD-L1 in pancreas tumor; depleting tumor-infiltrated CD8⁺ T cell–derived PD-L1 also provokes the effector T cells in TME (Diskin et al., 2020). Above all, this indicates that immune cell–derived PD-L1 also plays a vital role in establishing an immunosuppressive environment for tumor development and resisting antitumor therapy. Du et al. (2020) highlight the critical role of AKT–β-catenin axis in regulating the tumor-derived PD-L1. Considering β-catenin/TCF/LEF specifically binds to the promoter of CD274 and promotes the transcription of PD-L1, it is curious that β-catenin is also required for nontumor cells to maintaining the PD-L1 expression. Notably, unlike IFNs and other cytokine-mediated immune-driven expression of PD-L1, tumor-derived PD-L1 driven by oncogenes might not correlate with immune cell infiltration and might not respond to anti–PD-L1 treatment. Additionally, it was also reported that high PD-L1 expression in tumor-infiltrated macrophages or dendritic cells also associates with response to PD pathway blockade (Zou et al., 2016). The dominant role of dendritic cell–derived PD-L1 suggests the importance of T cell reactivation, while the dominant role of tumor-derived PD-L1 might point to immune evasion at the effector phase of T cell–mediated killing. Therefore, the role of immune-driven or oncogene-driven expression of PD-L1 on immune cells, stromal cells, or tumor cells to MK2206 and anti–PD-1 therapy is worth being determined. Identification of the key factors for maintaining APC or T cell–derived PD-L1 will be important for the development of new strategies to wake up antitumor immunity.

Currently, some AKT inhibitors, including MK2206, are widely tested in clinical trials for treatment cancers. Du et al. (2020) reveal the critical role of AKT–β-catenin in regulating tumor-derived PD-L1 and uncover the synergic effect of AKT inhibitor and anti–PD-1 treatment. This highlights the mechanisms of the combination of AKT inhibitor and anti–PD-1 therapy for clinical investigation.

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