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EDITORIAL

MEK Inhibition

A New Ally in Immunotherapy for Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (iCCA) is the most common biliary malignancy. iCCAs are desmoplastic tumors characterized by a dense tumor immune microenvironment populated by both cytotoxic T lymphocytes ($CD8^+$ T cells) and immunosuppressive cells, such as myeloid-derived suppressor cells and tumor-associated macrophages.[1] Surgical resection or liver transplantation are potentially curative treatment options for patients with early stage disease. However, most patients present with advanced-stage disease and therapeutic options are limited.[2] Understanding the complexity and diversity of the immune cells and their interaction has resulted in the development of cancer immunotherapies that modulate the host immunity against the tumor cells. However, immune checkpoint inhibitor monotherapy targeting the programmed death ligand-1 (PD-L1)m/PD-1 axis has had disappointing efficacy in iCCA.[3] Effective immunotherapeutics will likely use combination strategies to overcome the multiple layers of immune resistance in CCA.[1] Gain-of-function mutations of *KRAS* occur in approximately 18%–20% of iCCAs.[4,5] Activated mutations of *KRAS* lead to hyperactivation of the RAF-MEK-ERK pathway with consequent augmentation of cell proliferation and survival. MEK inhibition has demonstrated efficacy in *KRAS* driven and *KRAS* wild-type (WT) CCA in preclinical studies.[6,7] Trametinib, a MEK 1/2 inhibitor, is approved for *B-Raf* mutant melanoma and non–small cell lung cancer.[8]

To unleash the antitumor immune response by cytotoxic T cells against iCCA, overcoming the various elements of tumor immune evasion is essential. In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Wabitsch et al[9] address a key question: does modulation of the CCA tumor immune microenvironment improve effectiveness of immune checkpoint inhibitor. Using a unique syngeneic, orthotopic transplant mouse model of iCCA and a genetic iCCA mouse model, the authors demonstrated that trametinib treatment increases MHC-I and PD-L1 expression on SB1 cells, murine CCA cells that are *KRAS* WT. Although trametinib monotherapy resulted in reduction of the tumor burden, acceleration of tumor growth was observed when trametinib was discontinued. Accordingly, trametinib monotherapy did not confer a survival benefit in mice. One possible explanation for this may be that trametinib increased PD-L1 surface expression by tumor cells, an effect that may lead to promotion of T-cell exhaustion. Consistent with this observation, a trend toward an immune suppressive effect on $CD8^+$ T cells was noted with a decrease in effector function during trametinib therapy. This effect was abolished in the mice treated with the combination of anti-PD-1 and trametinib (Figure 1). These results suggest that trametinib monotherapy alone may have an immunosuppressive effect with an increase in PD-L1 expression and potential decrease in $CD8^+$ T-cell effector function. However, the increase in MHC-1 primes the immune system, making the tumor cells more immunogenic. Consequently, combination therapy with the addition of an agent targeting the PD-1/PD-L1 axis overcomes any potential immunosuppressive effect of trametinib while harnessing the immunogenic effect leading to augmentation of the antitumor immune response and a survival benefit. This dual function of MEK inhibition (both inhibiting and promoting $CD8^+$ T-cell effector function) highlights the complexity and layers of immune regulation that are characteristic of iCCA. This study also provides further evidence for a potential role of MEK inhibition beyond *KRAS*-mutated cancers. Trametinib has previously been shown to modulate the tumor microenvironment of *KRAS* WT CCA by affecting the vasculature and regulating cancer-associated fibroblasts.[7] Wabitsch et al[9] now demonstrate that trametinib can enhance immunogenicity in *KRAS* WT iCCA. Indeed, the trametinib-mediated increase in MHC-1 expression has the potential to enable recognition of a large variety of tumor antigens by memory T cells, constraining tumor immune evasion and risk of relapse.

Finally, this study emphasizes the pertinence and strength of preclinical models that closely mimic the human disease. The authors found that the murine *KRAS* WT iCCA cells used for this study, SB1 cells, had a signature that closely resembled a mutational signature present in a subset of human CCA with a poor prognosis. Thus, this model can be used to assess combinatorial therapeutic strategies using the mutational signature as a biomarker. The authors have demonstrated an intriguing and complex relationship among the tumor cells, immune cells, and tumor microenvironment while elucidating the potential of MEK inhibition to augment immune checkpoint inhibitor therapy.

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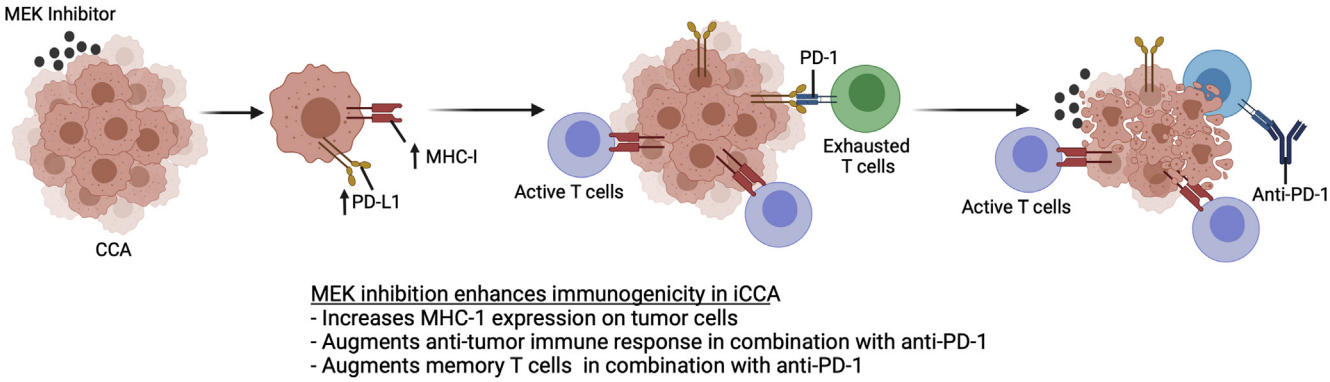

Figure 1. MEK inhibition enhances immunogenicity in iCCA. In preclinical models of iCCA, MEK inhibition enhances immunogenicity, and augments the antitumor immune response in combination with anti-PD-1.

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The authors disclose no conflicts.

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