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Novel Harnessing of Innate and Adaptive Anti-Cancer Immunity: NLRP3-Inflammasome Activation Facilitates Immune Checkpoint Blockade in the Treatment of Mesenchymal Stage IV Colorectal Cancer

Background: The role of the NLRP3 inflammasome in colorectal cancer (CRC) progression remains unclear (1). While some studies link high NLRP3 activity to cancer progression, others suggest protective roles, depending on the clinical context (2–4). Clinical trials mainly focus on inhibition of NLRP3 activity (5). Hence, we evaluated the effect of NLRP3 activation on metastatic CRC in vivo and in vitro.

Methods: In vitro experiments involved coculturing of peritoneal mouse immune cells with murine CRC organoids. Within, NLRP3 inflammasome activation was induced using EMT-244, a novel and potent NLRP3 activator. Therapeutic effects on the coculture were
quantified using viability assays. In vivo, we employed an orthotopic, organoid-driven mesenchymal stage IV CRC mouse model, which mimics an aggressive and treatment-resistant human CRC subtype (6). To evaluate the impact of EMT-244, immune histochemistry and fluorescence was performed.

Results: In vitro, we demonstrated an EMT-244-dependent reduction of CRC organoid viability during coculture ($p = 0.0498$). Importantly, this effect was not abundant when treating CRC organoids alone, highlighting the necessity of an immunological tumor microenvironment. In vivo experiments revealed that EMT-244, in combination with ICB,
significantly reduced liver and peritoneal metastatic burden compared to ICB monotherapy($p = 0.0114$ and $p = 0.0026$). Furthermore, liver metastases exhibited a significant decrease in Ki67 positivity ($p = 0.0157$) and an increase in TUNEL positivity ($p = 0.0388$) in the EMT-
244 + ICB group.

Conclusion: NLRP3 inflammasome activation by EMT-244 facilitates ICB in mesenchymal stage IV CRC, presenting a promising new immunological treatment approach for CRC metastases.

Preferred type of presentation

Poster Presentation only

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