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Hic-5 as a protector of podocytes from genotoxic cell death in chronic proteinuric glomerulopathies

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Podocytopathies are glomerular diseases characterized by structural alterations to podocytes, key components of the glomerular filter, and proteinuria. Current knowledge of the various pathomechanisms is limited and has not yet provided significant therapeutic leads. Pathologically, loss of postmitotic podocytes correlates with disease progression, and cell death has recently been implicated as a major contributor to podocyte loss.
Hic-5, a focal adhesion scaffold protein, is expressed in podocytes and has been shown to protect smooth muscle cells during vascular injury. However, the role of hic-5 in podocytes and in glomerular disease progression remains unknown. We have attempted to investigate the role of hic-5 in podocytopathies and the mechanisms influenced by hic-5 and hypothesize that hic-5 is a protective factor during glomerular injury.
To test this hypothesis, we investigated the presence of hic-5 in human podocytopathies in kidney biopsies, the difference in glomerular injury after toxic adriamycin exposure between hic-5 deficient mice and wildtype littermates, and mechanistically explored the relationship between hic-5 depletion and podocyte cell death *in vitro*.
Our results showed the significance of hic-5 in glomerular diseases by demonstrating the induction of hic-5 in podocytes in a subset of human podocytopathies. In addition, using a hic-$5^{-/-}$ mouse model, we could demonstrate that adriamycin leads to significantly increased proteinuria and glomerulosclerosis with increased podocyte loss in hic-$5^{-/-}$ mice compared to wildtype littermates.
Furthermore, our work provides mechanistic insights into the effects of hic-5 deficiency on cultured podocytes. Hic-5 depletion resulted in loss of actin stress fibers, but also increased cell death. Reduced levels of p21, an important check point inhibitor, led to pathogenic cell cycle activation in postmitotic cells and mediated sustained JNK and caspase-3 activation, ultimately causing increased cell death in hic-5-depleted cells.
Based on our results, we conclude that hic-5 plays an essential role in linking the focal adhesion hub to anti-apoptotic pathways in the podocyte, thereby reinforcing its response to injury and stress. Specifically, the presence of hic-5 in the podocyte appears to promote podocyte survival via reinforcing its resistance to JNK-mediated cell death. Understanding the effects of altered focal adhesion signaling on podocyte survival is highly relevant because therapeutic approaches to counteract podocyte loss by targeting and reinforcing podocyte-specific pro-survival pathways could be a valuable tool to prevent disease progression in human proteinuric diseases.