ID der Kurzfassung : **76**

Overcoming the resistance to influenza A virus infections in mice carrying a deletion in the host protease TMPRSS2 by exchange of amino acids in the hemagglutinin

Inhalt

Background:
Annual epidemics and occasional pandemics by influenza A virus (IAV) pose a severe threat to human health. Host cell factors that are required for viral spread but not for cellular survival represent ideal targets for anti-viral therapies. The cleavage activation of the influenza virus hemagglutinin (HA) by host cell proteases is essential for viral infectivity. Thus, host proteases represent very suitable target for the development of anti-viral drugs.

Methods:
We infected a mouse strain carrying a knock-out (KO) mutation in the host protease TMPRSS2 with IAVs carrying mutations in the HA and determined pathology and virus replication in infected lungs.

Results:
We showed that deletion of the HA-activating protease gene, *Tmprss2*, in knock-out (KO) mice inhibits spread of mono-basic H1N1 influenza viruses. Lung pathology was strongly reduced and mutant mice were protected from weight loss, death and revealed reduced viral load. After infection with influenza A virus expressing a H3, body weight loss and survival was as severe in *Tmprss2* KO mutants an in wild type mice. Modifications in the HA loop and interacting amino acids influenced viral replication and pathology in *Tmprss2* KO mice. Body weight loss and survival of *Tmprss2* KO mice was dependent upon cleavability of the mutated HA protein by the host protease.

Conclusions:
Our results validate the host protease TMPRSS2 as a potential drug target for anti-viral therapy.

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Viral Replication

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Evolution and Emerging viruses

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