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Impact of Genetic Variants in Inosine Triphosphate Pyrophosphatase and Interferon-λ4 on Natural History, Treatment Response and Ribavirin Pharmacology in Hepatitis C Virus Infection

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssal Arvid Carlsson, Medicinaregatan 3, fredagen den 15 maj 2020, klockan 09.00.

av Jesper Waldenström

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Avhandlingen baseras på följande delarbeten

I. Rembeck K, Waldenström J, Hellstrand K, Nilsson S, Nyström K, Martner A, Lindh M, Norkrans G, Westin J, Pedersen C, Färkkilä M, Langeland N, Buhl MR, Mørch K, Christensen PB, Lagging M. **Variants of the Inosine Triphosphate Pyrophosphatase Gene are Associated with Reduced Relapse Risk Following Treatment for HCV Genotype 2/3.** *Hepatology.* 2014;59(6):2131-9.

II. Waldenström J, Westin J, Nyström K, Christensen P, Dalgard O, Färkkila M, Lindahl K, Nilsson S, Norkrans G, Krarup H, Norrgren H, Buhl MR, Stenmark S, Lagging M. **Randomized Trial Evaluating the Impact of Ribavirin MonoTherapy and Double Dosing on Viral Kinetics, Ribavirin Pharmacokinetics and Anemia in Hepatitis C Virus Genotype 1 Infection.** *PLoS One*. 2016;11(5):e0155142.

III. Nystrom K, Wanrooij PH, Waldenstrom J, Adamek L, Brunet S, Said J, Nilsson S, Wind-Rotolo M, Hellstrand K, Norder H, Tang K, Lagging M. **Inosine Triphosphate Pyrophosphatase Dephosphorylates Ribavirin Triphosphate and Reduced Enzymatic Activity Potentiates Mutagenesis in Hepatitis C Virus**. *J Virol.* 2018;92(19).

IV. Waldenstrom J, Kåberg M, Alanko-Blomé M, Widell A, Björkman P, Nilsson S, Hammarberg A, Weiland O, Nyström K, Lagging M. **Interferon-λ4 Genetic Variants are Independently Associated with Spontaneous Clearance of Acute Hepatitis C Virus Genotype 1-3 Infection, and Inosine Triphosphate Pyrophosphatase Polymorphisms Impact on Immune Responses in Men.** *In Manuscript.*

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Avdelningen för infektionssjukdomar, Institutionen för biomedicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2020.

Abstract

Hepatitis C virus (HCV) impacts on global health with around 70 million chronically infected worldwide. The infection increases the risk of cirrhosis and primary liver cancer. The treatment until 2013 has been based on interferon-α and ribavirin, but is now replaced by direct acting antivirals. Ribavirin is still used in the most difficult-to-cure patients. This thesis evaluates host genetic variations in inosine triphosphate pyrophosphatase (*ITPA)* and interferon-λ4 (*IFNL4*) in relation to cure rates in patient treated with interferon-α and ribavirin as well as ribavirin pharmacology in the setting of chronic HCV infection, and spontaneous resolution of acute HCV infection. In a post-hoc analysis of 354 HCV genotype 2/3 infected patients receiving interferon-α and ribavirin, genetic variation in *ITPA* entailing reduced ITPase activity was associated with increased cure rates (**paper I**). Small inhibiting RNA aimed at *ITPA* reduced ITPase levels and increased the antiviral effect of ribavirin, ribavirin associated viral mutations and concentrations of ribavirin triphosphate intracellularly, *in vitro*. ITPase was also shown to be able to dephosphorylate ribavirin triphosphate (**paper III**). In a randomized trial, standard interferon-α and ribavirin treatment was compared to four weeks ribavirin monotherapy prior to combination treatment and to two weeks of ribavirin double dosage alongside with interferon-α. Both experimental strategies succeeded in reaching high ribavirin concentrations at earlier timepoints in dual therapy. Ribavirin monotherapy resulted in a viral decline associated with *IFNL4* genotype (**paper II)**. *IFNL4* genotype was associated with clearance in acute HCV genotype 1 as well as in genotype 2/3 infection. *ITPA* genotype showed significant associations with age at seroconversion and spontaneous resolution in males with favorable *IFNL4* genotype (**paper IV**).

Keywords: Hepatitis C virus, HCV, Inosine triphosphate pyrophosphatase, *ITPA,* interferon-λ4, *IFNL4,* ribavirin, interferon, PWID, IP-10.

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