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Conference Details

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Communication Title: Intrahepatic fibrin deposition drives liver regeneration after a partial hepatectomy in mice and humans.

ABSTRACT

When a vessel wall (endothelium) is damaged, a complex process called hemostasis is initiated to stop the bleeding. Platelet-plug formation is the first step to close the endothelium. Formation of fibrin, a process called coagulation, stabilizes the primary platelet-plug. Finally, a process called fibrinolysis will dissolve the blood clot. Coagulation consists of a complex sequence of enzymatic reactions, and is initiated when subendothelial cells that express the protein tissue factor (TF), are exposed to flowing blood. The activation of TF leads to the generation of thrombin. Thrombin not only converts fibrinogen into fibrin, but is also a potent activator of platelets. After a partial hepatectomy (PHx) in humans and mice, where up to 70% of the liver is removed, platelets rapidly accumulate in the liver remnant. Liver regeneration in rodents is delayed when platelets are depleted or functionally impaired. However, the exact mechanisms whereby platelets accumulate in the liver and promote regeneration are not completely understood. Recently, fibrin deposits, suggesting coagulation activation, were observed in the mouse livers after PHx. We tested the hypothesis that platelet-driven liver regeneration is functionally connected to activation of coagulation and fibrin deposition in the liver. Two-thirds PHx in wild-type mice triggered rapid intrahepatic accumulation of platelets, which was paralleled by intrahepatic coagulation, indicated by fibrin deposits. PHx-induced platelet accumulation and fibrin deposits were reduced in mice with liver-specific TF deficiency, and these changes were coupled to a reduction in liver regeneration assessed by hepatocyte proliferation 3 days after PHx. Thrombin activation of platelets did not contribute to liver regeneration after PHx, as regeneration was unaffected in mice that lack the thrombin receptor on their platelets. In contrast, fibrinogen depletion reduced platelet accumulation and hepatocyte proliferation after PHx, indicating that fibrin is central to liver regeneration after PHx. Consistent with the regenerative function of fibrin documented in this experimental setting, fibrin deposits were observed in intraoperative liver biopsies from patients undergoing PHx, with much decreased fibrin deposits in patients who suffered from liver dysfunction post-PHx. Moreover, low postoperative plasma fibrinogen levels were associated with liver dysfunction and mortality in patients undergoing PHx. **Conclusion:** The results suggest that a tightly interconnected mechanism involving interactions between platelets and hepatic fibrin deposits drives liver regeneration after PHx in both mice and humans.

COMMUNICATION OUTCOMES

The liver produces almost all coagulation factors, making altered hemostasis a significant concern in patients with liver disease. The lab's long-term goal is to understand the mechanisms whereby coagulation contributes to the pathogenesis of liver disease. My own long-term research interest is to understand the complex relationship between hemostasis and liver disease in both the fundamental and clinical setting.

Partial hepatectomy (PHx), in which up to 70% of the liver is removed, is a common surgical procedure to treat a variety of liver pathologies. After a PHx, the liver remnant rapidly regenerates to its original size. In some patients however, regeneration fails, due to poorly understood mechanisms. Liver failure still remains one of the most serious complications of PHx and represents a significant source of mortality. There are currently no clinical strategies available to improve liver regeneration. A better understanding of the mechanisms involved in regeneration would be essential for the treatment of patients from failing regeneration. We have found that both platelets and fibrin deposition in the liver remnant following PHx are crucial for adequate liver regeneration. Our results suggest that there is a functional crosstalk between platelets and fibrin, which stimulates regeneration in both mice and humans. In fact, we observed that low postoperative fibrinogen levels are associated with liver dysfunction and mortality after PHx. As there are currently no strategies available to improve liver regeneration, our work offers a tremendous step forward to improve postoperative liver function. Due to a poor risk/benefit ratio, including an increased risk for thrombosis, platelet transfusion seems an unlikely therapeutic strategy to avoid failing regeneration. Our data suggest that patients who undergo PHx might benefit immensely from fibrinogen supplementation, which has a better risk/benefit ratio, as stimulation of the regenerative response of the liver. These data warrant future (clinical) studies on exploring the benefits of fibrinogen supplementation in PHx to improve failing regeneration of the liver remnant.

The GRS/GRC is the premiere small-format scientific meeting that encourages open discussion about state-of-the-art research on topics of coagulation, platelets, anticoagulants, and associated diseases though formal presentations and social interaction. As this is exactly my area of work, attending this meeting will offer me a great opportunity to present our novel and important data and encourage the development of new collaborations, both for me personally, and the lab. The conference brings together a unique community of scientists, physicians, and pharma working on hemostasis. As my research interest lies in translation science, attending this meeting would allow me to network closely with physicians and the pharma. The GRS/GRC conferences are known for their prominent focus on professional development, in the form of special career sessions. These sessions will enable me to interact productively with senior investigators in an informal setting and will help me develop my personal professional network. Afternoons are focused on social interactions that enhance interactions, intellectual exchange, and foster new collaborations – a traditional and unique component of the GRS/GRC. Pioneers in the hemostasis field will be present, giving me the opportunity to interact with these excellent scientists. Therefore, attending this meeting would be extremely advantageous for my own scientific progress.