FP251

HMGB1 IN MYELOID CELLS DRIVES POSTISCHEMIC ACUTE KIDNEY INJURY BY PROMOTING NEUTROPHIL INFILTRATION

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INTRODUCTION: High-mobility group box 1 (HMGB1) is a nucleoprotein known to drive innate immunity when released from dying cells, e.g. from dying renal cells during postischemic acute kidney injury (AKI). Little is known about its function in myeloid cells in this context. We hypothesized that myeloid cell-specific deletion of HMBG1 can help to address this question.

METHODS: We generated conditional myeloid cell-specific HMGB1 deficiency in mice by crossing LysMCre knock-in mice with HMGB1 flox/flox mice. HMGB1 knockout mice (LysMCre-HMGB1 flox/flox mice) underwent unilateral ischemia-reperfusion injury (IRI) to induce ischemic acute tubular necrosis and AKI. Littermates carrying HMGB1 flox/flox without Cre were used as control. Renal function and histology were evaluated 24h after surgery.

RESULTS: The number of circulating leucocytes (neutrophil, monocyte, eosinophil, basophil and lymphocyte), red blood cell, and thrombocyte at baseline were equivalent in knockout and control mice. 24h after surgery, lack of HMGB1 in myeloid cells attenuated the drop of glomerular filtration rate (GFR) as compared to control mice (Fig. 1). This effect was associated with a reduced acute tubular necrosis score (Fig. 2) and renal cell death as evaluated with the terminal uridine nick-end labeling (TUNEL)+ cells (Fig. 3). Ischemia increased the numbers of infiltrating neutrophils, which was significantly reduced with HMGB1-deficiency in myeloid cells (Fig. 4). No differences were seen for the other myeloid cell types (macrophages, dendritic cells, mast cells, basophils, and eosinophils).

CONCLUSIONS: HMGB1 in myeloid cells drives postischemic tubular necrosis and renal failure probably by a specific effect on neutrophils. The molecular mechanisms underlying this phenomenon remain to be defined.

Figure 1

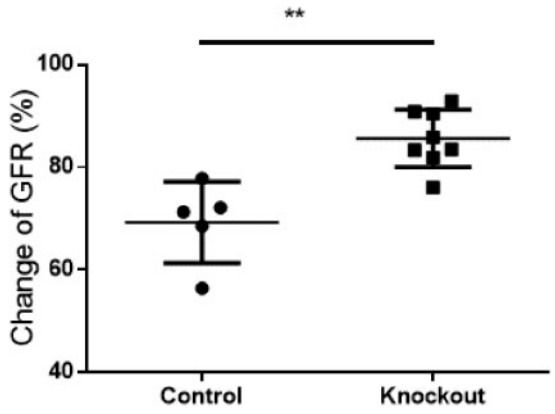

Figure 2

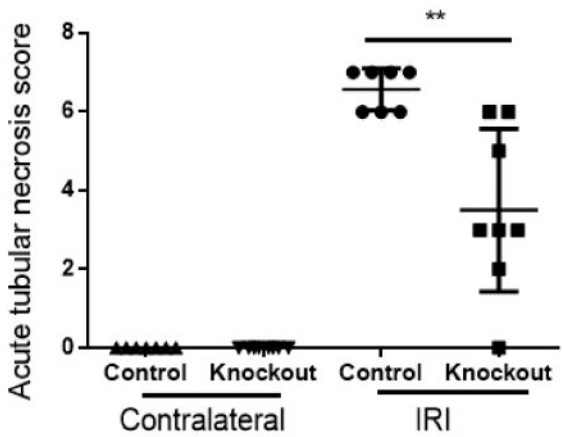

Figure 3

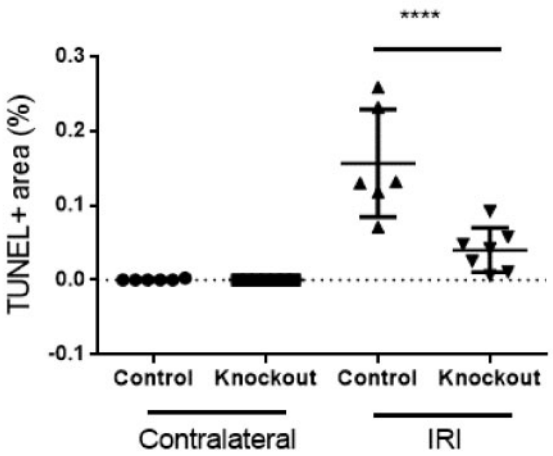

Figure 4