UKE Paper of the Month Januar 2023

Tissue resident iNKT17 cells facilitate cancer cell extravasation in liver metastasis via interleukin-22

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ABSTRACT:

During metastasis, cancer cells invade, intravasate, enter the circulation, extravasate, and colonize target organs. Here, we examined the role of interleukin (IL)-22 in metastasis. Immune cell-derived IL-22 acts on epithelial tissues, promoting regeneration and healing upon tissue damage, but it is also associated with malignancy. *Il22*-deficient mice and mice treated with an IL-22 antibody were protected from colon-cancer-derived liver and lung metastasis formation, while overexpression of IL-22 promoted metastasis. Mechanistically, IL-22 acted on endothelial cells, promoting endothelial permeability and cancer cell transmigration via induction of endothelial aminopeptidase N. Multi-parameter flow cytometry and single-cell sequencing of immune cells isolated during cancer cell extravasation into the liver revealed iNKT17 cells as source of IL-22. iNKT-cell-deficient mice exhibited reduced metastases, which was reversed by injection of wild type, but not *Il22*-deficient, invariant natural killer T (iNKT) cells. IL-22-producing iNKT cells promoting metastasis were tissue resident, as demonstrated by parabiosis. Thus, IL-22 may present a therapeutic target for prevention of metastasis.

BACKGROUND:

This work was a joint and interdisciplinary effort involving numerous UKE Departments and external Co-operators. The majority of the work was performed in the research group lead by Prof. Samuel Huber (I. Department of Medicine). The first authorship is shared between Dr. Anastasios Giannou, Dr. Jan Kempski and Dr. Ahmad Mustafa Shiri. The authors share a common research focus on chronic inflammation, tumor immunology, tumor cell dissemination and metastasis. Indeed, together we uncovered a novel mechanism, which could build the basis for a future therapy preventing and treating metastasis development.