specific miR-30s sponge (down-regulation) mice and podocyte specific miR-30a, miR-30c, miR-30d over expressing mice. First, we gave sponge mice vehicle, calcineurin/NFAT and ingegrin beta3 inhibitors separately. Then animals were sacrificed and evaluated for albuminuria, ultrastructural injury of podocyte, pathological changes and uPAR-integrin beta3 activity. Then we induced podocyte injury by LPS (20mg/kg, i.p.) on miR-30a, c, d over expressing mice. uPAR-integrin beta3 activity and podocyte injuries were detected after 48h.

RESULTS: In vitro, down-regulation of miR-30s via miR sponge activated uPAR-integrin beta3. It also caused cytoskeleton rearrangement and increased cell mobility. Inversely, miR-30a over-expression protected F-actin structure while inhibiting uPAR-integrin beta3 activation. These results indicated that miR-30s inhibited this pathway in podocyte. Moreover, both calcineurin inhibitor FK506 and NFAT inhibitor 11R-VIVT could mitigate uPAR-integrin beta3 activation caused by miR-30s sponge. It revealed that miR-30s restrained this pathway by targeting calcineurin/NFAT. It could reduce the nuclear translocation of NFAT. Finally, Rac1 and cdc42 are predominantly activated through miR-30s down-regulation. While uPAR and integrin beta3 inhibition at the same time can reduce their activation respectively.In vivo miR-30s podocyte specific sponge mice developed prominent albuminuria and podocyte foot process effacement. uPAR-integrin beta3 was also activated in glomerular. FK506, 11R-VIVIT, and integrin beta3 inhibitor could alleviate all the above injuries. Further more, LPS induced albuminuria, podocyte injuries and integrin beta3 activation in mice. While miR-30 over expression transgenic group exhibited minor injuries.

CONCLUSIONS: miR-30s maintain podocyte cytoskeleton stability by inhibiting uPAR-integrin beta3 activation both in vitro and in vivo. miR-30s constrain uPAR-integrin beta3 activity through targeting calcineurin/NFATc3. This pathway further restrains Rho subfamily molecules activation to protect podocyte.

SaO052 MIR-30 FAMILY PREVENTS UPAR-INTEGRIN β3 SIGNALING ACTIVATION TO PROTECT PODOCYTES

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INTRODUCTION AND AIMS: miR-30 family is a crucial molecule maintaining podocyte cytoskeleton homeostasis. But its mechanisms require further exploration. It has been widely accepted that urokinase. Plasminogen activator receptor (uPAR)-integrin beta3 signaling is a key factor of podocyte cytoskeleton damage. Interestingly, its up-stream transcription factor nuclear factor of activated T cell c3 (NFACTc3) is predicted to be miR-30 target.So the purpose of our study is to explore the miR-30s' podocyte protection mechanisms, and the involvement of the vital pathway uPAR-integrin beta3 activation.

METHODS: In vitro studies were performed with immortalized human podocyte (HPC). Under injurious stimulation and miR-30a over expression, uPAR-integrin beta3 signaling activation as well as podocyte F-actin were evaluated. In order to explore the regulatory mechanisms, we tested above injuries through miR-30s down-regulation, with or without uPAR siRNA and Calcineurin/NFAT inhibition. Finally, Rho subfamily molecules Rac1 and cdc42 activities were detected through above conditions.To perform in viv studies, we constructed two transgenic mice: podocyte