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ORAL ABSTRACTS

301.VASCULATURE, ENDOTHELIUM, THROMBOSIS AND PLATELETS: BASIC AND TRANSLATIONAL

Notch1 Regulates Hepatic Thrombopoietin Production

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Notch signaling is highly conserved and regulates cell-fate decisions in several developmental processes and cell functions. However, a role for Notch in hepatic thrombopoietin (TPO) production has not been described. We noted that mice with a deficiency in hepatic Notch1 had thrombocytopenia, and so investigated TPO production and other features of platelets in these mice. We found that the liver ultrastructure and hepatocyte function were comparable between control mice and Notch1-deficient mice. However, the Notch1-deficient mice had significantly lower plasma TPO and hepatic TPO mRNA levels, concomitant with lower numbers of circulating platelets and impaired megakaryocyte differentiation and maturation. Addition of exogenous TPO rescued megakaryocyte maturation and circulating platelet numbers. Additionally, JAK2/STAT3 phosphorylation was significantly inhibited in Notch1-deficient hepatocytes. RNA-seq analysis showed significantly reduced JAK-STAT signaling. JAK2/STAT3 phosphorylation and TPO production was also impaired in purified cultured Notch1-deficient hepatocytes after treatment with desialylated platelets. Interestingly, Notch1 deficiency downregulated the expression of HES5 but not HES1. Moreover, desialylated platelets promoted the binding of HES5 to JAK2/STAT3, leading to JAK2/STAT3 phosphorylation and pathway activation. Furthermore, blockage of Dll4 on desialylated platelets inhibited hepatocyte Notch1 activation and HES5 expression, JAK2/STAT3 phosphorylation and subsequent TPO production. In conclusion, our study identifies a novel regulatory role of Notch1 in hepatic TPO production, indicating that it might be a target for modulating TPO level.

Disclosures No relevant conflicts of interest to declare.

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