Susceptibility to chronic liver disease
- Role of environmental and genetic factors

Akademisk avhandling

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av

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Avhandlingen baseras på följande arbeten:

I. Burza MA, Romeo S, Kotronen A, Svensson PA, Sjöholm K, Torgerson JS, Lindroos AK, Sjöström L, Carlsson LM, Peltonen M. **Long-term effect of bariatric surgery on liver enzymes in the Swedish Obese Subjects (SOS) study.** *PLoS One 2013; 8 (3): e60495.*

II. Burza MA, Molinaro A, Attilia ML, Rotondo C, Attilia F, Ceccanti M, Ferri F, Maldarelli F, Maffongelli A, De Santis A, Attili AF, Romeo S, Ginanni Corradini S. **PNPLA3 I148M (rs738409) genetic variant and age at onset of at-risk alcohol consumption are independent risk factors for alcoholic cirrhosis**. *Liver International 2014; 34 (4): 514-520.*

III. Pirazzi C, Valenti L, Motta BM, Pingitore P, Hedfalk K, Mancina RM, Burza MA, Indiveri C, Ferro Y, Montalcini T, Maglio C, Dongiovanni P, Fargion S, Rametta R, Pujia A, Andersson L, Ghosal S, Levin M, Wiklund O, Iacovino M, Borén J, Romeo S. **PNPLA3 has retinyl-palmitate lipase activity in human hepatic stellate cells.** *Human molecular genetics 2014; 23 (15): 4077-4085.*

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Susceptibility to chronic liver disease
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ABSTRACT

The onset and the progression of chronic liver disease involve environmental and genetic factors. Hepatic stellate cells (HSCs) are important players in these processes and are the main storage site for retinol. We studied the role obesity, alcohol and patatin-like phospholipase domain-containing 3 (*PNPLA3)* I148M variant on the susceptibility to chronic liver disease. Moreover, we tried to understand the molecular mechanism underlying the association between *PNPLA3* and chronic liver disease.

In paper I we analysed the long-term effect of weight loss due to bariatric surgery on liver damage in a large prospective controlled cohort, the Swedish Obese Subjects study. We analysed changes in serum transaminases between follow-up and baseline values in the bariatric surgery and control groups. Serum transaminases at 2- and 10-year follow-up were lower in the bariatric surgery than in the control group. The transaminase reduction was proportional to the degree of weight loss. In addition, the prevalence of severe liver disease was lower in the surgery than in the control group during the follow-up.

In paper II we examined the effect of age at onset of at-risk alcohol intake and *PNPLA3* I148M variant on the incidence of alcoholic cirrhosis. Both variables were independent risk factors for the onset of alcoholic cirrhosis. However, the risk conferred by the 148M variant was higher in subjects who started at-risk drinking earlier than in those who started later.

In paper III, we tested the hypothesis that PNPLA3 is involved in the retinol release from HSCs. We found that PNPLA3 is regulated by the availability of retinol in HSCs and that it has an esterase activity on retinyl palmitate, which is impaired in the 148M mutant protein.

In conclusion, our data show that modifying environmental factors may affect the natural history of chronic liver disease and that the interplay between environmental and genetic factors defines the individual risk to the disease. Specifically, obesity-related chronic liver damage is reduced by sustained weight loss after bariatric surgery and this may prevent the onset of severe liver disease. Age of exposure to alcohol affects the degree of the risk conferred by *PNPLA3* I148M variant. In addition, we suggest that the retinol release from HSCs mediated by PNPLA3 may be one important step in the onset of chronic liver disease.

Keywords: chronic liver disease, susceptibility, human genetics, NAFLD, ALD, PNPLA3
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