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Editorial Open Access

The Role of Interferon-Inducible Transmembrane Proteins in Virus Infection

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Editorial

The interferon-inducible transmembrane proteins (IFITMs) family is a group of small membrane-associated interferon induced proteins. IFITMs are composed of three proteins, IFITM1, IFITM2 and IFTM3. IFITMs can be expressed in a wide range of vertebrates, including chickens, mice, humans and previous studies have demonstrated that IFITMs restrict some virus infections [1].

IFITMs have broad antiviral function

Several studies have demonstrated that overexpression of IFITMs could inhibit virus entry and infection of a variety of virus families (including orthomyxoviridae and flaviviruses) in cell culture systems [2,3]. Over-expression of IFITM1, IFITM2 or IFITM3 restricted early viral replication. On the contrary, knock-down of IFITM3 stimulated influenza A virus replication [4]. Researchers reported that IFITM3 is required for IFNα-induced anti-viral defense and restricts influenza A virus infection at viral entry and early-stage of virus life cycle. Knock-down of IFITM3 dampen 40%-70% of IFN's anti-viral effect. Thus, IFITM proteins are critical for the innate immunity to influenza A virus mediated by IFNs [5]. IFITMs have been demonstrated to suppress the replication of several flaviviruses including West Nile virus, dengue virus, hepatitis C virus and Zika virus [4]. IFITM1 and IFITM3 inhibit ZIKV infection at early stage of the viral life cycle. In addition, IFITM3 could inhibit ZIKV-induced cell death [6]. Another IFITMs superfamily member TMEM2 has been found to inhibit HBV infection by activating the Jak/STAT signaling pathway [7]. Notably, these restricted viruses were all encapsulated, containing the ssRNA genome, and were reported to enter cells by membrane fusion after endocytosis. However, some retroviruses, such as HIV-1 and Moloney leukaemia virus and Bunyaviridae, Crimean–Congo haemorrhagic fever virus, are obviously not affected by IFITMs. In the past studies, IFITMs were not shown to inhibit HIV-1 infection [4]. However, recent studies have reported that IFITM2 and IFITM3 could interact with HIV-1 Env protein in viral producer cells, leading to impaired Env processing and virion incorporation [8]. Meanwhile, some evidence showed that IFITM3 could also limit Non-enveloped Reoviridae, reovirus replication, suggesting that IFITMs affected a variety of viruses, not limited to viruses with envelopes [9].

Mechanisms of IFITMs restriction of virus infection

The IFITM proteins play an important role in each stage of the virus infection. Membrane fusion is a critical step for enveloped virus entry into the host cells. In the previous studies, IFITMs have been shown to block the membrane fusion to inhibit cytosolic entry of virus [2]. Cell-cell fusion assays showed that IFITM3 limits fusion between viral membrane and membrane of the host cells. Further studies using two-photon laser scanning and fluorescence lifetime imaging of Laurdan-labelled cells, with the impacts of oleic acid treatment on cell-cell fusion, suggested that IFITMs could also change spontaneous positive curvature in the outer leaflet of membranes[10]. Recent research suggests that IFITM3 interacts with vesicular membrane protein-associated protein A and destroys its binding to oxysterol-binding proteins that change the content of cholesterol in the endosomal membrane. Over-expression IFITM3 increased endosomal cholesterol, which may affect viral fusion in the endosomal membrane fluidity [11]. In addition, The IFITMs may modify endosomal or lysosomal vesicles, rendering them unsuitable for viral fusion. This can be achieved by altering the lipid composition of the vesicle membrane, either by inactivating the vesicles with non-specific proteases, or by interfering with the activity of the v-ATPase responsible for endosome acidification [12]. Meanwhile, IFITMs can change the rate or pattern of vesicle trafficking so that the virus is redirected to the non-fusion pathway. IFITMs also induce large vacuoles in many cell types, indicating that they interfere with vesicle trafficking and fusion [13]. Besides, previous studies found that IFITMs could directly linked to the virus, restricting virus interactions with host cell receptors to inhibit endocytosis and to reroute vesicular traffic to a nonproductive end [4].

Conclusion

The IFITMs is a family of small transmembrane proteins which are expressed in many cell types and they are strongly induced by IFNs. Although other functions have been proposed, one of the well-characterized functions of the IFITM proteins seems to be antiviral. IFITM3 significantly inhibited multiple viruses *in vivo*. Tissue culture studies have shown that other IFITMs limited the infection of other enveloped viruses. IFITMs reduce cell fusion in the early stages of viral infection, but the mechanism of action is still not completely determined. It is also unclear how IFITM proteins differentially inhibit different viruses and whether they can regulate the replication of other pathogens, including bacteria and parasites.

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