



Samenvatting proefschrift Vesna Stanulović

'Regulation of the Glutamine Synthetase Gene Expression in the Liver'

Promotiedatum: 20 december 2007
Universiteit van Amsterdam

Promotor:
Prof. dr. W.H. Lamers

Co-promotor:
Dr. T.B.M. Hakvoort

My thesis focuses on the regulation of glutamine synthetase (GS) expression in the liver. In adult mouse liver, GS is expressed in a narrow, 2-3 cell-layers thick rim of hepatocytes around the central veins, whereas it is virtually absent in the rest of the hepatocytes. This pattern of expression is regulated by three regulatory regions: the upstream enhancer, the first intron and the 3'-untranslated region. We show that these regulatory elements mediate the increase in GS expression upon glutamine depletion. This glutamine sensitivity of the GS gene is found to be dependent on the transcription factors DBP and Rev-erb, factors known to be involved in the circadian rhythm. Consequently, the involvement of DBP and Rev-erb is associated with circadian GS expression. We further report that HNF4 α binds to the upstream enhancer and inhibits GS expression in the periportal hepatocytes, thereby confining GS expression to the pericentral area. We propose that this is mediated via the recruitment of the chromatin-modifying enzyme histone deacetylase I. In contrast to HNF4 α , β -catenin supports GS expression in pericentral hepatocytes. Our investigation of the dynamics of GS, HNF4 α and β -catenin expression during embryonic and early postnatal development shows that the pericentral gradient of GS expression only develops after embryonic day 17 and parallels the development of pericentral β -catenin expression. At this point the pericentral gradient is very wide and its constriction to central veins during the perinatal period. This restriction in expression coincides with reappearance of HNF4 α and a translocation of β -catenin from the nucleus to the membrane. These findings suggest the presence of inhibitory interactions between activated β -catenin and HNF4 α during the development of the pericentral GS gradient. ◀

Aan de publicatie van dit proefschrift werd een financiële bijdrage geleverd door de Nederlandse Vereniging voor Hepatologie.

Voor proefschriftsamenvattingen zie:
www.hepatologie.org