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## Molecular mechanisms of platelet-mediated liver regeneration after partial hepatectomy

Kirschbaum, Marc

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**THE ROLE OF  
PLATELETS  
IN LIVER  
REGENERATION –  
WHAT DON'T WE  
KNOW?**

TON LISMAN  
MARC KIRSCHBAUM  
ROBERT J. PORTE

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In an elegant review published in the Journal, Meyer and coworkers summarize current knowledge on the role of blood platelets in liver regeneration (1). Better insight in how platelets act in amplifying liver regeneration following a partial hepatectomy might have important clinical consequences. Currently, no strategies to enhance liver regeneration to treat or avoid the 'small for size syndrome' are clinically available. Platelets are an unexpected, but interesting new target for clinical intervention aimed at accelerating liver regeneration. Given the vast clinical experience with platelet-modulating drugs in treatment of platelet-associated bleeding disorders or arterial thrombosis, implementation of platelet-targeted therapy for stimulation of liver regeneration is a realistic scenario. Nevertheless, many questions of the mechanism by which platelets promote liver regeneration remain unsolved.

In their review, Meyer and coworkers combine knowledge obtained from *in vitro* models with *in vivo* studies on liver regeneration after partial hepatectomy and *in vivo* studies on liver inflammation (notably lipopolysaccharide-induced liver injury). The authors propose that following partial hepatectomy, platelets are recruited to the liver sinusoids and the space of Disse by a yet unidentified mechanism after which they release molecules (notably proteins) that directly or indirectly stimulate liver regeneration. Internalization of platelets by liver endothelial cells or hepatocytes is proposed to contribute to platelet-mediated liver regeneration.

Although we agree with these proposed mechanisms, we would like to stress that many of these proposed steps have not yet been shown to contribute to liver regeneration *in vivo* as they are extrapolated from either *in vitro* models or *in vivo* models of inflammation, in which regeneration was not a primary read-out. It has yet to be demonstrated that release of alpha and dense granule content (containing growth factors and serotonin, respectively) within the liver remnant is required for platelet-mediated liver regeneration *in vivo*. Although it appears plausible that platelets deliver liver-directed mitogens to support regeneration, alternative scenarios deserve attention. For example, a role for serotonin in liver regeneration has been clearly established (2), and it has been reported that serotonin levels within platelets decrease following a partial hepatectomy in humans, which supports the theory that platelet granule excretion drives liver regeneration (3). However, a study from our center found no evidence for serotonin consumption in this setting (4). In addition, as indicated by Meyer, the reported role of serotonin in liver regeneration in animal models may not only be explained by a direct mitogenic effect of serotonin on liver cells, but can also be explained by functional defects of serotonin deficient platelets. Importantly, platelet serotonin depletion by selective serotonin reuptake inhibitors has clinically relevant effects on platelet function resulting in an increased bleeding risk and a protection from arterial thrombosis (5).

Thus, although increasing clinical and experimental evidence supports the stimulatory role of platelets in liver regeneration, the mechanisms remain incompletely identified. As the manuscript by Meyer and coworkers was under review, we have published a study

proposing an alternative scenario for the role of platelets in liver regeneration (6). Using *in vitro* models, we demonstrated that internalization of platelets by hepatocytes contributes significantly to platelet-mediated hepatocyte proliferation. In addition, we demonstrated that platelets internalized by hepatocytes transfer RNA to the hepatocyte. Transfer of RNA from platelets to hepatocytes contributed significantly to platelet-mediated hepatocyte proliferation. Platelets contain ~9500 mRNA and ~500 miRNA species (7), and we propose that functional transfer of either or both coding and regulatory RNA species from platelets to hepatocytes may be important drivers of platelet-mediated liver regeneration. It is conceivable that delivery of platelet-derived RNA to liver cells alters the phenotype of these cells to support the regenerative process, and an increasing literature on the role of miRNAs in liver regeneration supports this theory. Importantly, our studies also demonstrated platelet internalization in hepatocytes following a partial hepatectomy in mice, suggesting that RNA transfer also occurs during liver regeneration *in vivo*.

We fully agree with Meyer and coworkers that we need to expand our knowledge on mechanisms of platelet-mediated liver regeneration. In designing future experiments we should acknowledge that we are as yet unsure whether factors secreted by platelets (proteins or RNA) are relevant for platelet-mediated liver regeneration or that other properties of platelets drive liver regeneration. We should take effort to design rigorous *in vivo* studies to validate data obtained in cell culture models. Finally, we should realize that the mechanism of platelet-mediated liver regeneration may be different in the various clinical scenarios in which liver regeneration occurs. Therapies aimed at stimulation of liver regeneration are not only relevant in the context of a partial hepatectomy, but also in settings of acute liver failure, ischemia-reperfusion injury, and liver fibrosis. Future research should focus on the mechanisms of platelet-mediated liver regeneration in these distinct contexts.

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