SIGNIFICANCE STATEMENT

The IL-33 type 2 innate lymphoid cell (ILC2) axis plays an important role in tissue homeostasis, inflammation, and wound healing, but its importance in acute kidney inflammation and injury remains unclear. Using a mouse model of ischemia-reperfusion injury (IRI), IL-33 significantly prevented tissue injury and mortality through inducing kidney-resident ILC2 expansion. ILC2 mediated renoprotection mainly through production of amphiregulin and induction of M2 macrophages. In a humanized mouse model, treatment with human IL-33 or transfer of *ex vivo*–expanded human ILC2 protect against IRI. This study shows a major protective role of the IL-33–ILC2 axis in renal IRI, suggesting the possibility of targeting this pathway for novel therapeutic approaches.