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Cellular Regulation Of Hepatic Glucose Production: Control Of Glucose-6-phosphatase Activity By Caveolin-1

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Abstract:
Glucose-6-phosphatase (G6Pase) catalyzes the production of glucose, which is then released in the blood by GLUT2. However, the liver of Glut2-/- mice may also produce glucose via a vesicular pathway. We addressed in this study the involvement of Cav-1, the main protein of caveolae, in hepatic glucose production (HGP).
HGP and liver metabolites were measured in 16-hours fasted wild-type (WT) and transgenic mice with a constitutive deletion of Cav-1 (Cav1-/-) and with both a Cav1 deletion and a liver-specific deletion of Glut2 (L.Glut2-/-.Cav1-/-). The location of endogenous or fluorescent G6Pase and Cav-1 were studied by immunofluorescence, immunogold labelling and real time confocal microscopy.
Cav-1 deletion induced a 40% decrease of HGP associated with hepatic glycogen, G6P and triglyceride storage but without glucose accumulation. This suggests Cav-1 might control G6Pase activity rather than glucose export. Since G6Pase exhibited a putative Cav-1 binding site, we hypothesized Cav-1 could regulate G6Pase activity by controlling its cellular location. Cav-1 and G6Pase colocalized and moved together to the plasma membrane. The restricted location of G6Pase in the WT liver was abolished in vitro when the binding site of G6Pase to Cav-1 was mutated and in vivo in the Cav1-/- liver. Finally, the amount of gold immunolabeled G6Pase at the plasma membrane was decreased in the Cav1-/- liver. Since Glut2 is the canonical transporter of glucose in HGP, the absence of both Glut2 and Cav-1 should result in the inhibition of HGP. Accordingly, L.Glut2-/-.Cav1-/- mice did not produce glucose from their liver (6% of WT) and exhibited hepatic steatosis and glycogen storage in excess as mice with a hepatic deletion of G6Pase.
In conclusion, Cav-1 controls a G6Pase-dependant pathway alternative to Glut2 for the release of de novo glucose. This vesicular pathway depends on the interaction of Cav-1 with G6Pase allowing the latter to move to the plasma membrane and deliver glucose into the blood.
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