UKE Paper of the Month Juli 2020

IL22BP Mediates the Anti-Tumor Effects of Lymphotoxin Against Colorectal Tumors in Mice and Humans

Jan Kempski *, Anastasios D. Giannou *, Kristoffer Riecken, Lilan Zhao, Babett Steglich, Jöran Lücke, Laura Garcia-Perez, Karl-Frederick Karstens, Anna Wöstemeier, Mikolaj Nawrocki, Penelope Pelczar, Mario Witkowski, Sven Nilsson, Leonie Konczalla, Ahmad Mustafa Shiri, Joanna Kempska, Ramez Wahib, Leonie Brockmann, Philipp Huber, Ann-Christin Gnirck, Jan-Eric Turner, Dimitra E. Zazara, Petra C. Arck, Alexander Stein, Ronald Simon, Anne Daubmann, Jan Meiners, Daniel Perez, *Till Strowig, Pandelakis Koni, Andrey A. Kruglov, Guido Sauter,* Jakob R. *Izbicki, Andreas H. Guse, Thomas Roesch, Ansgar W. Lohse,* Richard A. Flavell, Nicola Gagliani[#] & Samuel Huber[#]
***** *shared first authorship*
[#] *shared last authorship*

Gastroenterology. 2020 Jun 18;S0016-5085(20)34833-2.

ABSTRACT:

Background & aims: Unregulated activity of interleukin 22 (IL22) promotes intestinal tumorigenesis in mice. IL22 binds the antagonist IL22 subunit alpha 2 (IL22RA2, also called IL22BP). We studied if alterations in IL22BP contribute to colorectal carcinogenesis in humans and mice.
Methods: We obtained tumor and non-tumor tissues from patients with colorectal cancer (CRC) and measured levels of cytokines by quantitative PCR, flow cytometry, and immunohistochemistry. We measured levels of Il22bp mRNA in colon tissues from wild-type, $Tnf^{-/-}$, $Lta^{-/-}$, and $Ltb^{-/-}$ mice. Mice were given azoxymethane and dextran sodium sulfate, to induce colitis and associated cancer, or intra-caecal injections of MC38 tumor cells. Some mice were given inhibitors of lymphotoxin beta receptor (LTBR). Intestine tissues were analyzed by single-cell sequencing to identify cell sources of lymphotoxin. We performed immunohistochemistry analysis of colon tissue microarrays from patients with CRC (1475 tissue cores, contained tumor and non-tumor tissues) and correlated levels of IL22BP with patient survival times.
Results: Levels of IL22BP were decreased in human colorectal tumors, compared with non-tumor tissues, and correlated with levels of lymphotoxin. LTBR signaling was required for expression of IL22BP in colon tissues of mice. Wild-type mice given LTBR inhibitors had an increased tumor burden in both models, but LTBR inhibitors did not increase tumor growth in Il22bp-/- mice. Lymphotoxin directly induced expression of IL22BP in cultured human monocyte-derived dendritic cells via activation of NF-κB. Reduced levels of IL22BP in colorectal tumor tissues associated with shorter survival times of patients with CRC.
Conclusions: Lymphotoxin signaling regulates expression of IL22BP in colon; levels of IL22BP are reduced in human colorectal tumors, associated with shorter survival times. LTBR signaling regulates expression of IL22BP in colon tumors in mice and cultured human dendritic cells. Patients with colorectal tumors that express low levels of IL22BP might benefit from treatment with an IL22 antagonist.

STATEMENT:

In this interdisciplinary work we identified a novel mechanism by which our immune system influences tumor progression. Our data show that IL22BP mediates the anti-tumor effects of lymphotoxin. Moreover, we found that IL22BP expression in the tumor can serve as a biomarker to identify patients with a worse clinical outcome. Of note, IL22 also has beneficial effects, and thus it is crucial to identify patients, who might benefit most from an IL22 blockade. Indeed, our data indicate that these patients could be selected based on the IL22BP expression level.

BACKGROUND:
Jan Kempski und Anastasios Giannou share the first authorship. They are both working in the research group of Prof. Dr. Samuel Huber (I. Department of Medicine) and interested in chronic inflammatory processes and tumor immunology. The work was performed in close cooperation with the Lab of Prof. Dr. Nicola Gagliani (I. Department of Medicine and Department of General, Visceral and Thoracic surgery) who supervised this work together with Prof. S. Huber. In total, 10 departments from the UKE were involved in this study.