RESEARCH HIGHLIGHT

# Mitochondrial PD-L1 modulates cancer immunotherapy

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**The expression and subcellular localization of immune checkpoint protein PD-L1 have been implicated to play an important role in cancer immunotherapy. In a recent paper published in *Cell Research*, Xie et al. report that promoting mitochondrial distribution of PD-L1 through targeting the ATAD3A-PINK1-mitophagy axis is a promising strategy to overcome chemoimmunotherapy resistance.**

Cancer immunotherapy has revolutionized cancer treatment with long-lasting responses in multiple types of human cancers, including triple-negative breast cancer (TNBC). Immune checkpoint inhibitors (ICIs) such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies are widely used in clinical practices to activate the immune system to eliminate cancer cells.[1] However, the overall efficacy is still unsatisfactory and only certain cancer types and a portion of patients respond to immunotherapy.[1] Although chemotherapy has been proven to improve the efficacy of immunotherapy in part through increasing PD-L1 expression, only a small portion of patients can benefit from such combination therapy. To date, lots of efforts have been devoted to determining the intrinsic and acquired resistant mechanism so as to improve the clinical response to immunotherapy and combination therapy together with other targeted therapy and/or chemotherapy.

In general, positive intratumor PD-L1 expression is a hallmark for the sensitivity to anti-PD-1/PD-L1 treatment. As a ligand of the checkpoint receptor PD-1, PD-L1 is a type I transmembrane protein, which is overexpressed and can be exploited by cancer cells to evade immune surveillance (Fig. 1a). Recent studies reveal that both the expression and localization of PD-L1 play important roles in cancer immune surveillance. The expression of PD-L1 can be regulated at transcriptional, translational and posttranslational levels,[2,3] while its subcellular localization also contributes to cancer immunity and sensitivity to immunotherapy. Moreover, PD-L1 can be secreted into the extracellular space to suppress T cell function[4] or translocate into nucleus to regulate immune-related gene transcription, sister chromatid cohesion, and pyroptosis.[4,5] (Fig. 1a).

As the energy plants of cells, mitochondria participate in cancer immune evasion through regulating either cancer cells or the immune system.[6] Dysfunction of mitochondria can cause different pathologies and initiate mitophagy to remove dysfunctional or superfluous mitochondria.[7] However, it remains largely elusive whether PD-L1 localizes at mitochondria and how mitochondrial distribution of PD-L1 regulates the response to immunotherapy. In a recent elegant study published in *Cell Research*, Xie and colleagues reported that mitochondrial distribution of PD-L1 is important for the response to a combined therapy using anti-PD-L1 antibody and chemotherapy drug paclitaxel in TNBC.[8] Mechanistically, mitochondrial protein kinase, PTEN induced kinase 1 (PINK1), recruits PD-L1 to the mitochondria for subsequent mitophagy-mediated degradation, and this process can be antagonized by paclitaxel-induced ATAD3A expression, which induced acquired resistance to ICI treatment. Therefore, targeting ATAD3A evokes a favorable tumor immune microenvironment and improves the efficacy of combination therapy of paclitaxel plus ICI.

Clinically, only a small portion of TNBC patients can benefit from immunotherapy or combination therapy of ICIs together with chemotherapy, such as paclitaxel.[9] To reveal the underlying mechanism for the insensitivity of TNBC to chemoimmunotherapy, Xie et al. demonstrated that PD-L1 locates on the outer membrane of mitochondria via electron microscopy, especially in those responder patients. Moreover, the chemotherapy drug paclitaxel reduced PD-L1 mitochondrial distribution, while paclitaxel did not influence the localization of PD-L1 on endoplasmic reticulum or Golgi complex. Notably, they found that the mitochondrial distribution of PD-L1 indicates better response to the combination therapy using anti-PD-L1 antibody plus nab-paclitaxel. To explore the mechanism of PD-L1 mitochondrial distribution, through further biochemical and imaging methods, the authors found that PD-L1 bound to a mitochondrial outer membrane protein, PINK1. In *PINK1* depletion cells, the colocalization of PD-L1 with TOM20-labeled mitochondria was significantly compromised. Mitochondrial PD-L1 was further degraded in a mitophagy-dependent manner, which can be suppressed by the autophagy/mitophagy inhibitor bafilomycin A1. Moreover, paclitaxel promoted the transcription of ATAD3A, a mitochondrial protein which plays a critical role in tumor progression.[10] Elevated ATAD3A expression suppressed PINK1 accumulation and mitochondrial distribution of PD-L1, subsequently disturbing mitophagy-mediated PD-L1 degradation. These results together support that mitochondrial distribution of PD-L1 is likely regulated by an ATAD3A-PINK1-mitophagy axis and provide new insight of PD-L1 degradation by mitophagy (Fig. 1b).

Whether targeting PD-L1 mitochondrial distribution, such as aiming at ATAD3A, could provide a new strategy to improve the efficacy of cancer immunotherapy? To this end, the authors further performed in vivo animal experiments, using *Atad3a*-depleted 4T1 cell-derived xenograft model in both immunodeficient and immunocompetent BALB/c mice. They found that depletion of *Atad3a* only suppressed the tumor growth of 4T1-derived tumor in immunocompetent mice, but not in

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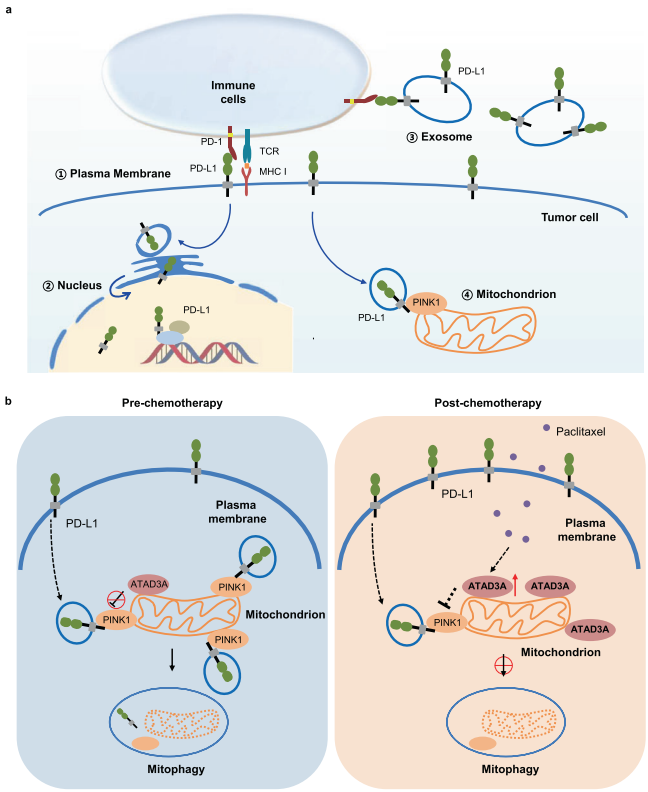


**Fig. 1 PD-L1 functions at multiple subcellular localizations. a** PD-L1 functions at different subcellular localizations, including ① plasma membrane; ② nucleus; ③ exosome; and ④ mitochondria, to regulate cancer immunity. **b** Schematic representation of PD-L1 regulation by ATAD3A-PINK1-mitophagy axis. Without paclitaxel treatment, PINK1 can recruit PD-L1 to mitochondrial outer membrane, leading to PD-L1 degradation through mitophagy. Upon paclitaxel treatment, ATAD3A is induced to suppress PINK1 and disrupt mitochondrial recruitment of PD-L1, resulting in PD-L1 accumulation on plasma membrane to suppress cancer immunity.

immunodeficient nude mice, suggesting that ATAD3A may help tumor cell to evade immune surveillance. This hypothesis was further supported by reduced PD-L1$^{+}$ tumor cells as well as increased infiltration of CD8$^{+}$ T cell populations and granzyme B secretion in *Atad3a* knockdown tumor samples. Furthermore, depletion of *Atad3a* significantly improved the efficacy of combination therapy using anti-PD-L1 antibody and paclitaxel in suppressing tumor growth in 4T1 syngeneic mouse model. Consistent with these findings, TNBC patients with low intratumor ATAD3A expression have longer survival after combination treatment with anti-PD-L1 antibody and paclitaxel compared with ATAD3A-high patients, which provides a promising strategy of personalized treatment of TNBC to overcome immunosuppression and resistance to chemoimmunotherapy.

Taken together, this work reveals that PINK1 can recruit PD-L1 to the outer membrane of mitochondria to promote mitophagy-mediated PD-L1 degradation which could be blocked by chemotherapy-induced mitochondrial protein ATAD3A. More importantly, it provides a new strategy to improve the efficacy of immunotherapy by targeting ATAD3A to increase mitochondrial distribution of PD-L1. Meantime, this elegant work also elicits some new directions warranting further in-depth investigation. How PD-L1 translocates to mitochondria? Whether mitochondrial distribution of PD-L1 regulates mitochondrial function such as mitophagy and mitochondrial metabolism? Whether mitochondrial PD-L1 distribution occurs only in TNBC or also in other cold tumor, such as prostate cancer? What is the upstream physiological signal(s) that regulates the mitochondrial distribution of PD-L1? Answering these questions might provide in-depth knowledge about different subcellular localizations of PD-L1 in contributing to cancer immunity and also help develop targeted combination therapy to overcome intrinsic and acquired resistance to immune checkpoint blockade treatments.

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## COMPETING INTERESTS

W.W. is a co-founder and consultant for the ReKindle Therapeutics.

## ADDITIONAL INFORMATION

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