CATCHING WORMS - EOSINOPHIL ETOSIS AND PROTECTIVE MECHANISMS AGAINST FILARIAE

A. Ehrens[1,2], C. Nieto Perez[1], A. Krez[1], C. Paffenholz[1], B. Lenz[1], F. Risch[1], N. Offermann[3], M. Koschel[1], E. Latz[4], M. Capasso[3], A. Hoerauf[1,2], M.P. Hübner[1,2]

[1]Institute for Medical Microbiology, Immunology and Parasitology, University Hospital Bonn, Germany
[2]German Center for Infection Research (DZIF), partner-site Bonn-Cologne, Bonn, Germany
[3]Department of Immunregulation, German Center for Neurodegenerative Diseases (DZNE) within the Helmholtz Association, Bonn, Germany
[4]Institute for Experimental Immunology, University Bonn, Bonn, Germany

Eosinophils are important effector cells mediating protective immunity against parasitic filarial nematodes. This is clearly shown in eosinophil-deficient mice infected with the rodent filarial nematode *Litomosoides sigmodontis*, which have a significantly higher adult worm and microfilaria (MF), the filarial progeny, burden compared to immunocompetent wildtype mice. The exact effector mechanism mediating protection has not been identified yet. Eosinophils have been shown to release extracellular DNA traps spiked with toxic granules during a process called ETosis, which mediates entrapping and killing of pathogens. We demonstrated that *L. sigmodontis* MF induce eosinophil ETosis *in vitro*, which is mediated by the dectin-1 receptor and the canonical inflammasome pathway. *In vivo*, the *L. sigmodontis* infection increases local DNA concentration, while blood circulating MF increase plasma DNA levels, which is dependent on eosinophils. Moreover, DNA traps facilitate the clearance of MF from the peripheral blood, indicating that ETosis is an essential protective mechanism by eosinophils. Since murine and human eosinophils release DNA traps in response to MF of the rodent filariae and of *Dirofilariae immitis*, the dog heartworm, filariae-induced ETosis appears to be a conserved mechanism. However, the role of ETosis in pathology development is less clear. Immune responses by granulocytes towards dead MF have been shown to contribute to dermatitis and vision impairment in onchocerciasis patients, while viable MF rarely elicit inflammation. Therefore, we identified the role of the NADPH oxidase and calcium-dependent ETosis during MF stimulation. Interestingly, we observed that viable and dead MF induce different ETosis signaling cascades, which could lead to the altered immune response in onchocerciasis patients towards viable and dead MF. In summary, we demonstrate the role of eosinophil ETosis during a filarial infection and the molecular signalling mechanism occurring during MF-induced eosinophil ETosis.

The study was supported by DZIF Translational Thematic Unit: Novel Antibiotics grants #09.701, the Deutsche Forschungsgesellschaft (DFG, German Reaearch Foundation grant HU2144/3-1) and the DFG under Germany's Excellence Strategy – EXC2151 – 390873048.