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ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Mohamad Amin Pourhoseingholi, PhD, Associate Professor, Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran 19835, Iran. aminphg@gmail.com

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

Ting Yang, Qiao-Qi Li, Yong-Mei Liu, Biao Yang

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Ting Yang, Qiao-Qi Li, Biao Yang, Department of Abdominal Oncology, Division of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Yong-Mei Liu, Division of Radiation Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Corresponding author: Biao Yang, MD, PhD, Professor, Surgeon, Teacher, Department of Abdominal Oncology, Division of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Chengdu 610041, Sichuan Province, China.
landayb@163.com

Abstract

Several studies have shown that the immune system is highly regulated by tryptophan metabolism, which serves as an immunomodulatory factor. The indoleamine 2,3-dioxygenase 1 (IDO1), as an intracellular enzyme that participates in 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 dendritic cells and T-cell proliferation in the liver and spleen. Second, the high expression of kynurenine induces and activates the aryl hydrocarbon receptor, resulting in upregulated programmed cell death protein 1 expression. Third, the induction of IDO1 can lead to loss of the T helper 17 cell/regulatory T cell balance, mediated by the proximal tryptophan catabolite from IDO metabolism. In our study, we found that overexpression of IDO1 upregulated CD8⁺ T cells and reduced natural killer T cells in pancreatic carcinoma in mice. Hence, it may be essential to pay more attention to tryptophan metabolism in patients, especially those who are tolerant to immunotherapy for PC.

Key Words: Immunosuppression; Pancreatic cancer stroma; T cell; Tryptophan metabolism; Xxx

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Core Tip: There are numerous lines of evidence for tryptophan metabolism, which serves as an immunomodulatory factor. Indoleamine 2,3-dioxygenase 1 (IDO1) overexpression inhibits the maturation of dendritic cells and T-cell proliferation in the spleen. The high expression of kynurenine induces and activates the aryl hydrocarbon receptor, resulting in upregulated programmed cell death protein 1 expression. The induction of IDO1 can lead to loss of T helper 17 cell/regulatory T cell balance. We also found that overexpression of IDO1 upregulated CD8⁺ T cells and reduced natural killer T cells in PC in mice.

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TO THE EDITOR

We have an interest in the recently published article by Goulart *et al*[1], which summarized 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* stated that immune cells including CD8⁺ T, natural killer (NK) cells, T helper 17 cells (Th17), and regulatory T cells (Tregs) are regulated by different cytokine factors. However, several studies have shown that the immune system is highly regulated by tryptophan metabolism. Indoleamine 2,3-dioxygenase 1 (IDO1), as an intracellular enzyme that participates in the metabolism of the essential amino acid tryptophan in the kynurenine (Kyn) pathway, is an independent prognostic marker for PC. There are numerous lines of evidence for tryptophan metabolism, which serves as an immunomodulatory factor. First, IDO1 overexpression inhibits the maturation of CD11c and dendritic cells, and T-cell proliferation in the liver and spleen[2]. Second, the high expression of Kyn induces and activates the aryl hydrocarbon receptor (AhR), resulting in upregulated programmed cell death protein 1 expression. Inhibition of the Kyn-AhR pathway can enhance the efficacy of antitumor adoptive T-cell therapy and reduce the rate of migration and invasion in both tumor-bearing mice and patients with cancer[3]. In *in vivo* experiments, inactivation of the Kyn-AhR pathway showed amelioration of IDO1-mediated immunosuppression[4]. In a clinical study, high expression of the AhR transcript was correlated with reduced CD8 T-cell infiltration and worse outcomes in patients with PC[5]. Third, the induction of IDO1 can lead to loss of the Th17/Treg balance *in vivo*. Similarly, loss of the Th17/Treg balance is mediated by the proximal tryptophan catabolite from IDO metabolism[6]. In our study, we found that overexpression of IDO1 upregulated CD8⁺ T cells and reduced NK T cells in both hepatic cancer and PC in mice. Hence, it may be essential to pay more attention to tryptophan metabolism in patients with PC, especially those who are tolerant to immunotherapy.

FOOTNOTES

Author contributions: Yang T, Li QQ, Liu YM, and Yang B designed the research study; Yang T and Li QQ performed the research; Yang T, Li QQ, and Yang B analyzed the data and wrote the manuscript; All authors read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Yong-Mei Liu 0000-0002-0346-1158; Biao Yang 0000-0003-2150-8690.

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