Pancreatic Cancer

Major finding: Activation of dectin-1 on macrophages drives adaptive immune suppression and PDAC progression.
Mechanism: Galectin-9 expressed on PDAC interacts with dectin-1 to drive tolerogenic programming of macrophages.
Impact: Targeting dectin-1 in combination with other immunotherapies may be a therapeutic strategy for PDAC.

ACTIVATION OF DECTIN-1 ON MACROPHAGES PROMOTES PANCREATIC CANCER

Pancreatic adenocarcinoma (PDAC) development and progression is significantly influenced by the presence of an inflammatory response mediated by innate immune subsets in the tumor microenvironment (TME), particularly M2-polarized tumor-associated macrophages (TAM) and cells of myeloid-monocytic lineages, but the drivers of the immune-suppressive phenotype of these monocytic subsets have not been definitively identified. The C-type lectin receptor dectin-1 (encoded by CLEC7A), which is expressed on macrophages and cells of the myeloid-monocytic lineages, is critical for the recognition of β-glucans to activate SYK and drive the antifungal immune response, but has no known role in antitumor immunity. To determine whether dectin-1 promotes antitumor immunity, Daley and colleagues assessed dectin-1 expression in tumors from transgenic mouse models of slow-growing and invasive PDAC and from human patients with PDAC. Dectin-1 was highly expressed in both murine and human patient PDAC tumors and in peritumoral leukocytes, macrophages, and monocytes; further, elevated levels of phosphorylated SYK and dectin-1 ligands were also present in murine PDAC and the inflammatory TME. Of the identified dectin-1 ligands, galectin-9 was confirmed to interact with dectin-1 and activate SYK, and was shown to be overexpressed in murine and human PDAC and tumor-infiltrating leukocytes. Treatment with a dectin-1 agonist accelerated murine PDAC progression; conversely, Clec7a ablation or the blockade of SYK or galectin-9 delayed murine PDAC progression. Specifically, Clec7a depletion in the extra-epithelial compartment, but not in transformed pancreatic epithelial cells, was protective against PDAC, and Clec7a depletion or the blockade of galectin-9 resulted in the M1 polarization of TAMs to promote the immunogenic differentiation of PDAC-infiltrating T cells in vitro and in vivo and reduce PDAC growth in vivo. These results describe how the dectin-1–galectin-9 axis drives the immunosuppressive T-cell phenotype and suggest that inhibition of dectin-1–mediated signaling is a potential immunotherapy that may synergize with other immunotherapies for the treatment of patients with PDAC.


Clinical Trials

Major finding: ADI-PEG 20 plus chemotherapy achieves partial responses in 7 of 9 patients with mesothelioma or NSCLC.
Concept: ADI-PEG 20 is well tolerated and induces a rapid and sustained depletion of circulating plasma arginine.
Impact: ADI-PEG 20 may be effective in ASS1-deficient tumors in combination with cytotoxic therapies.

ADI-PEG 20 DEPLETES ARGinine TO INDUCe ANTITUMOR ACTIVITY

Patients with advanced malignant pleural mesothelioma (MPM) or nonsquamous, non–small cell lung cancer (NSCLC) are often treated with cytotoxic chemotherapy (cisplatin plus pemetrexed), but new therapies are needed as the prognosis remains poor. Many patients with NSCLC and MPM exhibit reduced expression of the argininosuccinate synthetase 1 (ASS1) enzyme, which combines citrulline with aspartate to synthesize arginine. Thus, the tumors are dependent on exogenous arginine for growth. A pegylated arginine deiminase (ADI-PEG 20) has been developed for clinical use and converts arginine to citrulline to deplete arginine in ASS1-deficient tumors. Early preclinical and clinical studies have suggested that ADI-PEG 20 may have activity in multiple tumor types. Beddowes and colleagues performed an open-label phase I dose-escalation study evaluating ADI-PEG 20 in combination with pemetrexed and cisplatin. ADI-PEG 20 resulted in a rapid and sustained depletion of circulating plasma arginine. Most adverse events were grade 1–2, and no dose-limiting toxicities occurred at the determined recommended phase II dose. In total, 7 of 9 patients (78%) achieved partial responses, and the remaining 2 patients achieved stable disease. The median overall survival was 55.7 weeks and the median progression-free survival was 30.1 weeks, which is notable given the aggressive subtype of cancer treated in the study. Collectively, these findings indicate that ADIPEmCis is well tolerated and has antitumor activity in patients with ASS1-deficient MPM and NSCLC, supporting further investigation in larger clinical trials which are currently under way.

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