Crucial role of the calcium-binding proteins S100A8/A9 in controlling macrophage-mediated renal repair following ischemia/reperfusion.

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Background: Upon ischemia/reperfusion (I/R)-induced injury, several damage associated molecular patterns (DAMPs) are released including calcium-binding protein S100A8/A9. S100A8/A9 has a range of intra- and extracellular functions. Extracellular, S100A8/A9 can be recognized by Toll-like receptor (TLR)-4 and activation of this TLR is known to deleteriously contribute to renal I/R induced injury. Mice deficient for S100A9 displayed less I/R-induced cerebral injury. We hypothesize that S100A8/A9 also contribute to renal I/R-induced injury.

Methods: Wild-type (WT) and S100A9 KO mice (deficient for S100A8/A9 complex) were subjected to bilateral renal I/R and sacrificed after 1, 5 or 10 days. Mice were screened for renal function, damage, fibrosis and inflammation. Macrophage polarization was induced on isolated bone marrow derived and on peritoneal macrophages by incubation with Th1 or Th2 related cytokines to induce classically activated macrophages (called M1) or alternatively activated macrophage (called M2) respectively.

Results: Unexpectedly, S100A9 KO mice displayed similar renal dysfunction, damage and neutrophil-influx compared to WT mice, 1 day after I/R. Interestingly, S100A9 KO mice displayed an impaired repair mechanism 5 days post I/R as reflected by increased renal damage, sustained inflammation, induction of fibrosis and increased expression of collagen. This coincided with enhanced expression of M2 markers arginase-1 (Arg1) and interferon regulatory factor-4 (IRF-4). Expression of M1 markers nitric oxide synthase-2 (NOS2) and IRF5 were similar. In agreement with our in vivo observations, M2 polarized macrophages from S100A9 KO mice displayed higher expression of Arg1 compared to macrophages from WT mice whereas M1 polarization was similar between the two strains. Additional extracellular S100A8 or S100A9 induced M1, but not M2 macrophage polarization in WT macrophages.

Conclusions: We showed for the first time that S100A8/A9 prevents M2-type macrophages from becoming profibrotic, possibly through an intracellular pathway. S100A8/A9 plays a crucial part in controlling macrophage-mediated renal repair following I/R.