ID der Kurzfassung : **41**

TMPRSS2 is the major HA-activating protease for IAV, but not for IBV in the human respiratory tract

Inhalt

Cleavage of influenza A virus (IAV) and influenza B virus (IBV) hemagglutinin (HA) activation by host proteases is essential for virus infectivity.
The HA of most influenza viruses including seasonal H1N1, H3N2 and IBV as well as the zoonotic-H7N9 virus is cleaved at a single arginine residue by trypsin-like proteases. We identified TMPRSS2 as a protease present in the human airways that activates HA with a monobasic cleavage site *in vitro*. Further studies by us and others have demonstrated that TMPRSS2 is essential for infectivity and pathogenesis of H7N9 and H1N1 in mice. In contrast, H3N2 and IBV activation and spread is independent of TMPRSS2 expression and due to so far unknown protease(s). These studies demonstrated that IAV and IBV with monobasic HA cleavage sites differ in their protease specificity in mice.
Here, we investigated the role of TMPRSS2 in activation and replication of different IAV subtypes H1-H16 and IBV in primary human bronchial (HBE) cells and alveolar type II cells (ATII) cells by knockdown of TMPRSS2 expression using the peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO) T-ex5. T-ex5 treatment causes mis-splicing of TMPRSS2 mRNA and expression of a truncated inactive protease.
We found that knockdown of TMPRSS2 expression strongly suppressed proteolytic activation and spread of all tested IAV subtypes in HBE cells and ATII cells. In contrast, activation and replication of IBV was not affected by T-ex5 in the cells.
Our data suggest that TMPRSS2 is the major HA-activating protease for IAV, but not for IBV in the human respiratory tract.

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