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Granulocyte-colony stimulating factor ameliorates renal ischemia-reperfusion injury by recruiting myeloid-derived suppressor cells to kidney

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Objectives: Myeloid-derived suppressor cells (MDSC) are one of innate immune suppressors that contribute to tumor tolerance. Recently, granulocyte-colon stimulating factor (G-CSF) has been reported to recruit MDSCs and thereby play an immunoregulatory role in autoimmune diseases or transplantation.

Methods: Here, we investigated whether G-CSF can ameliorate renal ischemia-reperfusion injury (IRI) by recruiting MDSC to renal tissues using mouse models.

Results: Both G-CSF and G-CSF receptor mRNA levels increased in renal tissues after IRI. G-CSF treatment before IRI attenuated renal dysfunction as well as histologic injury score during the first 5 days. Levels of proinflammatory cytokines such as TNF-α, IL-12, IL-6, and MCP-1 decreased and renal IL-10 levels increased in the G-CSF group. G-CSF treatment decreased renal infiltration of macrophages and T cells, while it increased renal infiltration of MDSC ($CD11b^{+}Gr\text{-}1^{int}$, $Ly6C^{low}Ly6Gi^{nt}$). When G-CSF were administered after IRI, it also decreased serum levels of BUN and creatinine. Post-IRI G-CSF treatment increased renal infiltration of M2 macrophages, MDSC, and regulatory T cells on day 5. Furthermore, renal fibrosis (Masson-Trichrome staining, fibronectin, collagen IV) on day 28 was also decreased in the G-CSF group. When anti-Gr-1 depleting antibody was combined with G-CSF to remove mature neutrophils with saving MDSC, renal dysfunction by IRI was nearly completely ameliorated. Next, we isolated splenic $Gr\text{-}1^{+}$ cells from the mice that had experienced IRI with G-CSF treatment. These $Gr\text{-}1^{+}$ cells expressed high levels of arginase 1 and IL-10 with low iNOS. Furthermore, they suppressed T cell proliferation and their adoptive transfer attenuated renal dysfunction by IRI, indicating that G-CSF induced immunosuppressive MDSC in IRI.

Conclusions: In conclusion, G-CSF treatment before IRI attenuated acute renal injury and G-CSF treatment after IRI facilitated renal recovery with attenuation of renal fibrosis. Moreover, combination of G-CSF and anti-Gr-1 has synergistically beneficial effects on renal IRI by recruiting MDSCs with minimizing renal infiltration of mature neutrophils.