

# Interferon-Induced Transmembrane Protein: A Moonlighting Protein Against SARS-CoV-2 Infection or in Support of Invasive Ductal Breast Carcinoma?

Rinki Minakshi

DEPARTMENT OF MICROBIOLOGY, SWAMI  
SHRADDHANAND COLLEGE, DELHI UNIVERSITY

The interferon-induced transmembrane proteins (IFITMs), widely acting against invading viruses are ubiquitously expressed on the cellular membranes, were previously known for their prominent role in tumorigenesis. Studies productively showed that the entry restriction on SARS-CoV spike glycoprotein agreeably involved the action of frontier IFITM1, 2 and 3. On the contrary, overexpression of IFITM3 has been reported in Invasive ductal breast carcinoma (IDC) tissue specimens where lentivirus-delivered shRNA resulted in targeted silencing of IFITM3 mRNA expression. Despite acting protective against virus infection, expression of IFITM favors cancer migration as seen in IDC. The existence of such a phenomenon wherein a choice is made by the selection pressure on IFITM allele frequency in human population between opposing roles of the protein, needs to be untangled.

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## Introduction

The innate immunity, being an autonomous cellular arsenal against invading viruses, has strategically evolved its surveillance power as well as effector functions. The potent immune mediator, interferon (IFN), is widely secreted against invading viruses. The whole plethora of genes evoked in response to the secreted IFNs comprises of IFN-stimulated genes (ISGs), which function primarily by imposing modulation on multiple stages of viral replication event [1]. The interferon-induced transmembrane proteins (IFITMs), labelled as a moonlighting protein, are one such ubiquitously expressed ISGs, on the cellular membranes, that were previously known for their prominent role in tumorigenesis. Widened functional studies have extended striking role of IFITMs, wherein IFITMs not only interrupt host-virus membrane fusion but also impede infectious virion production in cell culture [2]. Normally, cells show basal expression levels of IFITMs, which significantly see an upsurge in their levels during virus infection [3].

As witnessed in studies using siRNA, IFITM1, -2 and -3 have acted by inhibiting infection establishment in influenza A virus (IAV), West Nile virus, dengue virus, Marburg virus, Ebola virus, HIV-1 and SARS-CoV [4]. The mechanistic details of this inhibition are still in its juvenile stage, but studies have emphasized that IFITM proteins inhibit enveloped viruses [5].

Studies productively showed that the entry restriction on SARS-CoV spike glycoprotein agreeably involved action of frontier IFITM1, 2 and 3 rather than concomitant ACE2 downregulation. The shRNA targeting of IFITM1 markedly enhanced SARS-CoV spike mediated entry without altering expression of ACE2. Moreover, the exploitation of other host factors apart from the primary receptor of the virus, cannot be overlooked in this mechanism [6]. Congruently, MERS-CoV entry has also been shown to be inhibited by IFITM proteins [5].

On the contrary, human coronavirus-OC43 (HCoV-OC43), the etiological agent of common cold, seizes IFITM proteins for their entry thereby proving the predictability of evasion tactics against IFITM restrictions by viruses [7].

Invasive ductal breast carcinoma (IDC), which accounts for approximately 80% of breast cancer cases, is initiated by a set of multifaceted pathogenesis mechanism and gene mutations. Overexpression of IFITM3 has been reported in IDC tissue specimens where lentivirus-delivered shRNA resulted in targeted silencing of IFITM3 mRNA expression. The study further proved that the knockdown of IFITM3 led to significant reduction in tumor viability [8]. There are several reports on the overexpression of IFITM3 in various tumors like human glioma, colon cancer, esophageal squamous cell carcinoma and hepatocellular carcinoma [9]. Another study showed that IFITM3 ameliorated inflammation and colitis-associated tumorigenesis [9]. On the contrary, IFITM3 overexpression lead to loss of fetus development in mice, which has been correlated with a similar pathology during Zika virus infection [9].

All the aforementioned studies notify about a highly significant aspect of IFITM expression where balance between high and low IFITM levels is evident as frequency of circulating alleles (single nucleotide polymorphism, SNP) in human population. The SNP rs12252T>C (minor IFITM3 allele) was significantly enriched in patients hospitalized during H1N1 pandemic (2009) [10]. Moreover, a meta-analysis revealed that IFITM3 rs12252 T>C polymorphism showed substantial association with the risk of developing severe influenza [11]. These SNPs resulted in diminished IFITM3 expression thereby suggesting that selection of fetus development might dominate endurance towards severe virus infection.

The current pandemic imposed by SARS-CoV-2 infection has been puzzling both scientific as well as medical fraternity. Deriving conclusive impetus from aforesaid studies, procuring experimental data on the potential role of IFITMs, might elucidate an aspect of host response during SARS-CoV-2 infection in cancer patients. Despite acting protective against virus infection, expression of IFITM favors cancer migration as seen in IDC. This again points towards the existence of a choice made by the selection pressure on IFITM allele frequency in human population. We emphasize more in-depth study on IFITM SNP and its functional association with cancer as well as SARS-CoV-2 infection, where the mystery behind two opposing effects of IFITM expression in host can be deciphered.

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