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Death-domain associated protein-6 (DAXX) mediated apoptosis in hantavirus infection is counter-balanced by activation of interferon-stimulated nuclear transcription factors

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ABSTRACT

Hantaviruses are negative strand RNA species that replicate predominantly in the cytoplasm. They also activate numerous cellular responses, but their involvement in nuclear processes is yet to be established. Using human umbilical vein endothelial cells (HUVECs), this study investigates the molecular finger-print of nuclear transcription factors during hantavirus infection. The viral-replication-dependent activation of pro-myelocytic leukemia protein (PML) was followed by subsequent localization in nuclear bodies (NBs). PML was also found in close proximity to activated Sp100 nuclear antigen and interferon-stimulated gene 20 kDa protein (ISG-20), but co-localization with death-domain associated protein-6 (DAXX) was not observed. These data demonstrate that hantavirus triggers PML activation and localization in NBs in the absence of DAXX-PLM-NB co-localization. The results suggest that viral infection interferes with DAXX-mediated apoptosis, and expression of interferon-activated Sp100 and ISG-20 proteins may indicate intracellular intrinsic antiviral attempts.

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Introduction

Hantaviruses are tri-segmented negative strand RNA micro-organisms that belong to the family *Bunyaviridae*. The large (*L*), medium (*M*), and small (*S*) genomic segments code for the viral RNA dependent RNA polymerase (RdRp), the glycoprotein precursor (GPC) of the 2 envelope glycoproteins (G1 and G2), and the nucleocapsid protein (*N*), respectively. Hantavirus replication occurs entirely in the cytoplasm. Shortly after virus entry and uncoating, the RdRp initiates positive strand mRNA synthesis from the genomic *L*, *M* and *S* RNAs (vRNAs) using a cap-snatching mechanism (Dunn et al., 1995; Garcin et al., 1995; Kolakofsky and Hacker 1991).

In postmortem tissues, hantaviruses are primarily found in endothelial cells, suggesting a cellular tropism essential for hantavirus pathogenesis (Zaki et al., 1995; Zhang et al., 1987). This hypothesis is further supported by *in vitro* studies that show endothelial cells are uniquely susceptible to hantavirus infection and support virus replication (Khaiboullina et al., 2000; Pensiero et al., 1992). Our group, as well as others, has shown that hantavirus infection activates specific cellular responses in endothelial cells (Khaiboullina et al., 2004; Geimonen et al., 2002). We have also demonstrated that many of these cellular responses are virus replication dependent (Khaiboullina et al., 2004; Khaiboullina et al., 2005). While the precise mechanism by which hantaviruses activate these cellular responses remains unknown, it is likely that they are mediated through nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and interferon regulatory factor-3 (IRF-3) (Khaiboullina et al., 2005; Sundstrom et al., 2001).

Pro-myelocytic leukemia nuclear bodies (PML-NBs) are nuclear sub-structures associated with the nuclear matrix, which have been implicated in numerous cellular processes, including transcription, post-translational modifications, oncogenesis, innate immunity and several antiviral responses (Grisendi et al., 2005; Borden 2002). The composition of PML-NBs is heterogeneous and includes constitutively expressed essential constituents such as pro-myelocytic leukemia protein (PML), interferon-stimulated

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