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The novel involvement of podocyte autophagic activity in the pathogenesis of lupus nephritis

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Objectives : Lupus nephritis (LN) is oneof the most common and severe complications in systemic lupus erythematosuspatients, and the mechanism underline the pathogenesis ofLNis still unknown.Autophagyplays vital roles in maintaining cell homeostasis and is involved in the pathogenesis of manydiseases.In this study, we investigated the role of autophagy in the progression of LN.

Methods : Autophagic activities in podocytes of both LN patients and mice were evaluated. Podocytes were enumerated by electron microscopy, and autophagic activity was evaluated by immunohistochemistry and Western blot analysis. Apoptotic activity was evaluated by immunofluorescence staining, TUNEL assays and flow cytometric analysis.

Results : Significantly greater podocyte injury and increased autophagosomes were observed in LN patients. Differentiated mouse podocytes in the LN group showed reduced nephrin expression and increased apoptosis, as well as significantly higher levels of apoptosis-related proteins (cleaved caspase-3, Bax and Bcl-2). In the LN group, the increased number of autophagosomes was accompanied by increased LC3-II/LC3-I ratios and decreased p62, suggesting increased autophagic and apoptotic activity in podocytes. Blockade of autophagic activity by 3-MA or siRNA-mediated silencing of Atg5 resulted in decreases in LC3-II/LC3-I ratios, podocyte apoptosis and damage in the LN group. Rapamycin treatment decreased LC3-II/LC3-I ratios, but enhanced LN-induced apoptosis and apoptosis-related protein expression.

Conclusions : This study demonstrates that autophagic activity of podocytes is a crucial factor in renal injury; thus, inhibiting this activity during the early stages of LN is implicated as a potential therapeutic strategy for delaying the progression of LN.

Keywords : Lupus Nephritis; Autophagy; Podocyte; Apoptosis; Rapamycin