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Tertiary lymphoid tissue formation directed by heterogeneous fibroblasts causes maladaptive repair of aged kidneys

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Acute kidney injury (AKI) is a common clinical condition, which is characterized by a rapid fall in glomerular filtration rate, frequently as a result of an ischemic or nephrotoxic renal insult. AKI is associated with a high mortality rate, subsequent chronic kidney disease (CKD), and other types of organ failure. The incidence of AKI is increasing worldwide especially in aged population, which is an enormous global economic burden and a major public health issue.
Unlike reversible AKI in the young, AKI in the elderly is often irreversible and leads to CKD or end stage renal disease (ESRD). However, why an aged kidney fails to repair itself and progresses to CKD or ESRD has not been fully investigated, and thus there are no effective therapeutic tools that could improve survival after AKI in the elderly.
Recently, we demonstrated that aged mice, but not young mice, developed multiple renal tertiary lymphoid tissues (TLTs) after kidney injury. TLT size was associated with impaired renal function, and increased expression of pro-inflammatory cytokine, indicating possible contribution of TLTs to sustained inflammation after injury.
We previously reported that most resident fibroblasts in the kidney are lineage labeled with P0-Cre, and under pathological conditions, P0-Cre lineage-labeled fibroblasts transdifferentiate into myofibroblasts and contribute to fibrosis.
In the present study, we found that, in the aged injured kidney, P0-Cre lineage-labeled resident fibroblasts diversified into several phenotypically distinct fibroblasts, and maintained a microenvironment for TLT formation.
Furthermore, removal of TLTs by the administration of dexamethasone and CD4 neutralizing antibody improved renal outcomes.
Importantly, aged but not young human kidneys also form TLTs that have cellular and molecular components similar to those of mouse TLTs. Therefore, the inhibition of TLT formation may offer a novel therapeutic strategy for AKI in the elderly.