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Role of Unconventional Immunosuppressive cells in Renal Ischemia-Reperfusion Injury

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Renal ischemia-reperfusion injury (IRI) is regarded as acute inflammatory responses where both innate and adaptive immune cells play important roles in injury and subsequent repair processes. The final fate of renal IRI is determined by the balance between immune effector cells and immune suppressors. Regulatory T cells, a representative immune suppressor cells, have been shown to ameliorate acute injury of renal IRI, facilitate recovery and attenuate chronic fibrosis after IRI. Recently, several unconventional adaptive and innate immune suppressors such as regulatory B cells and myeloid-derived suppressor cells are introduced to suppress various immune responses. Apparently discrepant data about role of B cells in renal IRI and important role of innate immunity in renal IRI inspired us to study role of these two nonconventional immune suppressors in renal IRI. Adoptive transfer of Bregs prior to or following IRI attenuated renal IRI. Anti-CD45RB treatment prior to IRI increased the renal infiltration of $CD19^{+}Tim\text{-}1^{+}$ Bregs and regulatory T cells. Anti-CD45RB decreased serum creatinine levels, pathologic injury score, and tubular apoptosis. Levels of IL-1β, IL-6, MCP-1, IFN-γ, and IL-17 were decreased, whereas IL-10 was increased in the CD45RB group. Following IRI, anti-CD45RB with or without anti-Tim-1 also induced Bregs, thereby improving renal function and tubular regeneration. In RAG1 knockout mice with B cell transfer, TCRα knockout mice, and wild-type mice with T cell depletion, anti-CD45RB increased Bregs and attenuated IRI. However, anti-CD45RB did not attenuate IRI in RAG1 knockout mice with T cell transfer or μMT mice and induced only mild improvement in wild-type mice with B cell depletion. Furthermore, B cells from IL-10 knockout mice did not show anti-CD45RB-mediated renal protection against IRI, in contrast to those from wild-type mice. Therefore, these data suggest anti-CD45RB as a potential therapeutic strategy in renal IRI by induction of $IL\text{-}10^{+}$ Bregs.
Granulocyte-colony stimulating factor (G-CSF) treatment prior to IRI attenuated acute renal dysfunction, as well as tissue injury and renal tubular apoptosis, after IRI. Additionally, G-CSF treatment suppressed renal infiltration of macrophages and T cells, as well as renal levels of IL-6, MCP-1, IL-12, TNF-α, and IFN-γ, while increasing levels of IL-10, arginase-1, and reactive oxygen species (ROS). Moreover, G-CSF treatment following IRI improved the recovery of renal function and attenuated renal fibrosis on day 28. G-CSF treatment increased renal infiltration of MDSCs ($F4/80^{-}CD11b^{+}Gr\text{-}1^{int}$), especially granulocytic MDSCs ($CD11b^{+}Ly6G^{int}Ly6C^{low}$), with splenic $F4/80^{-}CD11b^{+}Gr\text{-}1^{+}$ cells sorted from G-CSF-treated mice displaying higher levels of arginase-1, IL-10, and ROS relative to those from control mice. Furthermore, these splenic cells effectively suppressed *in vitro* T cell activation mainly through arginase-1 and ROS, and their adoptive transfer attenuated renal IRI. These data suggested therapeutic potential of MDSCs and G-CSF in renal IRI. In conclusion, immunosuppressive cell therapy including Bregs and MDSCs as well as Tregs or their inducing agents could be a promising strategy to control renal IRI.