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Liver Regeneration of Small in situ Injury

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Abstract : Liver is the center of detoxification and exposed to toxic metabolites all the time. It is highly regenerative after injury, with the ability to restore even after 70% partial hepatectomy. Most of the previous studies were using hepatectomy as injury models for liver regeneration study. There is limited understanding of small-scale liver injury, which can be caused by either low dose drug consumption or hepatocyte routine metabolism. Although these small in situ injuries do not cause immediate symptoms, repeated injuries will lead to aberrant wound healing in liver. Therefore, the cellular dynamics during liver regeneration is critical for our understanding of liver regeneration mechanism. We aim to study the liver regeneration of small-scale in situ liver injury in transgenic mice labeling actin (Lifeact-GFP). Previous studies have been using sample sections and biopsies of liver, which lack real-time information. In order to trace every individual hepatocyte during the regeneration process, we have developed and optimized an intravital imaging system that allows in vivo imaging of mouse liver for consecutive 5 days, allowing real-time cellular tracking and quantification of hepatocytes. We used femtosecond-laser ablation to make controlled and repeatable liver injury model, which mimics the real-life small in situ liver injury. This injury model is the first case of its kind for in vivo study on liver. We found that small-scale in situ liver injury is repaired by the coordination of hypertrophy and migration of hepatocytes. Hypertrophy is only transient at initial phase, while migration is the main driving force to complete the regeneration process. From cellular aspect, Akt/mTOR pathway is activated immediately after injury, which leads to transient hepatocyte hypertrophy. From mechano-sensing aspect, the actin cable, formed at apical surface of wound proximal hepatocytes, provides mechanical tension for hepatocyte migration. This study provides important information on both chemical and mechanical signals that promote liver regeneration of small in situ injury. We conclude that hypertrophy and migration play a dominant role at different stages of liver regeneration.

Keywords : hepatocyte, hypertrophy, intravital imaging, liver regeneration, migration
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