Structural Basis of Drug Resistance of Hepatitis C Virus Serine Protease Variants

S. Schweizer[1], C. Welsch[2], I. Antes[1]

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

[2]Department of Medicine and the Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Hepatitis C virus (HCV) infections affect 3% of the world's population and represent an increasing global health problem. [1,2] In most cases, HCV infection becomes chronic, which in turn can entail severe long-term afflictions like liver cirrhosis and cancer. [1] The hepatitis C virus, identified in the last 1980s, is spread as an ensemble of similar variants, so-called viral quasispecies. [3] Owing to this genetic diversity, vaccine and drug development is a challenging task. The NS3/4A serine protease of HCV plays a pivotal role in the viral life cycle. [4,5] It is considered as an attractive drug target for development of direct-acting antiviral agents (DAA) against hepatitis C. [4,6] The ketoamide compounds boceprevir [7] and telaprevir [8], which bind covalently to the serine protease, will be first to be approved for clinical use. Rapid drug resistance development is due to the pre-existing viral variants, which are selected from the viral quasispecies population. Thus, resistance against DAA is considered a major problem in future treatment. [9,10] It is an important challenge to gain a detailed understanding of the molecular mechanisms leading to resistance and to design more effective drugs, which are less susceptible to resistance.

To elucidate the structural basis of the binding properties and resistance behavior of natural viral variants, we performed molecular dynamics simulations of the wild type NS3/4 serine protease and protease inhibitor-resistance related viral variants, V55A/I and R155K/Q/T. The calculations indicate a rather unexpected correlation between the binding site flexibility and experimentally observed antiviral activity: The wild type protease exhibits increased binding site flexibility compared to the resistant variants, which allows the protease to adjust its conformation more easily during the ligand-binding process. In addition, the conformational more rigid resistant variants possess smaller binding pockets, which makes it more difficult for possible inhibitors to enter the binding site. Thus, our studies show that a combination of reduced binding site flexibility and sterically constricted binding pockets decrease the susceptibility of the protease, which might be a general escape mechanism of the HCV serine protease.

[1] WHO (E. Barnes), *Viral Cancers – Hepatitis C Virus*, **2010**.
[2] Lavanchy, *Liver International*, **2009**, *29*, 74-81.
[3] J. Cristina, M. del Pilar Moreno, G. Moratorio, *Virus Research*, **2007**, *127*, 185-194.
[4] S.-L. Tan (ed.), *Hepatitis C Viruses*, **2006**, *Horizon Bioscience*.
[5] B. D. Lindenbach, C. M. Rice, *Nature*, **2005**, *436*, 933-938.
[6] R. De Francesco, G. Migliaccio, *Nature*, **2005**, *436*, 953-960.
[7] S. Venkatraman et al., *J. Med. Chem.* , **2006**, *49*, 6074-6086.
[8] C. Lin, A. D. Kwong, R. B. Perni, *Infectious Disorders – Drug Targets*, **2006**, *6*, 3-16.
[9] T. L. Kieffer et al., *Hepatology*, **2007**, *46*, 631-639.
[10] C. Welsch et al., *Genome Biol*., **2008**, *9*, R16.