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Monocyte/macrophage function in mice with somatic inactivation of lipoprotein receptor related proteins

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5. Summary

SorLA and sortilin have recently been identified as receptors, with elements characteristic of the Vps10p domain receptor family, as well as, the low density lipoprotein receptor family. These receptors are of unknown function, expressed predominantly in brain and in haematopoietic cells. They bind several ligands engaged in intracellular sorting, as well as, endocytosis and signal transduction. The aim of this study was to detect SorLA and Sortilin presence on mRNA and protein level in monocytes/macrophages and to study their regulation and function by using SorLA and Sortilin KO mice. We studied their role in THP-1 monocytes, PMA induced THP-1 macrophages and macrophages of sorLA and sortilin knockout mice. mRNA of SorLa and Sortilin was measured by real time RT-PCR. Protein was determined by Western blot. mRNA and protein expression of both receptors was changed during cell differentiation from monocytes to macrophages. Specific cytokines like M-CSF, PDGF-BB, IFNγ, TGFß-1 and neurotensin, differentially regulated the expression, of both sorLA and sortilin, in a dose- and time-dependent manner. Inhibition with actinomycin D indicated that the observed induction was, at least partly, a transcriptional event. Studies in sorLA and sortilin deficient mice showed a decrease in the number of recruited thioglycollate activated peritoneal macrophages accompanied by distinct morphological features. Confocal microscopy revealed a profound modification of actin-cytoskeletal arrangement in peritoneal macrophages of SorLA-deficient mice. Flow cytometry demonstrated an impaired ability of FITC-dextran uptake by peritoneal macrophages of sorLA and sortilin knockout mice. We

conclude that in monocyte/macrophages sorLa and sortilin expression was influenced by cytokines and differentiation. SorLA and Sortilin deficient mice show phenotypic characteristics indicative of a disturbed cytoskeletal organisation accompanied by impaired phagocytic function. Present findings provide new insights into the role of SorLA and Sortilin in monocyte/macrophage function.