MIR-34A PROMOTES OXIDATIVE DAMAGE AND SENESCENCE OF PRIMARY RENAL GLOMERULAR MESANGIAL CELLS BY INHIBITING AUTOPHAGY-RELATED GENE 9A

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Glomerular mesangial cells are an important type of residential cells in the kidneys. Senescence-related changes in mesangial cells play an important role in renal aging process. However, the aging mechanism of mesangial cells is unknown. Autophagy is a key protective mechanism and can maintain a stable intracellular environment in eukaryotes by degrading the damaged and senescent organelles and biological macromolecules and is closely associated with senescence and age-related diseases. MicroRNA (miR) is associated with senescence. However, the mechanism how miR-34 regulates the senescence of mesangial cells is not well understood.

In this study, we investigated the regulating mechanisms of mesangial cell damage and senescence by miR-34a.

We first observed the changes in the expression levels of miR-34a and its target gene autophagy-related gene 9A (Atg9a) in primary glomerular mesangial cells from old rats. We then transfected a miR-34a overexpression or Atg9a shRNA vector into primary mesangial cells from young rats to observe the effect of miR-34a overexpression or Atg9A knockdown on autophagy activity, oxidative damage, and senescence in the primary glomerular mesangial cells.

The results showed that in the mesangial cells from old rats, miR-34a was significantly upregulated and its target gene Atg9a was significantly downregulated. Transfection and overexpression of miR-34a in the primary mesangial cells from young rats could downregulate levels of Atg9A and autophagosome formation marker LC3; upregulate autphagic degradation markers p62/SQSTM1 and polyubiquitin aggregates; increase the levels of oxidative damage products 8-OHdG, malondialdehyde (MDA) and protein carbonyl; increase the positive staining percentage of cell senescence marker SA-beta-gal; and increase formation of senescence-associated heterochromatin foci (SAHF). Transfection of Atg9a shRNA into primary cells from young rats produced cellular phenotypes similar to that of miR-34a overexpression.

These results suggest that miR-34a can inhibit autophagy function, increase oxidative damage, and accelerate the senescence of mesangial cells by downregulating Atg9A expression.