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Background and objectives During inflammation and tissue damage, pathogens and dying cells are ingested by different phagocytes such as macrophages and dendritic cells. Both the nature and the activation state of the respective phagocyte determine the resulting immune response, which ranges from specific immunity to tolerance. A regulated uptake of apoptotic cells (AC) imposes a special task on the innate immune system to prevent autoimmunity.

Mechanisms regulating the sorting of apoptotic material into different phagocyte compartments, therefore, provide an important "tolerance-checkpoint" during the clearance of AC. In this study, the authors investigated the potential role of enzymatic lipid oxidation by 12/15-lipoxygenase (12/15-LO) in the uptake and sorting of AC.

Materials and methods The authors both studied the clearance of AC and resulting immunological consequences in WT and 12/15-LO−/− animals in vitro and in vivo, respectively.

Results During peritonitis, uptake of AC was confined to a population of 12/15-LO-expressing, alternatively-activated resident macrophages (resMΦ). ResMΦ utilised 12/15-LO-derived oxidation-products of phosphatidylethanolamine to selectively block the MFG-E8-dependent uptake of AC into freshly recruited inflammatory Ly6Chigh monocytes (infMΦ). In the absence of 12/15-LO, this uptake pattern was deranged and infMΦ started to engulf apoptotic cells.

Moreover, this disturbed clearance in 12/15-LO−/− animals resulted in a markedly increased OT-II T cell-proliferation in vitro and in vivo, respectively, when challenged with ovalbumin-transgenic AC. In consistence, the authors observed a break in self-tolerance in aged 12/15-LO-deficient mice including spontaneous production of autoantibodies and occurrence of glomerulonephritis, which both exacerbated after apoptotic challenge in the pristane-induced model of experimental murine lupus.

Conclusion Our data point towards a so far unrecognised role for lipid oxidation during the maintenance of self-tolerance and identify a mechanism, which orchestrates the cell- and context-specific uptake of antigens by different subsets of phagocytes, imposing a new paradigm in our understanding of the clearance of apoptotic cells.

13 12/15-LIPOXYGENASE ORCHESTRATES THE CLEARANCE OF APOPTOTIC CELLS AND MAINTAINS IMMUNOLOGIC TOLERANCE

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