Cell Cycle 13:13, 2022–2023; July 1, 2014; © 2014 Landes Bioscience

Liver proliferation: The GUCD1/NEDD4–1 connection

Comment on: Bellet MM, et al. Cell Cycle 2014; 13:1902–11; PMID:24743017; http://dx.doi.org/10.4161/cc.28760

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http://dx.doi.org/10.4161/cc.29535

In order to preserve its role(s) in the control of metabolism and detoxification, the liver possesses the unique ability to fully recover its original mass and function after injury.[1,2] Following surgical removal or cell loss caused by toxic or viral damage, quiescent hepatocytes trigger a proliferative process, so that the initial liver mass is restored.[1,2] Such a complex process, known as liver regeneration (although "compensatory hyperplasia" would describe this phenomenon more accurately) involves a plethora of finely orchestrated cellular and molecular events that are only partly known. Indeed, while the regeneration process is well described histologically, the related molecular mechanisms have been only partially characterized. Considerable scientific efforts in this field resulted in the identification of a large cohort of genes whose modulation significantly affects the liver regeneration process.[1,2] However, an exhaustive understanding of this process in terms of signaling cascades is hampered by the remarkable complexity of interactions between different pathways. For instance, simultaneous and/or sequential modes of activation and operation may characterize distinct pathways during the regeneration process, affect different liver cell types, and be present only at certain stages of liver regeneration.[1,2] Also, the role of some genes/pathways involved in liver regeneration remains to be clarified. Furthermore, a significant degree of redundancy in terms of genes involved in liver regeneration takes place in this phenomenon, adding a further layer of intricacy to the whole story.[1,2]

To identify genes that are highly expressed and might play a prominent role along liver regeneration, a cDNA library from rat regenerating liver was constructed and screened by Bellet et al.[3] Genes strongly associated with liver proliferation were successfully identified. Among them, the authors characterized a highly conserved and ubiquitously expressed gene, guanylyl cyclase domain containing 1 (GUCD1).[3] Noticeably, the levels of GUCD1 mRNA were found to peak 2 h after partial hepatectomy, when immediate early genes are upregulated, and between 24 and 72 h, corresponding to the hepatocyte proliferative phase, suggesting that GUCD1 might play an important role in hepatocyte proliferation. In a panel of human cancer cell lines, GUCD1 mRNA levels were upregulated when compared with normal livers. However, a discrepancy between mRNA and protein expression was detected in the same cell lines, suggesting that GUCD1 might be regulated at the post-transcriptional level. A similar increase of GUCD1 mRNA but not protein levels was also detected in human hepatocellular carcinoma (HCC) specimens when compared with non-tumorous surrounding counterparts. Subsequent yeast 2-hybrid interaction assay and functional studies identified E3 ubiquitin protein ligase neural precursor cell expressed, developmentally downregulated gene 4 (NEDD4–1) as a binding partner that regulates GUCD1 stability via proteasome mediated-degradation.[3]

This elegant study suggests an important role of GUCD1 and its binding partner NEDD4–1 in liver proliferation. While no functional studies have been performed on the role of GUCD1 in cancer to date, NEDD4–1 has been found to contribute to carcinogenesis via its ability to downregulate important tumor-suppressor genes, such as phosphatase and tensin homolog (PTEN) and Sprouty 2 (Spry2).[4,5] In light of these previous findings, what is then the scope of GUCD1/NEDD4–1 interaction in liver growth? The authors hypothesize that GUCD1 might be involved in triggering hepatocyte proliferation, with NEDD4–1-mediated degradation being responsible for GUCD1 downregulation at the end of the process (**Fig. 1**).[3] This intriguing hypothesis suggests that fine-tuning of GUCD1 levels is necessary to allow the proper proliferation of normal and malignant hepatocytes, while abnormally elevated levels of GUCD1 are detrimental for liver growth. Nonetheless, a tumor-suppression function of GUCD1 cannot be excluded either. The elevated GUCD1 levels during hepatocyte proliferation might in fact represent a counteracting mechanism to unconstrained growth that is overridden by NEDD4–1-dependent proteolysis. According to this alternative scenario, it has been demonstrated that Spry2's tumor-suppressive potential is abolished by NEDD4–1 ubiquitination in human HCC, despite a strong Spry2 mRNA upregulation in the same specimens.[5] Furthermore, the preliminary data from Bellet et al. envisage the possibility of GUCD1 being negatively modulated by the cAMP pathway,[3] whose role in promoting liver regeneration and carcinogenesis is well established.[6,7] The generation of liver-specific conditional knockout or transgenic mice for GUCD1 and NEDD4–1 genes would be highly helpful to finally elucidate the role of the GUCD1/NEDD4–1 interaction in liver regeneration and cancer.

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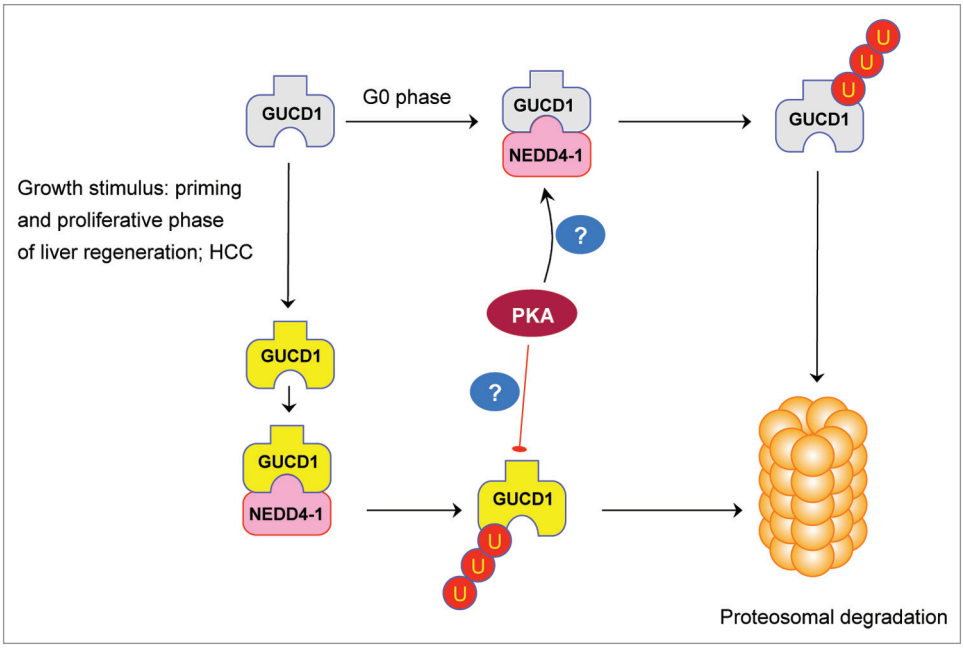

Figure 1. Molecular circuitry regulating GUCD1 levels in the liver. In G0 phase (gray box), GUCD1 is bound to NEDD4–1, ubiquitinated (U), and targeted for proteosomal degradation. In liver regeneration and hepatocellular carcinoma (HCC), GUCD1 mRNA is induced (yellow box). Subsequently, GUCD1 undergoes proteolysis upon binding to NEDD4–1. GUCD1 downregulation might be promoted by cAMP pathway effectors, such as PKA, acting on both GUCD1 and NEDD4–1.