Thromboxane A2 receptor signaling attenuates monocrotaline-induced liver injury by affecting endothelial cells, but not platelets

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Sinusoidal obstruction syndrome (SOS) is a major complication of chemotherapy and hematopoietic stem cell transplantation. The early stage of SOS is characterized by liver sinusoidal endothelial cell (LSEC) injury accompanied by platelet aggregation. Thromboxane A_2 (TxA_2) induces platelet aggregation through the thromboxane prostanoid (TP) receptor. In this study, we explored the role of TP signaling in a monocrotaline (MCT)-induced model of SOS using male C57BL/6 mice (wild type) and TP-deficient ($TP^{-/-}$) mice. Relative to WT mice, $TP^{-/-}$ mice exhibited more severe MCT-liver injury, as indicated by elevated levels of alanine aminotransferase (ALT) and coagulative necrosis. Extensive accumulation of platelets in the liver was observed in both WT and $TP^{-/-}$ mice; however, there was no significant difference between the genotypes. TP expression co-localized with CD31-positive LSECs. MCT treatment caused LSEC destruction, concomitant with elevated expression of matrix metalloproteinases (MMPs) and adhesion molecules in WT mice, and LSEC damage was further exacerbated in $TP^{-/-}$ mice. Viability of isolated LSECs stimulated with MCT from $TP^{-/-}$ mice was lower, whereas mRNA levels of MMPs and adhesion molecules were higher; U46619, a TxA_2 agonist, reduced these levels in WT mice. These data suggest that TP signaling has no effect on platelet accumulation during MCT-induced liver injury, but instead prevents injury by suppressing LSEC damage.