UKE Paper of the Month September 2021

Efferocytosis fuels malignant pleural effusion through TIMP1

Lilan Zhao, Anastasios D. Giannou, Yang Xu, Ahmad Mustafa Shiri, Imke Liebold, Babett Steglich, Tanja Bedke, Tao Zhang, Jöran Lücke, Pasquale Scognamiglio, Jan Kempski, Anna Woestemeier, Jing Chen, Theodora Agalioti, Dimitra E. Zazara, Diana Lindner, Melanie Janning, Jan K. Hennigs, Rajesh M. Jagirdar, Ourania S. Kotsiou, Sotirios G. Zarogiannis, Yasushi Kobayashi, Jacob R. Izbicki, Sourav Ghosh, Carla V. Rothlin, Lidia Bosurgi, Samuel Huber, Nicola Gagliani

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ABSTRACT:
Malignant pleural effusion (MPE) results from the capacity of several human cancers to metastasize to the pleural cavity. No effective treatments are currently available, reflecting our insufficient understanding of the basic mechanisms leading to MPE progression. Here, we found that efferocytosis through the receptor tyrosine kinases AXL and MERTK led to the production of interleukin-10 (IL-10) by four distinct pleural cavity macrophage (Mϕ) subpopulations characterized by different metabolic states and cell chemotaxis properties. In turn, IL-10 acts on dendritic cells (DCs) inducing the production of tissue inhibitor of metalloproteinases 1 (TIMP1). Genetic ablation of Axl and Mertk in Mϕs or IL-10 receptor in DCs or Timp1 substantially reduced MPE progression. Our results delineate an inflammatory cascade—from the clearance of apoptotic cells by Mϕs, to production of IL-10, to induction of TIMP1 in DCs—that facilitates MPE progression. This inflammatory cascade offers a series of therapeutic targets for MPE.

STATEMENT:
Supported by a multidisciplinary and international team, the scientists Lilan Zhao, Anastasios D. Giannou, and Yang Xu joined effort to discover a new immune-mediated mechanism responsible for the development of malignant pleural effusion (MPE), the lethal consequence of several human cancers. Using a mouse model of MPE, Zhao, Giannou, and Xu identified first that through the receptor tyrosine kinases AXL and MERTK, macrophages phagocytose the apoptotic cells in the pleural cavity and then secret the cytokine IL-10. Second, they showed that when macrophage-derived IL-10 is knock ed out, there is a significant reduction of MPE formation. Finally, the authors found that IL-10 acts on DCs which produce the tissue inhibitor of metalloproteinases 1 (TIMP1) and that MPE formation is significantly reduced in the absence of TIMP1. In short, this study delineates the inflammatory cascade behind MPE formation. Currently, there are no treatments for these terminally ill patients, and this study, through the use of ethical animal research, provides the scientific community with a series of targets (e.g. IL-10, TIMP1) that will foster the development of therapies. This study is a result of an integrated scientific program lead by Nicola Gagliani, Samuel Huber, and Lidia Bosurgi from the Departments of General, Visceral and Thoracic Surgery and Medicine at UKE.

BACKGROUND:
This work was performed at the Department of General, Visceral and Thoracic Surgery and Center for Internal Medicine in the groups of Nicola Gagliani, Samuel Huber and Lidia Bosurgi. It was part of the MD thesis of Dr. med. Lilan Zhao in collaboration with Dr. med Anastasios D. Giannou and Dr. med Yang Xu within the DFG funding (GA 2441/3-1, HU 1714/10-1, SFB841). Both authors have strong research interests in the field of cancer immunology.