Commentary

Cyclin dependent kinase 5—a novel target to enhance the antitumor immune response

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Cyclin dependent kinase 5 (Cdk5) is a serine/threonine kinase that has initially been discovered in the neuronal system and is essential for CNS development and function (1). During recent years, important functions of Cdk5 in various tumors have been elucidated and the genetic knockdown of Cdk5 as well as the inhibition of its kinase activity by small molecules has shown potent anti-cancer effects (2-5). Therefore, Cdk5 has emerged as a promising target for anti-cancer therapy.

Dorand *et al*. now elucidate a novel function of Cdk5 in cancer: their findings highlight a central role of Cdk5 in antitumor immunity (6). Cancer cells often activate immune-inhibitory signals that allow the tumor to escape immune surveillance (7). Cancer immunotherapy by targeting immune checkpoints such as the programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway enables the development of antitumor immune responses and has achieved major therapeutic benefit (8). According to the study by Dorand *et al*., inhibition of Cdk5 might represent a new option to enhance the antitumor immune response.

By using subcutaneous medulloblastoma (MB) tumor models, Dorand *et al*. show that, whereas Cdk5 deficient tumors grew normally in immunodeficient mice, in immunocompetent C57BL/6 mice implanted with Cdk5-deficient tumor cells tumor-free survival was strongly increased and tumor size was reduced compared to mice implanted with control tumors. Moreover, Dorand *et al*. observed an inverse correlation of Cdk5 expression and T cell infiltration in human MB, suggesting that the rejection of Cdk5-deficient tumors was T cell dependent. In fact, Dorand *et al*. could trace the rejection of Cdk5-deficient tumors back to $CD4^+$ T cells as the depletion of $CD4^+$ T-cells or $CD4^+$ and $CD8^+$ T-cells together abrogated the reduced tumor incidence and the growth of Cdk5-deficient tumors whereas the depletion of only $CD8^+$ T cells had no effect. Moreover, Cdk5-deficient tumors grew normally in mice deficient for major histocompatibility complex II (MHC-II) which is recognized by the T cell CD4 co-receptor. Importantly, injection of WT-tumor cells into mice that had rejected Cdk5-deficient tumors before did not result in tumor establishment, meaning that Cdk5-deficiency could induce potent antitumor immune memory generation.

The PD-L1 is often overexpressed on tumor cells and allows cancer cells to evade immune elimination. PD-L1 binding to the PD-1 receptor at T cells halts T cell response which serves as a key immune checkpoint and ensures appropriate immune response. Tumor cells use the PD-1/PD-L1 pathway to escape the detection and elimination by the immune system. Therefore, targeting immune checkpoints such as the PD-1/PD-L1 pathway is used to overcome anti-cancer immunity resistance and has shown promising results in anti-cancer treatment (8). Of note, Dorand *et al*. elucidate a link between PD-L1 and Cdk5 by demonstrating that Cdk5 and PD-L1 expression co-occur in human tumors. Moreover, they observed that the basal expression as well as the interferon gamma (IFNγ)-driven upregulation of PD-L1 was reduced in tumor cells that were deficient for Cdk5 or treated with the small molecule Cdk5 inhibitor roscovitine. IFNγ is the most potent inducer of PD-L1 (9). IFNγ can also induce p35 and thereby activate Cdk5

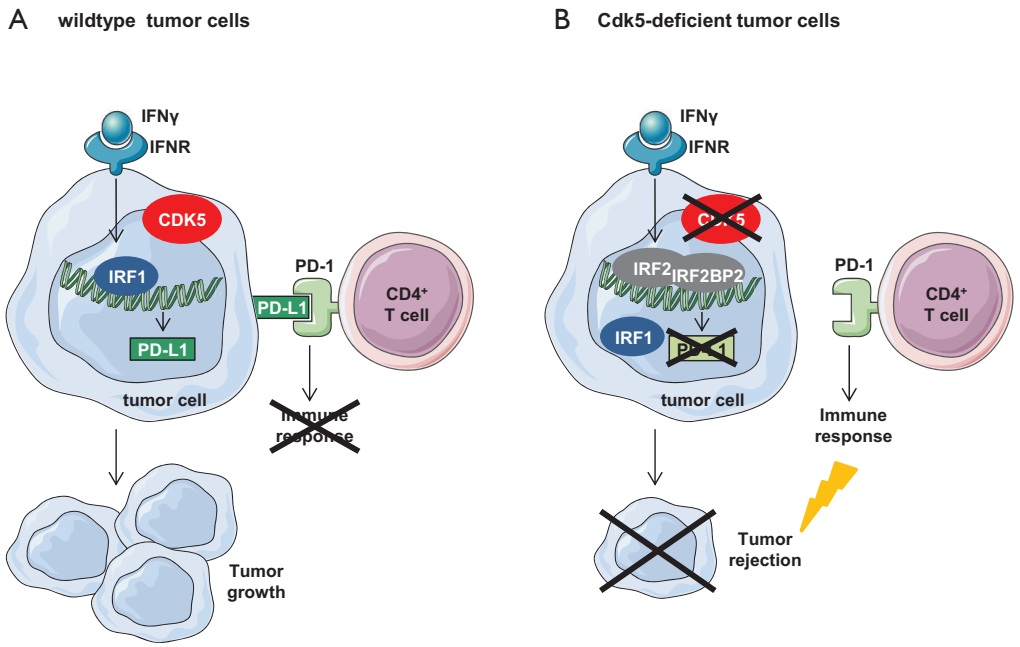

Figure 1 Inhibition of Cdk5 induces antitumor immunity by decreasing PD-L1 expression. (A) In wildtype tumor cells, IFNγ stimulation leads to IRF1-mediated transcription of PD-L1 and expression of PD-L1 at the tumor cell. PD-L1 binds to PD-1 at Cd4+ T cells which inhibits antitumor immune response and results in tumor initiation and growth; (B) in Cdk5-deficient tumor cells, IRF2 and IRF2BP2 inhibit induction of PD-L1 transcription by IRF1 and results in reduced expression of PD-L1. This induces immune response and results in tumor rejection. Cdk5, cyclin dependent kinase 5; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; IRF1, interferon regulatory factor-1; IFNR, interferon receptor; IFNγ, interferon gamma.

(10,11) which was in line shown by Dorand *et al*. As underlying mechanism responsible for the reduced PD-L1 expression in response to IFNγ stimulation in Cdk5-deficient cells Dorand *et al*. observed increased levels and prolonged half-life of interferon regulatory factor-2 (IRF2) and IRF2BP2, which are negative regulators of PD-L1. IFNγ induces IRF1-driven transcription of PD-L1 (12) which is inhibited by IRF2 that suppresses the function of IRF1 by binding to the same DNA sequence and therefore inhibits the transcription of IFNγ induced genes (13,14). IRF2BP2 acts as a co-repressor with IRF2 (15). By applying a phosphoproteomic screen, Dorand *et al*. found that the phosphorylation of IFN2BP2 was increased in Cdk5-deficient cells and suggest that (a) kinase(s) which phosphorylates IFN2BP2 might be inhibited by Cdk5. An overview about the findings of Dorand *et al*. is provided by *Figure 1*.

In summary, the study by Dorand *et al*. elucidates a new function of Cdk5 in the regulation of the PD-1/PD-L1 immune checkpoint in cancer cells and suggests the inhibition of Cdk5 as a potential target to improve the antitumor immune response.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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