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The novel neutrophil population, Siglec-F+ neutrophils, induced renal fibrosis by collagen production

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Objectives: Neutrophils are the major innate immune cells in the homeostatic kidney, but their roles in renal inflammation were not well characterized. Recent studies on lung, heart, and nasal epithelium showed that a distinct subset of neutrophils with the expression of key eosinophil marker, Siglec-F emerged in various inflammation. The functionally activated, novel neutrophil subsets were located only in the inflammatory milieu, therefore the emergence of the subset as well as their roles in renal inflammation remain unknown.

Methods: C57BL/6 male mice were subjected to of unilateral ureteral obstruction (UUO), unilateral ischemic reperfusion injury (uIRI) or sham operation. The injured kidney was investigated for histological evaluation, gene expression, and immune cell analysis. To deplete neutrophils expressing Siglec-F, Siglec-F and Ly-6G depletion antibodies were treated on days 0 and 3 after surgery. Morphology and function of the sorted Siglec-F+ neutrophils were assessed using H&E staining and flow cytometry. Gene expressions related to fibrosis were measured by real-time qPCR.

Results: Here, we showed the roles of Siglec-F+ neutrophils in the murine model of chronic kidney disease (CKD). We found that Siglec-F expressing neutrophils became the major immune cells in UUO-induced kidney, and its frequency was correlated with fibrosis progression. However, Siglec-F+ neutrophils were only restricted to the inflamed kidney, not to the contralateral kidney nor circulation. Morphologically, neutrophil hypersegmention was more prevalent in Siglec-F+ neutrophils than conventional neutrophils, both sorted from the inflamed kidney. Siglec-F+ neutrophils expressed collagen 1 and α-smooth muscle actin, which implied their direct roles in fibrosis. TGF-beta and GM-CSF were the key factors that induce Siglec-F expression on neutrophils. Treatment of Siglec-F-and Ly-6G-depletion antibodies that targeting Siglec-F+ neutrophils significantly reduced the disease progression, especially the collagen content (49.9% reduction by Siglec-F depletion).

Conclusions: Together, these findings unveiled the novel neutrophils in renal fibrosis and suggested a new therapeutic target in CKD.

Figure 1. Depletion of Siglec-F protects renal fibrosis by selective inhibition of pro-fibrotic Siglec-F expressing neutrophils