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# T cells in pancreatic cancer stroma : tryptophan metabolism plays an important role in immunoregulation

Tryptophan metabolism in pancreatic cancer

**Abstract**

Several studies have shown that immune system is highly regulated by tryptophan metabolism which seved as immunomodulatory factor.The indoleamine 2,3-dioxygenase 1 (IDO1), as an intracellular enzyme which participates in the metabolism of the essential amino acid tryptophan in the kynurenine pathway, is an independent prognostic marker for pancreatic cancer(PC). First, overexpression of IDO1 inhibits the maturation of DCs and T-cell proliferation in liver and spleen. Second, highly expression of kynurenine induces and activates aryl-hydrocarbon receptor +ACY-nbsp+ADs-results in upregulates PD-1 expression. Third, the induction of IDO1 can lead to the loss of TH17/Treg+ACY-nbsp+ADs-balance, mediated by the proximal tryptophan catabolite from IDO metabolism. In our study, we found that overexpression of IDO1 upregulates the CD8+- T cells and reduce NKT cells in pancreatic carcinoma in mice. Hence, it may essential to pay more attention to tryptophan metabolism in patients especially who were tolerant to immunotherapy with PC.

**Key Words:** Immunosuppression; Pancreatic cancer stroma; T cell; tryptophan metabolism

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**Core Tip:** There are numerous evidences for tryptophan metabolism served as an immunomodulatory factor. The indoleamine2,3-dioxygenase1 (IDO1) overexpression inhibits the maturation of DCs and T-cell proliferation in spleen. Highly expression of kynurenine induces and activates aryl hydrocarbon receptor results in upregulates PD-1 expression. The induction of IDO1 can lead to the loss of TH17/Treg balance. We also

found that overexpression of IDO1 upregulates the CD8+T cells and reduce NKT cells in PC in mice.

## TO THE EDITOR

We have an interest in the recently published article by Goulart *et al*, (1) summarizing that the pancreatic cancer (PC) immune landscape, T cell interactions and immune dysfunction, T cell phenotype and functions, T cell exhaustion, and immunotherapy in PC. In this review, Goulart *et al*, summarized that the immune cells, including CD8+T, NK, Th17, and Treg cells are regulated by different cytokine factors. However, several studies have shown that immune system is highly regulated by tryptophan metabolism. As we all known, indoleamine 2,3-dioxygenase 1 (IDO1), as an intracellular enzyme which participates in the metabolism of the essential amino acid tryptophan (TRP) in the kynurenine (KYN) pathway, is an independent prognostic marker for PC. There are numerous evidences for tryptophan metabolism served as an immunomodulatory factor. First, IDO1 overexpression inhibits the maturation of CD11c and DCs, and T-cell proliferation in liver and spleen (2). Second, highly expression of KYN induces and activates aryl hydrocarbon receptor (AhR) results in upregulates PD-1 expression. Inhibition of Kyn-AhR) pathway can enhance antitumor adoptive T cell therapy efficacy, and reduce the rate of migration and invasion in both tumor-bearing mice and patients with cancer (3). In vivo experiments, inactivation of Kyn-AhR pathway showed ameliorate IDO1-mediated immunosuppression(4). In a clinical study, higly transcript of AhR were correlated with reduced CD8 T cell infiltration and worse outcomes in patients with PC(5). Third, the induction of IDO1 can lead to the loss of TH17/Treg balance in vivo. Similarly, the loss of TH17/Treg balance is mediated by the proximal tryptophan catabolite from IDO metabolism(6). In our study, we found that overexpression of IDO1 upregulates the CD8+ T cells and reduce NKT cells in both hepatic cancer and pancreatic carcinoma in mice. Hence, it may essential to pay more attention to tryptophan metabolism in patients with PC, especially in those who were tolerant to immunotherapy.

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