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CDK20 inhibition and immune checkpoint blockade: bringing cancer biology and tumour immunology together to develop novel treatment options for HCC

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On 22 September 2017 the Food and Drug Administration granted accelerated approval to nivolumab for the treatment of hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib. Approval was based on a 154-patient subgroup of a multicentre, open-label trial conducted in patients with HCC and Child-Pugh A cirrhosis who progressed on or were intolerant to sorafenib.¹ With an overall response rate of close to 15%, which lasted in more than 90% of the patients 6 months or longer, immune checkpoint blockade has become a treatment option for patients with HCC after many years of failures in drug development. However, these data also call for future combination studies, which will increase the number of patients responding to immunotherapy. But what is the best combination partner for an immune checkpoint inhibitor in HCC?

While immune checkpoint inhibitors successfully lead to activation of T cells in patients with HCC,² they have no effect on the microenvironment and possible immunosuppressive mechanisms such as regulatory T cells and myeloid-derived suppressor cells (MDSCs). MDSCs represent a population of immature myeloid cells, composite of two major subsets, monocytic CD14⁺ MDSC and polymorphonuclear CD14^{neg} MDSC. They are potent suppressors of tumour-specific immune responses and are associated with poor outcome in HCC.^{3–5} Until today it is not entirely clear what leads to the accumulation of MDSCs in patients with HCC.

In *Gut*, Zhou and colleagues⁶ from the Chinese University of Hong Kong describe a novel concept of how activation of cell cycle-related kinase (CCRK) in the tumour leads to a nuclear factor-kappa B/interleukin (IL)-6-dependent mechanism, ultimately resulting in accumulation of polymorphonuclear (PMN)-MDSCs and impaired antitumour immunity in mice. In contrast, *Ccrk* knockdown led to fewer MDSC and improved CD8⁺ T cell function in mice. Interestingly, *Ccrk* depletion also upregulated programmed death - ligand 1 (PD-L1)

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expression on tumours, which led to the hypothesis that a targeted inhibition of *CCRK* in combination with anti-PD-L1 therapy may be more effective. This was tested and confirmed in an orthotopic murine HCC model using hepa 1–6 cells in C57Bl/6 mice. Finally, the authors also demonstrated an accumulation of MDSCs in patients with HCC, and more importantly a correlation of *CCRK* expression with MDSC frequencies and outcome in these patients. Functional studies confirmed an IL-6-dependent induction of human PMN-MDSC. In summary, the authors provide convincing evidence from human clinical samples and murine studies that HCC intrinsic *Ccrk*/IL-6 pathway renders T cell dysfunction through the induction of PMN-MDSC and that targeting *Ccrk* may also lead to changes in antitumour responses, which can be enhanced using immune checkpoint inhibitors (figure 1).

The important questions are: Can we test this combination now in the clinic and how much can we conclude the murine data? Let's first study the murine data in more detail. The authors used luciferase transduced hepa 1–6 cells. These cells are derived from a murine hepatoma (BW7756), which initially arose in a C57/L mouse in 1957. This mouse strain is different from the C57BL/6 mice used in this study. The tumour cells are potentially more immunogenic due to minor major histocompatibility complex (MHC) incompatibilities, and the expression of a foreign protein, luciferase, may even enhance its immunogenicity. Furthermore, the authors established a transgenic murine model in which human *CCRK* was expressed in murine hepatocytes. This model allowed to study the effect of *CCRK* expression in hepatocytes on myeloid cells and MDSC, but in the absence of actual liver tumours. In addition, the authors focused on PMN-MDSC, while we and others have described an accumulation of monocytic MDSCs in patients with HCC. At this point it is not clear whether PMN-MDSC or monocytic MDSC is the driving force of immunosuppression in HCC.

Despite these shortcomings, this is a very interesting and novel study with potentially a very high clinical impact. As the authors mention in their discussion, there are now a number of different reports (not in HCC), which all describe the same theme, namely that tumour intrinsic factors drive different immunosuppressive mechanisms such as suppression of dendritic cells via beta-catenin signalling in melanoma cells⁷ and silencing of T helper cytokines via enhancer of zeste homo-logue 2 (EZH2)-mediated epigenetic signalling.⁸ Finally, an Akt strain transforming (AKT)-mechanistic target of rapamycin has been shown to drive PMN-MDSC in breast cancer.⁹ More recently a new study has shown that CDK4/6 inhibition may trigger antitumour immunity and enhance CD8 T cell function, which can be further enhanced by the addition of immune checkpoint inhibitors.¹⁰ All these studies clearly suggest that only combined efforts of different specialties together (in this case tumour immunologists and experts in cell cycle and cell cycle-dependent kinases) will ultimately lead to potentially more effective therapies for patients with HCC.

So coming back to the question whether to target *CCRK* in patients with HCC and combine such treatment with an immune checkpoint inhibitor. Since *CCRK* targeting drugs are not on the market, it may be easier to block IL-6 and combine this treatment with an immune checkpoint inhibitor. However, more preclinical studies are needed.

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Figure 1.

(A) CCRK induces IL-6 production and PMN-MDSC accumulation inhibiting T cells and supporting tumour growth. (B) CCRK inhibition or IL-6 blockade inhibits PMN-MDSC induction, promotes T cell activity and inhibits tumour growth. However PD-L1 expression is enhanced in HCC upon CCRK inhibition, which impairs T cell function. (C) Combined CCRK and PD-L1 blockade leads to effective T cell-mediated anti-HCC immunity. CCRK, cell cycle-related kinase; HCC, hepatocellular carcinoma; IL-6, interleukin-6; MDSC, myeloid derived suppressor cell; NFkB, nuclear factor-kappa B; PD-L1, programmed death - ligand 1; PMN, polymorphonuclear.