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Uric Acid-induced NLRP3 Inflammasome Contribute to Diabetic Kidney Injury

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Background: Despite of the fact that hyperuricemia is frequently found in a diabetic nephropathy, the definite cause and effect between hyperuricemia and kidney injury have not well investigated yet. Recently, reports showed IL-1β secreting NLRP3 inflammasome in cytoplasm plays a role as a sensor of the innate immune injury in metabolic disease. Therefore, we investigated the cause and effects of hyperuricemia and kidney injury in diabetic nephropathy to demonstrate the role of NLRP3 inflammasome in uric acid-induced kidney injury in diabetes.

Methods: We designed four animal groups as following; 1) LETO (Long Evans Tokushima Otsuka); 2) OLETF (Otsuka Long Evans Tokushima Fatty); 3) OLETF+HFD (high fructose diet) for 16 weeks; 4) OLETF+HFD+allopurinol (10 mg/dL in drinking water). HK-2 (Human renal proximal tubule cells) and THP1 (Human acute monocytic leukemia cell line) were cultured and stimulated with uric acid.

Result: OLETF+HFD group showed a higher serum uric acid (1.4±0.1 vs 2.2±0.4 mg/dL) and urinary albumin creatinine ratio (350±72 vs 594±102 μg/mg) than OLETF group. In the OLETF+HFD group, the increase trend of NLRP3 and IL-1β expression in kidney was observed. Immunohistochemical staining of CD68+ cells showed significant increase in HFD group compared to OLETF group. Allopurinol attenuated HFD induced hyperuricemia and NLRP3 activation-related renal inflammation. Uric acid-induced NLRP3 activation and IL-1β secretion in THP1 cells were also observed. During the THP1 and HK-2 co-culture it is confirmed that IL-1β secreted in THP1, plays a pivotal role in activating IL-1βR1, MyD88 and IRAK4 signaling in HK-2 cells. This up-regulated IL-1βR1 signaling was resulted in NF-κB activation in HK-2 cells.

Conclusion: According to these results we can conclude that hyperuricemia activates NLRP3 inflammasome of macrophage and contribute in renal injury by secretion of IL-1β.

Key Words: Uric acid, NLRP3 inflammasome, Diabetic nephropathy