

Pyruvate Dehydrogenase Kinase 4: A Key Mediator for Metabolic Regulation of Liver Regeneration

SEE ARTICLE ON PAGE 504

Given the central biochemical role the liver plays in all vertebrates, major liver damage would be expected to cause perturbations in lipid and glucose metabolism. These could be due simply to the absence of normal liver function, but the study by Zhao et al.⁽¹⁾ in this issue defines the metabolic changes observed as integral to a process of rationalizing the needs for liver regeneration without lethal harm to the competing needs of the rest of the body. When liver mass suffers a major loss by experimental hepatic resection, or presumably by injury during evolution, the remaining hepatic tissue is damaged. Portal pressure is increased due to restriction of portal vein outflow,⁽²⁾ and the concentration of

lipopolysaccharides carried by portal blood from the gut is increased.⁽³⁾ These changes are a signal for the liver to regenerate. Until now, hypoglycemia during regeneration and the accumulation of lipid droplets in the surviving remnant have been unexplained except as an incidental manifestation of the law of mass action causing overload or general metabolic insufficiency until organ capacity is restored.

Specific molecular mechanisms that control liver regeneration have been extensively studied in a rodent model of partial hepatectomy, e.g., as detailed by Huang and Rudnick.⁽⁴⁾ Several humoral factors and their intracellular targets were identified as key players in liver regeneration, such as cytokines (e.g., tumor necrosis factor alpha, interleukin-6), growth- and matrix-derived factors (hepatocyte growth factor, epidermal growth factor receptor ligands), secondary messenger cascades (e.g., Wnt-dependent β -catenin signaling), and transcription factors (e.g., nuclear factor kappa B, signal transducer and activator of transcription 3, CCAAT-enhancer binding protein beta). Emerging data and evidence suggest metabolic regulation may play an important role in initiating regenerative responses following experimentally induced hepatic insufficiency and controlling liver regeneration. However, the molecular mediators that coordinate metabolism with liver regeneration remained unknown.

Now, Zhao et al.⁽¹⁾ have demonstrated that pyruvate dehydrogenase kinase 4 (PDK4), a critical regulator of glucose and lipid metabolism, plays a key role in regulating liver regeneration after partial hepatectomy and that PDK4 inhibition reprograms glucose and lipid metabolism to promote liver regeneration by enhancing hepatic insulin/protein kinase B signaling and activating an adenosine monophosphate-activated protein kinase/forkhead box protein O1/cluster of differentiation 36 regulatory axis of lipid. In knockout mice without PDK4 activity, regeneration was faster than in the wild-type mice, but the knockout animals often died; regeneration was headed toward success, but the animal succumbed. This finding is

Abbreviation: PDK4, pyruvate dehydrogenase kinase 4.

Received February 17, 2020; accepted February 29, 2020.

© 2020 The Authors. Hepatology Communications published by Wiley Periodicals, Inc., on behalf of the American Association for the Study of Liver Diseases. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep4.1506

Potential conflict of interest: Dr. Sun owns stock in, consults for, advises, and owns intellectual property rights in MedRegan LLC. Dr. Burdick has nothing to report.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Zhaoli Sun, M.D., Ph.D.
Department of Surgery
Johns Hopkins University School of Medicine
733 North Broadway
Baltimore, MD 21205
E-mail: zsun2@jhmi.edu
Tel.: +1- 410-955-3182

an important step toward a better understanding of the metabolic regulation of liver regeneration. A few questions are worthy of discussion.

Is Hepatic Steatosis an Initial Response to Metabolic Regulation of Liver Regeneration?

Liver regeneration in response to experimentally induced hepatic insufficiency begins with hypoglycemia, followed by increased plasma free fatty acids and hepatic triglyceride.⁽⁴⁾ A systemic catabolic response characterized by declining lean and adipose tissue mass was observed in mice 12 hours after surgery.⁽⁵⁾ Those changes resulted in marked steatosis in regenerating liver at 12 to 24 hours. Hepatic steatosis is commonly observed in livers injured by a variety of diseases and is evidence of altered hepatic metabolism.

These results suggest alterations in metabolism are essential for normal liver regeneration. Development of hypoglycemia and hepatic steatosis following major liver injury rather than being negative consequences of hepatic insufficiency may be essential for initiating liver regeneration. Elucidating metabolic regulation of liver regeneration and defining molecular mediators linking metabolism and liver regeneration may potentially identify novel therapeutic targets.

Is PDK4 a Molecular Mediator Linking Metabolism and Liver Regeneration?

The link between alterations in metabolism to the regulation of liver regeneration was well studied, but the specific responsible molecular mechanisms remained unclear. Zhao et al.⁽¹⁾ have shown that PDK4 is a key metabolic enzyme involved in fuel switching between glucose and free fatty acids and is also required for metabolic reprogramming. Knocking out PDK4 results in lower blood glucose

levels, better glucose tolerance, and greater insulin sensitivity in chow-fed mice.⁽⁶⁾ Zhao and colleagues found that PKD4 was up-regulated after partial hepatectomy and that PDK4 knockout resulted in greater hypoglycemia, extended hepatic steatosis (up to 2 days), and accelerated liver mass recovery after partial hepatectomy. Further, PDK4 deficiency improved hepatic insulin sensitivity and promoted fatty acid uptake. Thus, PKD4 is a key molecular mediator in metabolic regulation of liver regeneration.

Can PDK4 Be a Therapeutic Target for Liver Regeneration?

Understanding this key metabolic activity might lead toward more successful use of donated “fatty livers” for organ transplantation. In addition, the possibility that an aberrant signal activating PDK4 (perhaps related to an effect of increased dietary calories) might eventually help in prevention of nonalcoholic steatohepatitis.

Although PDK4 inhibition promoted hepatocyte proliferation and liver mass recovery, it increased mortality following partial hepatectomy. This is probably due to a greater decrease in blood glucose levels. Another study⁽⁷⁾ demonstrated that cell-cycle arrest and DNA damage repair in remnant liver at an early stage are essential for survival following partial hepatectomy. It seems PDK4 inhibition promotes cell proliferation without cell-cycle arrest and thus results in improper regeneration in PDK4-knockout mice. This needs to be further investigated before pursuing a therapeutic strategy targeting PDK4.

James Burdick
Zhaoli Sun
Department of Surgery
Johns Hopkins University School of Medicine
Baltimore, MD

REFERENCES

- 1) Zhao Y, Tran M, Wang L, Shin DJ, Wu J. PDK4-deficiency reprograms intrahepatic glucose and lipid metabolism to facilitate liver regeneration in mice. *Hepatol Commun* 2020;4:504-517.

- 2) Golriz M, Majlesara A, El Sakka S, Ashrafi M, Arwin J, Fard N, et al. Small for Size and Flow (SFSF) syndrome: an alternative description for posthepatectomy liver failure. *Clin Res Hepatol Gastroenterol* 2016;40:267-275.
- 3) Rudich N, Zamir G, Pappo O, Shlomai Z, Faroja M, Weiss ID, et al. Focal liver necrosis appears early after partial hepatectomy and is dependent on T cells and antigen delivery from the gut. *Liver Int* 2009;29:1273-1284.
- 4) Huang J, Rudnick DA. Elucidating the metabolic regulation of liver regeneration. *Am J Pathol* 2014;184:309-321.
- 5) Gazit V, Weymann A, Hartman E, Finck BN, Hruz PW, Tzekov A, et al. Liver regeneration is impaired in lipodystrophic fatty liver dystrophy mice. *Hepatology* 2010;52:2109-2117.
- 6) Jeoung NH, Harris RA. Pyruvate dehydrogenase kinase-4 deficiency lowers blood glucose and improves glucose tolerance in diet-induced obese mice. *Am J Physiol Endocrinol Metab* 2008;295:E46-E54.
- 7) Tachibana S, Zhang X, Ito K, Ota Y, Cameron AM, Williams GM, et al. Interleukin-6 is required for cell cycle arrest and activation of DNA repair enzymes after partial hepatectomy in mice. *Cell Biosci* 2014;4:6.