UKE Paper of the Month October 2016

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Arc/Arg3.1 governs inflammatory dendritic cell migration from the skin and thereby controls T cell activation

Friederike Ufer, Pablo Vargas, Jan Broder Engler, Joseph Tintelnot, Benjamin Schattling, Hana Winkler, Simone Bauer, Nina Kursawe, Anne Willing, Oliver Keminer, Ora Ohana, Gabriela Salinas-Riester, Ole Pless, Dietmar Kuhl, Manuel A. Friese

ABSTRACT:
Skin-migratory dendritic cells (migDCs) are pivotal antigen-presenting cells that continuously transport antigens to draining lymph nodes and regulate immune responses. However, identification of migDCs is complicated by the lack of distinguishing markers, and it remains unclear which molecules determine their migratory capacity during inflammation. We show that, in the skin, the neuronal plasticity molecule activity regulated cytoskeleton-associated protein/activity-regulated gene 3.1 (Arc/Arg3.1) was strictly confined to migDCs. Mechanistically, Arc/Arg3.1 was required for accelerated DC migration during inflammation because it regulated actin dynamics through nonmuscle myosin II. Accordingly, Arc/Arg3.1-dependent DC migration was critical for mounting T cell responses in experimental autoimmune encephalomyelitis and allergic contact dermatitis. Thus, Arc/Arg3.1 was restricted to migDCs in the skin and drove fast DC migration by exclusively coordinating cytoskeletal changes in response to inflammatory challenges. These findings commend Arc/Arg3.1 as a universal switch in migDCs that may be exploited to selectively modify immune responses.

STATEMENT:
Dendritic cells orchestrate immune responses as they transport antigens from sites of inflammation to the lymph organs that serve as central hubs for immune activation. The neuronal plasticity molecule Arc/Arg3.1 was previously believed to be restricted to neurons of the central nervous system. Now, in an interdisciplinary approach we detected Arc/Arg3.1 for the first time in the immune system, where it is exclusively expressed in migratory dendritic cells and thereby allows for the first time specific identification of migrating DCs. As Arc/Arg3.1 regulates cytoskeletal changes in dendritic cells that is pivotal to accelerate migration in response to inflammation by interfering with its function we could ameliorate T cell responses and the disease course of the preclinical disease models of multiple sclerosis and allergic contact dermatitis.
Therefore our work opens a novel therapeutic strategy to identify fast migrating dendritic cells that can be targeted for immunotherapy in autoimmunity or tumour immunology.

BACKGROUND:
Most of the experimental work was performed by Dr. med. Friederike Ufer, who is clinically working at the Department of Neurology and at the same time conducting basic research at the Institute of Neuroimmunology and Multiple Sclerosis that is headed by Prof. Dr. Manuel Friese who also conceived this study. This study arose from a fruitful collaboration with Prof. Dr. Dietmar Kuhl, ZMNH. Collaboration with Dr. Pablo Vargas, Institute Curie Paris, helped to decipher the underlying mechanism. Manuel Friese received for this project an Exploration Grant from the Boehringer Ingelheim Stiftung and a grant by the UKE Deanery in preparation of the Excellence Initiative.