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EDITORIAL

Tumor Suppressor Down-Regulation Promotes Hepatocyte Proliferation: A New GANKster on the Block

Hepatocellular carcinoma (HCC) is ranked as the sixth most common neoplasm and the third leading cause of cancer death worldwide.[1] HCC incidence is expected to continue to increase in many regions of the world. HCC often is diagnosed late and only 30% to 40% of patients can receive partial resection or liver transplantation, which is currently the most effective therapy available.

Hepatocarcinogenesis is a complex process that involves dysregulation of various cellular and molecular signaling networks, imbalance of oncogenes and anti-oncogenes, and differentiation of liver cancer stem cells. Better understanding of the molecular mechanisms underlying hepatocyte and liver cancer cell proliferation is required to develop novel effective therapies for HCC. Previous work has highlighted the role of gankyrin, a 25-kilodalton protein containing 7 ankyrin repeats, in several key pathways involved in malignant transformation and HCC, including signal transducer and activator of transcription 3/AKT, Rac1/Janus kinase, and transforming growth factor-β/SMAD3.

Gankyrin initially was identified as an oncogene overexpressed in HCC. As a component of the 26S proteasome, gankyrin mediates proteasome-dependent protein degradation. In particular, gankyrin participates in the negative regulation of 2 major tumor-suppressor proteins: Rb and p53. Gankyrin antagonizes p53 by interacting with Mouse double minute 2 homolog, enhancing proteasomal degradation of p53. Via direct interactions with Rb, gankyrin triggers proteasome degradation of Rb. Gankyrin also has been found to interact with other tumor-suppressor proteins. Gankyrin overexpression has been correlated with poor prognosis in different tumor types.[2] Such studies have suggested the importance of gankyrin in HCC progression through post-translational modification of tumor-suppressor proteins.

It has been suggested that increased gankyrin expression is associated with HCC proliferation. However, a lack of appropriate animal models has made it difficult to examine the exact contribution of this oncogene in hepatocyte proliferation in vivo. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, D'Souza et al[3] provide further insight into the role of gankyrin as a regulator of hepatocyte proliferation through down-regulation of tumor-suppressor proteins using liver-specific gankyrin knockout (GANK-LKO) mice.

The study showed that GANK-LKO mice did not have any morphologic and histologic changes in the liver under normal conditions. However, transcriptome analysis showed alterations in genes involved in the immune system, lipid metabolism, cell proliferation, and carcinogenesis when gankyrin was lost. CCAAT/Enhancer Binding Proteinα (C/EBPα), c-jun, and nuclear factor-κB were down-regulated significantly, suggesting the role of gankyrin in hepatocyte proliferation.

D'Souza et al[3] then showed increased hepatocyte proliferation within 24 hours of gankyrin overexpression in wild-type mice by injecting gankyrin plasmid. Because gankyrin alone was able to trigger DNA replication in normal hepatocytes, they suggested that gankyrin is a potent initiator of hepatocyte proliferation. To further analyze their hypothesis, D'Souza et al[3] investigated hepatocyte proliferation in GANK-LKO mice subjected to partial hepatectomy and CCl_4-induced liver damage. Proliferating hepatocytes were decreased significantly upon partial hepatectomy or CCl_4 treatment when compared with control mice.

Gankyrin has been shown to suppress various tumor-suppressor proteins, some of which are lost in HCC. To investigate the possible mechanism ameliorating the proliferative capacity of GANK-LKO livers after partial hepatectomy and CCl_4 treatment, D'Souza et al[3] examined whether gankyrin deletion resulted in altered levels of 4 - tumor suppressors: CUG triplet repeat, RNA binding protein 1 (CUGBP1), C/EBPα, Hepatocyte nuclear factor 4 alpha (HNF4α), and Rb. All 4 tumor suppressors were reduced significantly in control mice, whereas no reductions were observed in GANK-LKO mice. The evidence is compelling and suggestive that gankyrin promotes hepatocyte proliferation through reduction of these 4 tumor-suppressor proteins.

A recently discovered nontoxic small molecule, cjoc42, repressed gankyrin activity by blocking gankyrin's interaction with the proteasome.[4] Here, D'Souza et al[3] treated human and mouse liver cancer cells, Huh6 and Hepa1c1c7, with cjoc42. CUGBP1, C/EBPα, p53, and HNF4α levels were increased significantly by cjoc42 treatment. Interestingly, D'Souza et al[3] provided evidence that gankyrin directly interacts with the tumor suppressors. cjoc42 inhibited gankyrin interaction with both the proteasome and the tumor suppressors, and cjoc42-treated cancer cells showed reductions in proliferation.

In conclusion, D'Souza et al[3] provided further mechanistic evidence underlying the importance of gankyrin-mediated regulation of hepatocyte and HCC cell proliferation by reducing the expression of key tumor-suppressor proteins. In conjunction with a recent report showing that knockout of gankyrin suppressed HCC growth,[5] this study provided further insight into a potential molecular target for treating HCC by modulating tumor cell growth and proliferation. In addition, findings correlating gankyrin overexpression with poorer survival and advanced cancer stage render it an

appealing and potentially novel prognostic tumor biomarker.[6] However, given the heterogeneity of hepatocarcinogenesis and multiple signal transduction pathways regulated by gankyrin, we must tread with caution and further deconstruct its molecular network.

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Conflicts of interest
The authors disclose no conflicts.

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