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허혈성 급성신손상 후 만성신질환으로의 진행에 있어서 M2 대식세포의 역할

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The Role of M2 Macrophage in the Progression of Chronic Kidney Disease Following Acute Kidney Injury

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Background: Acute kidney injury (AKI) is a major risk factor for progression of chronic kidney disease (CKD). Although inflammation is mainly involved in the pathogenesis of ischemic AKI, the mechanism that link AKI to CKD remains unclear. Recently, macrophages were shown to shift their phenotype from M1 to M2 and these M2 macrophages facilitate recovery. In this study, we examined the alteration of macrophage phenotype during the extended period of recovery phase following ischemia/reperfusion injury (IRI) and tried to verify their roles in the development of renal fibrosis in a mouse model of I/R-CKD progression by using two different strategies of monocyte/macrophage depletion.

Method: Renal pedicle was clamped unilaterally for 40 minutes and on day 7, 14 and 28 after IRI, phenotype of monocyte/macrophage, cytokine expression, renal fibrosis were assessed. To determine the role of monocyte/macrophage subset in renal fibrosis, liposome clodronate (LC) was injected or CD11c-DTR transgenic mice were used. Depletion was initiated on day 3 following IRI.

Results: Throughout the recovery phase of IRI, mRNA expression of M2 marker (Arginase-1) in kidney was markedly increased (85 fold of sham) compared to M1 marker (iNOS). Flow cytometric analysis also revealed the predominant macrophage subset was F4/80+CD206+ M2-phenotype macrophages but not F4/80+CD206- M1-phenotype macrophages during the recovery phase. On day 28 after IRI, renal fibrosis was clearly shown with increased type IV collagen and TGF-B. Injection of LC resulted in preferential depletion of M2 macrophages and it was associated with significant reduction of kidney IL-6, type IV collagen, TGF-B; and ultimately improved renal fibrosis, suggesting the important contribution of M2 macrophage in the development of renal fibrosis. On the other hand, injection of diphtheria toxin to CD11c-DTR transgenic mice resulted in depletion of CD11chigh cells with relatively preserving M2 macrophages and had minimal impact on renal fibrosis as well as tissue level of cytokines.

Conclusion: Although known to be important in facilitating recovery, M2 macrophages are thought to be main culprit in the development of renal fibrosis following IRI. Better understanding of heterogeneous function of macrophages is necessary to develop strategies to prevent the development of fibrosis following IRI.

Key Words: 급성신손상, 신섬유화, 대식세포
Acute kidney injury, Renal fibrosis, Macrophage