Preclinical data support ongoing clinical trials testing IDO inhibitors as a treatment for cancer

July 19 2012

Inhibitors of indoleamine 2,3-dioxygenase (IDO) are being assessed in clinical trials as a potential treatment for recurrent or refractory solid tumors. Clear genetic rationale for these trials, together with evidence that primary and metastatic lung tumors might be particularly susceptible to the drugs, is now reported in a preclinical study published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Our data provide preclinical genetic validation for the ongoing clinical trials testing IDO inhibitors in cancer patients," said Alexander Muller, Ph.D., associate professor at Lankenau Institute for Medical Research in Wynnewood, Pa. "We also believe that our results indicate that these drugs could have particular impact in patients with lung adenocarcinoma and lung metastases, conditions for which there is an urgent, unmet need for new therapeutic options."

The ongoing clinical trials were initiated based on pharmacological studies that indicated that IDO inhibitors can enhance the effectiveness of other therapies in mouse models of cancer. Genetic evidence to support the concept was lacking. Muller and his colleagues, therefore, set out to determine the effect of disrupting the IDO gene on tumor development in mice.

"It was very important to us to use models of disease as physiologically relevant as possible," he said. "We chose the KRAS-induced lung

carcinoma model as our model of primary disease since tumors can be induced selectively in the lung and are driven by mutations in a gene known to be affected in approximately 20 percent of nonsmall cell lung cancers. We modeled metastatic disease using the 4T1 mouse breast cancer cell line, which very efficiently metastasizes to the lung after being engrafted in the mammary glands of mice. This is one of only a few breast cancer models with the capacity to metastasize efficiently to sites affected in human breast cancer patients."

Genetically-induced IDO deficiency reduced lung tumor burden and improved survival in both models.

"This genetic confirmation of the importance of IDO in lung tumor development is essential support for the clinical trials," said Muller. "However, we were also hoping to garner insight into the mechanisms by which IDO impacts tumor development. In this regard, our findings linking IDO to increased vascularization and modification of the inflammatory environment are critical. These data indicate that IDO has a far more expansive role in tumorigenesis than we might have thought."

Analysis of differences between the lungs of IDO-sufficient and -deficient tumor-bearing mice in the KRAS-induced lung carcinoma model revealed that levels of the pro-inflammatory molecule IL-6 were markedly lower in the absence of IDO. Levels of this known tumor-promoting factor were also lower in the model of metastasis when IDO was absent.

Additional work in the model of metastasis indicated that IDO-potentiated IL-6 production and promoted metastasis to the lung by driving the expansion and immunosuppressive function of a population of cells known as myeloid-derived suppressor cells (MDSCs). MDSCs are well-characterized, potent inhibitors of antitumor immune responses.

"It was very satisfying to be able to experimentally close the loop and clearly define a mechanism by which IDO promotes metastatic outgrowth to the lung, at least in the 4T1 breast cancer model," said Muller. "We think that this mechanism might also link with the vascular effects of IDO. IDO promotes tumorigenesis in many different ways, and we are looking to see if we can take clinical advantage of some of these."

Muller has financial interests in the clinical development of IDO inhibitors for the purpose of treating cancer and other diseases.

Provided by American Association for Cancer Research

Citation: Preclinical data support ongoing clinical trials testing IDO inhibitors as a treatment for cancer (2012, July 19) retrieved 26 April 2024 from https://medicalxpress.com/news/2012-07-preclinical-ongoing-clinical-trials-ido.html

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