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PP2Ac α positively regulates mice liver regeneration termination through AKT/GSK3 β /Cyclin D1 pathway

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Background & Aims: Liver injury triggers a highly organized and ordered liver regeneration (LR) process. Once regeneration is complete, a stop signal ensures that the regenerated liver is at appropriate functional size. The inhibitors and stop signals that regulate LR are unknown, and only limited information is available about these mechanisms.

Methods: A 70% partial hepatectomy (PH) was performed in hepatocyte-specific (PP2Ac $_{-}$), deleted (PP2Ac $_{-/-}$) and control (PP2Ac $_{+/+}$) mice. LR was estimated by liver weight, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and cell proliferation; and the related cellular signals were analyzed.

Results: We found that the catalytic subunit of PP2A was markedly up-regulated during the late stage of LR. PP2Ac $_{-/-}$ mice showed prolonged LR termination, an increased liver size compared to the original mass and lower levels of serum ALT and AST compared with control mice. In these mice, cyclin D1 protein levels, but not mRNA levels, were increased. Mechanistically, AKT activated by the loss of PP2Ac $_{-}$ inhibited glycogen synthase kinase 3 (GSK3 β) activities, which led to the accumulation of cyclin D1 protein and accelerated hepatocyte proliferation at the termination stage. Treatment with the PI3K inhibitor wortmannin at the termination stage was sufficient to inhibit cyclin D1 accumulation and hepatocyte proliferation.

Conclusions: PP2Ac $_{-}$ plays an essential role in the proper termination of LR via the AKT/GSK3/Cyclin D1 pathway. Our findings enrich the understanding of the molecular mechanism of LR termination control and provide a potential therapeutic target for treating liver injury.

Biography

Bin Xue has completed his PhD from Nanjing Normal University and was a Visiting Scholar at Harvard School of Medicine. He is the Director of Nanjing University School of Translational Medicine Lab. He has published more than 25 papers in reputed journals.

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