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YAP Activation Mediates Myofibroblast Transformation and Senescence during Repeated Treatment with Cisplatin in Kidney Fibroblasts

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Objectives : Cisplatin is an effective chemotherapy drug used to treat a variety of cancer, but it has nephrotoxic side effects leading to acute kidney injury and subsequently chronic kidney disease (CKD). In our preceding research, we established a CKD model in kidney fibroblasts induced by repeated cisplatin administration (RAC), revealing that RAC induces the transformation of kidney fibroblasts into myofibroblasts through cellular senescence. However, the intricate mechanisms governing this process remain incompletely understood. The transcriptional coactivator Yes-associated protein (YAP), recognized for its pivotal role in cellular organ size control, was the focal point of our investigation into its involvement in cisplatin-induced transformation of kidney myofibroblasts and cellular senescence.
Methods : In this study, we investigated the role of YAP in cisplatin-induced transformation of kidney myofibroblasts and cellular senescence.
Results : In NRK-49F rat kidney fibroblasts, RAC enhanced cellular and nuclear attachment surface area, cell volume and flattening ratio on time-dependent. RAC time dependent upregulated α-smooth muscle actin (α-SMA) and p21 expression, suggesting that RAC induces kidney fibroblast to senescence myofibroblast transformation on time-dependent. We found that RAC induced YAP nuclear to cytoplasmic translocation and increased p-YAP expression, which indicated that RAC induces YAP inactivation. To determine whether YAP inactivation induces fibroblasts transformation into senescent myofibroblasts, we used Verteporfin as an inhibitor of the YAP-TEAD interaction, that Verteporfin fails to induce transformation of fibroblasts into myofibroblasts, but reduced RAC-induced cellular hypertrophy and senescence.
Conclusions : Taken together, our comprehensive findings suggest that YAP activation plays a pivotal role in cellular senescence and myofibroblast transformation during repeated cisplatin administration in kidney fibroblasts.