GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Involvement of ERK1/2 signaling in proliferation of eight liver cell types during hepatic regeneration in rats

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Genet. Mol. Res. 12 (1): 665-677 (2013)
Received February 13, 2012
Accepted December 18, 2012
Published March 11, 2013
DOI http://dx.doi.org/10.4238/2013.March.11.14

ABSTRACT. It has been well established that ERK1/2 signaling, often subdivided into nine types of pathways, can regulate the hepatocyte proliferative response during liver regeneration. However, the effect of ERK1/2 signaling on the proliferation of other hepatic cell types remains unclear. We isolated and purified 8 liver cell types at 10 time points after 2/3 hepatectomy in adult rats. For each cell type, mRNA expression changes for ERK1/2 signaling-involved genes were monitored up to 168 h, using microarrays. Real-time PCR assays were performed for array data verification. The expression levels of these genes varied considerably between different cell types. Integrating microarray results with gene synergical analysis, at the priming phase, activation of integrin/Grb2/Ras pathway in hepatocytes apparently contributed to G0/G1 transition. Two other pathways, G-protein/EPAC/Rap1 and G-protein/PKA/Rap1, were stimulated in hepatic stellate cells, while RTK/PKC/Ras and RTK/Grb2/Ras were stimulated in Kupffer cells. At the progressive phase, the ERK1/2 pathway is involved in hepatocyte replication; three pathways, namely Ca^{2+}/PKC/Ras, RTK/Grb2/Ras and

G-protein/EPAC/Rap1, were found to play roles in biliary epithelial cell proliferation, while RTK/PKC/Ras and RTK/Grb2/Ras were involved in Kupffer cell proliferation, and G-protein/PKC/Ras in pit cell proliferation. At the terminal phase, the promotive effect of the ERK1/2 pathway on replication of hepatocytes, biliary epithelial cells, oval cells, hepatic stellate cells, Kupffer cells, and dendritic cells was considerably reduced, possibly due to their differentiation at the end of regeneration. G-protein/PKC/Ras, integrin/Grb2/Ras and G-protein/PKA/Rap1 pathways were active in sinusoidal endothelial cells, perhaps to aid in their proliferation. We conclude that ERK1/2 has a signaling role in the regulation of proliferation of 8 cell types during liver regeneration process.

Key words: Liver restoration; Liver cell types; Gene synergy; ERK1/2 signaling pathway; Gene expression profiling

