ID der Kurzfassung : **55**

Phosphorylation of TRIM28 enhances the expression of IFN-β and proinflammatory cytokines during HPAIV infection of human lung epithelial cells.

Inhalt

Human infection with highly pathogenic avian influenza viruses (HPAIV) is often associated with severe tissue damage due to hyperinduction of interferons and proinflammatory cytokines. The reasons for this excessive cytokine expression are still incompletely understood, which has hampered the development of efficient immunomodulatory treatment options. The host protein TRIM28 associates to the promoter regions of over 13.000 genes and is recognized as a genomic corepressor and negative immune regulator. TRIM28 corepressor activity is regulated by post translational modification, specifically phosphorylation of S437, which modulates binding of TRIM28 to the heterochromatin-binding protein HP1. Here, we identified TRIM28 as a key immune regulator leading to increased IFN-β and proinflammatory cytokine levels during infection with HPAIV. Using avian- and human- derived influenza A virus strains as well as HPAIV, we could demonstrate that strain-specific phosphorylation of S473 is induced by a signaling cascade constituted of PKR, p38 MAPK and MSK1 in response to RIG-I-independent sensing of viral RNA. Furthermore, using chemical inhibitors as well as knockout cell lines, our results suggest that phosphorylation of S473 facilitates a functional switch leading to increased levels of IFN-β, IFN-γ and other cytokines. In summary, we have identified TRIM28 as a critical factor controlling excessive expression of type I and II IFNs as well as proinflammatory cytokines during HPAIV infection. In addition, our data indicate a novel mechanism of PKR-mediated IFN-β expression, which could lay the ground for novel treatment options aiming at rebalancing dysregulated immune responses during severe HPAIV infection.

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