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## On the role of platelets in the pathogenesis of viral hepatitis

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To the Editor:

We read with interest the commentary by Ulrich Spengler (1) where he evaluated a recent manuscript by Lang et al. (2) on the role of platelet-derived serotonin in the pathogenesis of viral hepatitis. We were somewhat surprised to see that work constituting the foundation of the above-mentioned study was not cited. A few years ago our group started investigating the role of platelets in the pathogenesis of viral hepatitis, using different mouse models that include transgenic mice replicating hepatitis B virus (HBV) at high levels in the hepatocyte and mice infected with hepatotropic adenoviruses and arenaviruses (i.e. lymphocytic choriomeningitis virus [LCMV]). Similar to humans infected with HBV or hepatitis C virus (HCV), liver disease in these models is mostly a consequence of the virus-specific CD8 T cell response aimed at viral clearance. We found that platelets play a previously unrecognized role in viral hepatitis. Upon activation, platelets contribute to liver disease and viral clearance by promoting the recruitment of virus-specific cytotoxic T lymphocytes (CTL) into the liver (3). Further experiments suggested that this effect depends on specific interactions between platelets and CTL likely occurring within the hepatic microcirculation and helping CTL to extravasate, reach target cells and perform pathogenic and antiviral effector functions (4–6). We confirmed these results in follow-up studies by showing reduction of hepatic CTL recruitment after pharmacological inhibition of platelet activation (7). The paper by Lang et al. nicely reiterates a role for platelets in the pathogenesis of liver disease and provides a novel mechanistic hint. They identified serotonin as a potential molecular mediator of CTL recruitment and liver damage in LCMV-infected mice. Although the use of LCMV as a model for human HBV and HCV infection must be taken cautiously (unlike HBV and HCV that infect hepatocytes almost exclusively, LCMV infects primarily non-parenchymal cells of the liver such as Kupffer cells (8)), the study by Lang et al. raises important questions. Where does serotonin come from during liver inflammation? Is it platelet-derived as the authors seem to suggest? What cells respond to serotonin? What serotonin receptors are involved? The answers to these questions are important if we envisage future manipulations of serotonin-dependent pathways designed to either counteract excessive liver damage or, conversely, promote the hepatic homing and antiviral potential of CTL induced by therapeutic vaccines. In addition to serotonin, it is likely

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that other platelet-derived molecular mediators of liver damage will be discovered in the years to come, allowing us to better understand the complex interplay between platelets and CTL in the inflamed liver microenvironment.

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