Role of the prostaglandin I_2-IP system in liver regeneration of mice

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Inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha, are the major priming factors in liver regeneration facilitating the G_1-phase transition of hepatocytes. Previously, we showed that prostaglandin (PG) I_2 stimulates the expression of IL-6 mRNA via its receptor IP in the remnant liver of mice after 70% partial hepatectomy. The relation between PGI_2 and TNF-alpha, however, remains undetermined. Therefore, we examined the relation using primary cultured Kupffer cells and hepatocytes. Kupffer cells were stimulated with TNF-alpha for 30 minutes. TNF-alpha up-regulated the expression level of IL-6 mRNA in cultured wild-type (WT) Kupffer cells. Interestingly, IP agonist significantly increased the TNF-alpha induced up-regulation of IL-6 mRNA, and this accelerative effect of IP agonist disappeared in *IP*$^{-/-}$ Kupffer cells. We next stimulated cultured hepatocytes with TNF-alpha for 72 hours. After 72 hours, the expression level of IP mRNA increased significantly compared with that in vehicle treatment. We next examined whether IP activation can induce phosphorylation of cAMP-regulatory element binding protein (CREB) in the TNF-alpha stimulated hepatocytes using the Western blot assay, because IP belongs to a G_s-coupled receptor family, and CREB phosphorylation stimulates hepatocyte proliferation. Indeed, IP agonist induced the phosphorylation of CREB, which effect disappeared in vehicle treated WT hepatocytes. These results suggest that PGI_2 facilitates liver regeneration in cooperation with TNF-alpha.