UKE Paper of the Month April 2024

Apoptotic cell identity induces distinct functional responses to IL-4 in efferocytic macrophages

Imke Liebold, Amirah Al Jawazneh, Christian Casar, Clarissa Lanzloth, Stephanie Leyk, Madeleine Hamley, Milagros N. Wong, Dominik Kylies, Stefanie K. Gräfe, Ilka Edenhofer, Irene Aranda-Pardos, Marie Kriwet, Helmuth Haas, Jenny Krause, Alexandros Hadjilaou, Andra B. Schromm, Ulricke Richardt, Petra Eggert, Dennis Tappe, Sören A. Weidemann, Sourav Ghosh, Christian F. Krebs , Noelia A-Gonzalez, Anna Worthmann, Ansgar W. Lohse, Samuel Huber, Carla V. Rothlin, Victor G. Puelles , Thomas Jacobs, Nicola Gagliani*, Lidia Bosurgi*

Science, 2024, 384(6691):eabo7027

ABSTRACT:

Macrophages are functionally heterogeneous cells essential for apoptotic cell clearance. Apoptotic cells are defined by homogeneous characteristics, ignoring their original cell lineage identity. We found that in an interleukin-4 (IL-4)–enriched environment, the sensing of apoptotic neutrophils by macrophages triggered their tissue remodeling signature. Engulfment of apoptotic hepatocytes promoted a tolerogenic phenotype, whereas phagocytosis of T cells had little effect on IL-4–induced gene expression. In a mouse model of parasite-induced pathology, the transfer of macrophages conditioned with IL-4 and apoptotic neutrophils promoted parasitic egg clearance. Knockout of phagocytic receptors required for the uptake of apoptotic neutrophils and partially T cells, but not hepatocytes, exacerbated helminth infection. These findings suggest that the identity of apoptotic cells may contribute to the development of distinct IL-4–driven immune programs in macrophages..

STATEMENT:

Our study shows for the first time that the cellular identity of an apoptotic cell matters and influences the transcriptomic and functional signature of the corresponding phagocytic macrophages. Therefore, apoptotic cells generated in a damaged tissue are an additional factor, which modulate macrophages' functional heterogeneity. These results highlight the fact that apoptotic cells should not be seen simply as dying cells with homogenous features, but rather as a trigger of functional diversity based on their content and their cellular identity. Furthermore, our work shows that feeding of macrophages with selected apoptotic cell types can commit macrophages toward the acquisition of specific functions. This novel strategy may expand macrophages' efficacy and potential for therapeutic application, as in the case of chronic liver diseases for which macrophage-based cell therapies are already ongoing.

BACKGROUND:

The research was conducted in the group of Lidia Bosurgi (I. Department of Medicine, UKE and Bernhard-Nocht-Institute for Tropical Medicine, BNITM) under the co-supervision of Nicola Gagliani (I. Department of Medicine & Department of General, Visceral and Thoracic Surgery, HCTI, UKE). The research is part of Imke Liebold's Ph.D. and post-doctoral training.

The study was conducted in collaboration with researchers at the BNITM, in particular Thomas Jacobs, and with many researchers at the UKE, including Ansgar Lohse and Samuel Huber. The project was mainly funded by the DFG as part of the CRC 841 "Liver Inflammation: Infection, immune regulation and consequences".