Structural Basis of Drug Resistance in Hepatitis C Viral NS3/4A Serine Protease

Sabine Schweizer[1], Christoph Welsch[2], and Iris Antes[1]

[1]Protein Modelling, Center for Integrated Protein Science Munich at the Department of Life Science, Technical University Munich, Emil-Erlenmeyer-Forum 8, D-85354 Freising

[2]Department of Internal Medicine, J. W. Goethe University, Theodor-Stern-Kai 7, D-60590 Frankfurt/Main

Hepatitis C virus (HCV) infections affect 3% of the world's population and are a serious global health problem [1]. The virus is spread as a mixture of genetic variants so-called quasispecies. This genetic heterogeneity is a major problem in HCV vaccine and drug development as it allows the virus to easily escape under selective pressure and to become resistant against direct-acting antiviral agents (DAA) [2-5]. The HCV NS3/4A serine protease is considered a most promising drug target in DAA development [6,7].

We present molecular dynamics studies of the wild type NS3/4A serine protease and two types of protease inhibitor-resistance related viral variants. The analysis of the structural influence of low- to medium-level resistance mutations V55A/I and R155K/Q/T on the protease ligand-binding properties suggests two structure-based escape mechanisms: First, conformational changes in the hydrophobic core region of the enzyme lead to constriction of the binding cavity sterically hampering inhibitor binding. This effect is especially important for ketoamide inhibitors, a class of drugs, from which Victrelis™ (boceprevir) and Incivek™ (telaprevir) have been approved by the U.S. Food and Drug Administration (FDA) only recently. Second, mutations that affect the salt bridge network within the binding pocket can entail a weakening of electrostatic interactions with the inhibitor and lead to conformational changes that influence the shape of the binding site and thus the binding behavior. Overall, our studies provide an explanation of the experimental resistance data on a molecular basis and reveal a deeper insight into general molecular mechanisms conferring resistance, which will help to improve the efficacy of next-generation DAAs.

[1] WHO (E. Barnes), *Viral Cancers – Hepatitis C Virus*, **2010**.
[2] S. Margeridon-Thermet, R.W. Shafer, *Viruses*, **2010**, *2*, 2696–2739.
[3] L. Ring, H. Dahari, R.M. Ribeiro, A.S. Perelson, *N. Engl. J. Med.*, **2011**, *364*, 2417-2428.
[4] S. Susser et al. *Hepatology*, **2009**, *50*, 1709-1718.
[5] C. Welsch et al. *Antimicrob. Agents Chemother.*, **2012**, in press, doi: 10.1128/AAC.05184-11.
[6] S.-L. Tan (ed.), *Hepatitis C Viruses*, **2006**, *Horizon Bioscience*.
[7] R. De Francesco, G. Migliaccio, *Nature*, **2005**, *436*, 953-960.