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Invited Mini Review

Does IFITM3 link inflammation to tumorigenesis?

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Uncontrolled chronic inflammation, in most cases due to excessive cytokine signaling through their receptors, is known to contribute to the development of tumorigenesis. Recently, it has been reported that the antiviral membrane protein interferon-induced transmembrane protein 3 (IFITM3), induced by interferon signaling as part of the inflammatory response after viral infection, contributes to the development of B-cell malignancy. The unexpected oncogenic signaling of IFITM3 upon malignant B cell activation elucidated the mechanism by which the uncontrolled expression of inflammatory proteins contributes to leukemogenesis. In this review, the potential effects of inflammatory cytokines on upregulation of IFITM3 and its contribution to tumorigenesis are discussed. [BMB Reports 2022; 55(12): 602-608]

INTRODUCTION

A recent global outbreak of the Coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has strongly underlined the importance of the human immune system in response to viral infection. In contrast to the essential role of inflammation in the host's defense against pathogens, multiple inflammatory pathways leading to hyperinflammation, such as cytokine storm, defined as excessive production and uncontrolled release of pro-inflammatory cytokines and chemokines, have been pointed out as the main cause of severe COVID-19 disease and associated complications such as tissue damage, acute respiratory distress syndrome (ARDS) and sepsis (1, 2). As a result, the critical role of an effective initial host immune response that controls devastating inflammatory dysregulation has received increased attention.

Infection with COVID-19 elicits a host immune response that is triggered by viral RNA recognition by pattern recognition receptors such as Toll-like receptors (TRLs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs), which induces expression of cytokines, chemokines, and interferons (IFNs) (1). Upon binding of IFN to its receptor, IFN activates Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway and induces expression of IFN-stimulated genes (ISGs) such as IFITM3, an essential protein for early restriction of viral infection (3). Hence, delayed type I INF signaling allows the virus to replicate and cause a cytokine storm, resulting in uncontrolled secretion of cytokines IL-1β, IL-6, IL-8, IFN-γ and TNF-α that are known to exacerbate the severity of COVID-19 disease (4).

A well-known risk factor for several types of cancer is an exceedingly uncontrolled inflammatory response, alongside the challenges of viral diseases. Approximately 20% of cancers are preceded by chronic inflammation that affects all stages of tumorigenesis, including tumor initiation and tumor progression through genomic instability, proliferation and survival of premalignant cells (5). Although IFITM3 plays a host-protective role in preventing the spread of viruses such as influenza A, SARS-CoV, Chikungunya, West Nile virus, cytomegalovirus, and respiratory syncytial virus, it has also been reported that IFITM3 plays a dual role in the growth, proliferating, and migrating of cancer cells (6, 7).

Overexpression of IFITM3 has been reported in colon cancer, glioma, gastric cancer, breast, prostate, lung, and liver cancer and has been correlated with poor clinical outcomes in colon cancer, head and neck squamous cell cancer, acute myeloid leukemia, acute lymphoblastic leukemia, and mantle cell lymphoma (8-14). In particular, IFITM3 transiently interacts with activated B cell receptor (BCR) complex, the membrane-bound form of immunoglobulin (mIg) in B cells, upon antigen binding. It also plays an essential role in BCR-PI3K signaling, which enables the activation, differentiation, antibody production of B cells thus mediates the active adaptive immune response against foreign antigens. On the other hand, constitutive accumulation of IFITM3 on cell membrane amplified oncogenic signaling required for malignant transformation of B cells and initiation of B-lymphoid leukemia and lymphoma. BCR-ABL1, a Philadelphia chromosome-derived fusion gene, encodes the constitutively active conformation of oncogenic tyrosine kinase that mimics active BCR downstream signaling cascade (15). BCR-ABL1 constitutively phosphorylates IFITM3 at Y20, which

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prevents endocytosis and degradation of IFITM3, leading to an excessive accumulation on the cell surface, thus promoting the development of B cell malignancies (14). Therefore, the host cell-protective, pro-inflammatory, and pro-tumorigenic role of IFITM3 is an important model to understand the mechanisms by which uncontrolled activation of inflammation affects the development of cancer.

REGULATION OF IFITM3 EXPRESSION BY IFN, IL-1 AND IL-6

Interferon is known as a primary cytokine that increases expression of IFITM3. Type I IFNs, one of the first cytokines expressed in response to viral infection, are produced approximately 12-hours post viral infection (16). Therefore, in order to immediately stop viral replication during SARS-CoV-2 infection, type I IFN signaling must be activated in a timely manner (17). At the infection site, activated NK cells also express type II interferons. Thereby, increased antigen-presenting capabilities of antigen-presenting cells (APCs), which stimulate Th1 cells, 48 hours after infection, play a critical role in the activation of the adaptive immune system (18, 19).

IFITM3 expression is increased by IFN receptor-mediated activation of the JAK/STAT pathway upon IFN binding, and it is known that the level of IFITM3 expression is increased by 8 to 20 times between 4 and 8 hours by an interferon signaling cascade (20). Then, accumulated IFITM3 proteins in endosomal membranes induce negative membrane curvature through insertion of the amphipathic helix (amino acids, 59 to 68) into the cytoplasmic leaflet of an endosomal membrane, resulting in the stabilization of the hemifusion structure of the host endosomal-viral membrane with increased membrane rigidity, which thus prevents pore formation and traps viruses inside the endosome (3). During these events, negative membrane curvature was facilitated by the presence of cholesterol. Although the amphipathic helix of IFITM3 has been reported to interact directly with cholesterol (21), the detailed impact of IFITM3-mediated cholesterol accumulation on a "virus-trap" remains to be elucidated. Interferon also induces the expression of IFITM3 in immune cells, including B- and T-cells. IFITM3-Tyr20 is phosphorylated by Src family kinases upon the activation of BCR signaling, inducing the accumulation of IFITM3 that forms the BCR complex on the cell surface. In this case, basic amino acids in the conserved intracellular loop (CIL) domain of IFITM3 provide electrostatic charge to bind to negatively charged phosphatidylinositol (3,4,5)-trisphosphate (PIP3) that was transiently synthesized by BCR, hence IFITM3 concentrates PIP3 in proximity to active BCR complex on lipid rafts and promotes PIP3-mediated signaling cascades including PI3K/AKT, BTK and PLCγ. Therefore, IFITM3 plays a central role in BCR-mediated B-cell activation. Furthermore, the cholesterol-dependent structural stability of lipid raft, a cholesterol-rich microdomain, is essential for BCR activation (22). Therefore, the role of the amphipathic helix of IFITM3 as a cholesterol-binding motif on cell surfaces is currently under investigation.

IFITM3 expression has been reported to be elevated by pro-inflammatory cytokine signaling, including IL-1, IL-6, and Oncostatin M (OSM), in addition to interferon (23). IL-1 is mainly secreted by monocytes and macrophages and is known as the master proinflammatory cytokine that regulates local and systemic inflammation and thus plays an important role in immune responses against foreign antigens and in autoimmune diseases (24). Pyroptosis, a form of necrotic and highly inflammatory programmed cell death, is triggered by cytopathic viruses, including SARS-CoV-2 as part of the viral replication cycle. Infection and replication of cytopathic viruses could cause caspase-1-mediated pyroptosis, triggering a wave of local inflammatory responses through the release of inflammatory cytokines, including IL-1β, which has been cleaved into a biologically active form by caspase-1 during a process of pyroptosis (25). As a result, augmented local concentrations of IL-1β contribute to cytokine storms with local tissue damage observed in COVID-19 patients (26). Therefore, patients with severe COVID-19 outcomes exhibits higher levels of IL-1β compared to patients with mild symptoms (27). Uncontrolled inflammation is known to predispose individuals to various types of cancer, which is highly implicated in approximately 15% to 20% of all human cancers (28). IL-1-mediated chronic inflammatory conditions exert a critical role in initiation, progression, and metastasis (29-31). IL-1 has been reported to be overexpressed in several tumors including melanoma, pancreatic, breast, colon, head and neck, and lung cancer. IL-1 helps to maintain the accumulation of reactive oxygen species (ROS), and nitric oxide (NO) that cause genomic instability and mutations (32). Therefore, patients with IL-1 producing tumors have been associated with poor prognosis (33). In B-cell malignancies, IL-1 promotes the conversion of indolent to active multiple myeloma (MM) cells. Autocrine or paracrine production of IL-1 increase IL-6 in the environment of bone marrow (BM) and functions as a key growth factor for MM via activation of JAK/STAT- and the GTPase/mitogen-activated protein kinase (RAS/MAPKs)-signaling pathway (34). However, the role of IFITM3, mediated by pro-inflammatory signaling from IL-1 and IL-6, in different tumor types has not yet been investigated.

In response to infections, IL-6 is primarily secreted by plasmacytoid dendritic cells (pDCs), which play a critical role in the differentiation of B cells into antibody-secreting plasma B cells (35). IL-6, a pro-inflammatory cytokine, plays a vital role in mediating innate and adaptive immune responses by promoting monocyte infiltration into the site of infection, resulting in inhibition of Treg activation (36) and induction of differentiation of Th17 and T follicular helper cells (Tfh) that play a critical role in germinal center formation and affinity maturation of B cells (37). In addition to modulating inflammation and hematopoiesis through well-controlled immune responses, IL-6 is a major contributor to uncontrolled chronic inflammation, including autoimmune diseases, infectious diseases, and cancers including colon, prostate, breast, pancreatic, ovarian,

melanoma, and lung adenocarcinoma, hepatocellular carcinoma and hematologic malignancy (38). Therefore, elevated IL-6 levels are correlated with poor prognosis and metastasis (39). Hyperactivation of the JAK/STAT3 signaling pathway is considered to be the main cause of IL-6-induced tumorigenesis, but the contribution of IL-6-mediated IFITM3 expression to inflammatory-triggered tumorigenesis has not yet been investigated.

MOTIFS, DOMAINS, AND POST-TRANSLATIONAL MODIFICATION OF IFITM3

IFITM3 is a molecular barrier that blocks viral fusion with host cell membrane by altering curvature and stiffness of membrane. The function of IFITM3 is highly dependent on its motifs, domains, and post-translational modifications.

Although the topology of IFITM3 varies in different cell types, IFITM3 is a type 2 transmembrane protein composed of cytoplasmic N-terminus (amino acids, 1 to 57), intramembrane domain (amino acids, 58 to 80), CIL as a novel PIP3-binding motif, transmembrane domain (amino acids, 108 to 128), and short extracellular C-terminus (amino acids, 128 to 133) in B cells (14). Phosphorylation at Y20 blocks the interaction of ^{20}YEML^{23} with binding to the μ2 subunit of the AP-2 complex because intact tyrosine at YxxΦ endocytosis motif (where X is any amino acid and Φ represents amino acids with hydrophobic side chains such as Val, Leu, or Ile) is necessary for endocytosis through AP-2 clathrin-mediated endocytic adaptor protein. Therefore, phosphorylation at Y20 by Src family kinases, including Fyn or Lyn, disrupts endocytosis of IFITM3 leading to relocation on the cell surface and resulting in reduced antiviral activity at endosomal membrane (7).

In addition, intact Y20 plays an important role in the degradation through ubiquitination of IFITM3. The E3 ubiquitin ligase NEDD4 binds to ^{17}PPNY^{20} motif, a conserved PPxY motif, and induces ubiquitination at K24, K83, K88, and K104 to promote the degradation of IFITM3. Therefore, phosphorylation of Y20 accumulates IFITM3 on cell surface by blocking endocytosis and increasing stability (7, 14). Although phosphorylation at Y20 plays an important role in the function of IFITM3, the phosphatase that mediates dephosphorylation of Y20 is still unknown.

S-palmitoylation of IFITM3 occurs at conserved cysteine residues at C71, C72, and C105 by palmitoyltransferases including ZDHHC3, ZDHHC7, ZDHHC15, and ZDHHC20, which increases hydrophobic affinity promoting anchoring of the amphipathic helix to cell membrane (40). Two phenylalanines, F75 and F78, located in the intramembrane domain of IFITM3, when expressed on the membrane, could allow IFITM3 to physically interact with other IFITM family members (41). Although it was necessary for the restriction of orthomyxovirus, the function of the CIL motif at position (amino acids, 81 to 108) between the intramembrane domain and the transmembrane domain is not well understood. Interestingly, it was recently identified that five basic amino acids including K83, R85, R87, K88 and K104 interacts with negatively charged phospholipids such as phosphatidylinositol 4,5-bisphosphate (PIP2) and PIP3. In particular, K83 and K104 preferentially interact with negatively charged PIP3 over PIP2 through electrostatic interaction at membrane-solution interface, allowing IFITM3 to efficiently accumulate PIP3 on lipid rafts where the PI3K signaling complexes reside in B cells (14). However, the role of the five basic amino acids K83, R85, R87, K88, and K104 as the PIP3-scaffolding motif has not yet been explored in other cancers.

IFITM3-MEDIATED ONCOGENIC SIGNALING PATHWAYS

B-cell malignancies

The signaling of (pre)-B cell receptor (BCR) or its oncogenic mimics such as BCR-ABL1 is critical to the development of several B cell malignancies, including acute lymphoblastic leukemia, diffuse large B cell lymphoma, Burkitt's lymphoma, follicular lymphoma, marginal zone B-cell lymphoma, and mantle cell lymphoma (42).

Upon antigen binding to BCR, BCR translocate into lipid raft, a cholesterol-rich membrane microdomain, initiates signalling cascades. Cross-linking of BCR by antigen triggers activation of spleen tyrosine kinase (SYK), Bruton agammaglobulinemia tyrosine kinase (BTK) and Src family kinase such as Lyn and Fyn (22). Subsequently, activated Src family kinases phosphorylate several co-receptors including CD19, a well-known B-cell marker that functions as a BCR-coreceptor and positively regulate BCR signaling. Phosphorylation of CD19 at YXXM motifs in its cytoplasmic domain by Lyn allows recruitment of the tandem SH2 domains of phosphatidylinositol 3-kinase (PI3K) p85 regulatory subunit (43), resulting in the release of catalytic subunit p110 from tonic inhibition. PI3 kinase then catalyzes the production of phosphatidylinositol-3, 4, 5-triphosphate (PIP3) by adding phosphate to phosphatidylinositol-4, 5-bisphosphate (PIP2). Negatively charged PIP3 in inner lipid bilayer serves as a docking site to recruit AKT serine/threonine kinase via positively charged interface of Pleckstrin homology (PH) domain to the lipid raft, resulting in the subsequent activation of signaling cascades at the site of BCR-Ag ligation. PIP3 also recruits BTK through its PH domain, resulting in calcium flux and cellular activation essential for BCR-induced positive selection of normal B cells and for the survival and proliferation of malignant B cells (44-46).

The PH domain, characterized by a 7-stranded β-barrel followed by a C-terminal α-helix with a positively charged pocket targeting anionic PIP headgroups, consists of approximately 120 amino acids and shows low sequence conservation (47). In contrast to the PH domain, IFITM3 harbors a phospholipid-binding motif within a CIL motif located at the membrane-solution interface consisting of only 28 amino acids, including five basic amino acids that provide electrostatic interactions with negatively charged PIP3, and to a lesser extent, PIP2. In normal resting B cells, IFITM3 was mainly localized in endosomal

membrane. However, activation of Src family kinases upon B cell activation phosphorylates IFITM3 at Y20, blocks binding of IFITM3 to endocytosis machinery and thereby induces accumulation of IFITM3 on surface, leading to the formation of IFITM3-CD19-BCR complex at surface (Fig. 1). The PIP3-scaffoding capacity of IFITM3 induces massive accumulation of PIP3 proximal to the BCR-signalosome and amplifies BCR-signaling within lipid rafts. Therefore, IFITM3 enables B-cell activation, development of B1- and marginal-zone B-cells, and affinity maturation for the generation of antigen-specific antibodies in the germinal center (14).

In B cell leukemia, oncogenic kinases that mimic BCR signaling phosphorylate IFITM3 at Y20 in the absence of antigen, causing accumulation and interaction of IFITM3 with BCR, PI3K signaling elements, and integrin receptors on the surface. Therefore, IFITM3 positively regulates BCR, PI3K, and integrin signaling, thus enabling proliferation, survival, and self-renewal of malignant B cells and contributing to the initiation of transformation of premalignant B cells *in vivo*. In line with this, IFITM3 was identified as a top-ranking predictor of poor clinical outcomes in six clinical cohorts, including pediatric and adult B-ALL and mantle cell lymphoma (14).

In addition to PIP3 binding, IFITM3 was recently reported to bind to cholesterol via F63 and F67 within its amphipathic helix, amino acids 56 to 69. Interestingly, point mutations (F63Q and F67Q) of IFITM3 disrupted antiviral function against Influenza A virus (IAV) (48) suggesting that cholesterol accumulation via amphipathic helix of IFITM3 plays a crucial role by enhancing membrane stiffness, altering membrane curvature and fluidity (49). Given that CD19/PI3K/AKT signaling in B cells depends on cholesterol-dependent lipid raft stability (50), it would be intriguing to look into how IFITM3-dependent cholesterol accumulation and PIP3 in lipid rafts affect immunological response, inflammation, and leukemogenesis.

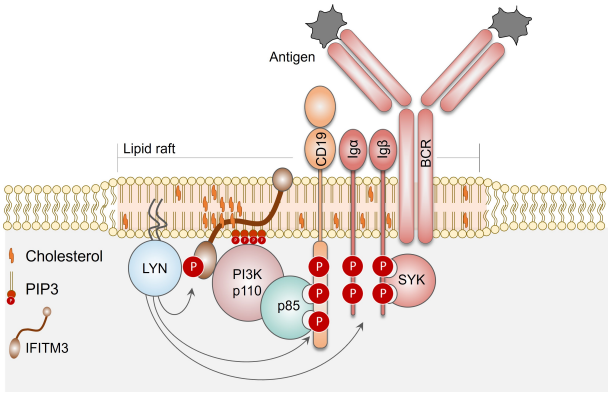

Fig. 1. Activated BCR signaling or its oncogenic mimics activate SRC family kinases such as LYN, resulting in phosphorylation of CD19-Y482/513 and IFITM3-Y20. Phosphorylated tyrosine residues on CD19, which provide docking sites for the SH2 domains of the PI3K regulatory subunit p85, facilitates localization and activation of PI3K to the lipid raft on plasma membrane. Transiently synthesized PIP3 by the PI3K catalytic subunit p110 stably accumulated by IFITM3 at the BCR signalosome. IFITM3, therefore, stabilizes the BCR signalosome, supports PIP3-mediated recruitment of downstream effector molecules such as BTK and ATK, enhances BCR signaling or BCR-mimicking oncogenic signaling. The effect of the amphipathic helix of IFITM3-mediated cholesterol accumulation at lipid raft on BCR signaling has not yet been investigated.

Breast cancer

It was identified that IFITM3 expression was significantly upregulated in invasive breast ductal carcinoma tissue specimens compared to non-invasive breast cancer specimens, while IFITM3 was not detected in normal specimens. In MCF-7 and MDA-MB-231 cells, lentiviral shRNA knockdown of IFITM3 expression resulted in lowered cell growth, altered cell cycle progression, and diminished capacity for self-renewal (51). However, detailed oncogenic mechanism driven by IFITM3 is still missing in breast cancer. Interestingly, several genetic aberrations associated with genes involved in PI3K signaling pathway have been identified in breast cancer. For instance, gain-of-function mutations of the PIK3CA gene that encodes p110α subunit, are the most common genetic aberrations in breast cancer and have been found in 30% to 40% of hormone receptor-positive (HR^+) or HER2-positive breast cancer and approximately 9% of triple-negative breast cancer (TNBC) (52). Instead of the gain-of-function mutation, it has been observed that TNBC tumors exhibit PTEN and INPP4B gene inactivation mutations (53). In addition, abnormal activation of integrin has been implicated in the pathology of metastasis in human breast cancer (54). These results suggest that IFITM3 as a PIP3 scaffold may potentially contribute to the development and progression of breast cancer.

Colon cancer

IFITM3 is highly expressed in colon tumors compared to normal colon tissue through Krupple-like factor 4 (KLF4)-mediated transcriptional regulation. KLF4 is a transcription factor that plays a crucial role in colon cancer progression and metastasis. KLF4 bound specifically to IFITM3 promoter and resulted in aberrant IFITM3 expression. It is known that KLF4 interacts with beta-catenin and inhibits Wnt/β-catenin signaling by blocking recruitment of the transcriptional coactivator p300/CBP. However, the exact mechanism of IFITM3 related to Wnt/β-catenin signaling has not yet been identified, although knockdown of IFITM3 suppressed colon cancer proliferation, colony formation, migration, and invasion. Although the Wnt/β-catenin signaling pathway is the most studied as a driver of colon cancer development, mutations in PI3KCA were significantly correlated with poor clinical outcomes (55). Interestingly, IL-6, proinflammatory cytokine, and integrin receptors such as α5β1, α5β6 are indicators of poor prognosis in patients with coloron cancer (56). Blockade of PI3K signaling leads to downregulation of integrin α5β1, thereby suppressing cell attachment and increasing apoptosis (57). Although chronic inflammation is an

important risk factor for the development of colon cancer, the molecular mechanisms by which oncogenic signaling mediates inflammation to coloron cancer are still unknown (58). Therefore, the pathogenic effects of abnormal activation of IFITM3/PI3K/Integrin signaling upon IL-6-mediated inflammatory response need to be elucidated.

Gastric cancer

In gastric cancer, dysregulated integrin-related signaling pathway, such as focal adhesion kinase (FAK), p21-activated kinase (PAK) triggers epithelial-mesenchymal transition (EMT) (59-61). Interestingly, in B cell malignancies, IFITM3 localized on surface interacts with integrins and strongly induces phosphorylation of PAK1/3 at Ser192/204 and FAK at Tyr576/577 (14). Invasive gastric cancer tissues were reported to overexpress IFITM3 in immunohistochemistry, while IFITM3 was negatively or weakly detected in adjacent normal tissue. Knockdown of IFITM3 with shRNA in GC cell lines negatively regulates proliferation, and inhibits cell migration, suggesting that IFITM3 is a potential oncogene in human GC. However, the role of IFITM3 in the context of integrin signaling pathway in gastric cancer has not yet been investigated.

Lung cancer

Abnormal expression of integrin receptors such as α5β1, αvβ3 and αvβ6 is known as poor prognostic marker in non-small cell lung cancer (NSCLC). Interestingly, IL-8, a pro-inflammatory cytokine, was overexpressed in lung tissue through integrin αvβ6-mediated MAPK/ERK signaling pathway, thereby promoting tumor growth and metastasis (62). In addition, Integrin β1 promoted tumorigenesis of lung adenocarcinoma via extracellular matrix (ECM)-independent FAK activation (63, 64). Integrin-ECM adhesion also activates PI3K, catalyzes PIP3 production, and recruits Integrin-linked kinase (ILK), a serine-threonine kinase with the PH domain that promotes NSCLC proliferation, survival, and invasion. Given that IFITM3 amplifies PI3K signaling by acting as a PIP3 scaffold protein, IFITM3 is expected to be involved in oncogenic signaling. In lung adenocarcinoma, IFITM3 was positively detected in malignant stages but not in early-stage of cancer samples in immunohistochemistry. Knockdown of IFITM3 with shRNA in H1299 cells inhibited cell proliferation, invasion, and migration (65). However, the exact mechanism of how IFITM3 contributes to proliferation and migration remains to be elucidated.

Hepatocellular carcinoma

In hepatocellular carcinoma (HCC), IFITM3 positively regulated expression of MMP9 via p38/MAPK pathway, which led to induction of invasion and metastasis of HCC *in vivo*. Accordingly, HCC patients with high level of IFITM3 showed worse clinical outcomes than HCC patients with low level of IFITM3. IFITM3 positively regulated phosphorylation of p38 at T180 and Y182, however, the mechanism by which IFITM3 was involved in activation of p38/MAPK has not yet been identified. The role of IFITM3 as a PI3K amplifier should be investigated since abnormal activation of PI3K/AKT/mTOR signaling is observed in approximately 50% of HCC patients (66).

Prostate cancer

It was found that IFITM3 expression was abnormally elevated in prostate cancer cells, which was positively correlated with poor prognostic grades. In prostate cancer cell lines, IFITM3 positively regulated proliferation and survival via activation of p38/MAPK signaling pathway (67). In this study, IFITM3-Smad4 complex promoted bone metastasis of prostate cancer cells by activating TGF-β-Smads-MAPK signaling pathway, which induces EMT of epithelial tumor cells. However, no evidence was shown on how IFITM3 interacts with Smad4 and how the IFITM3-SMAD4 complex activates TGF-β/MAPK signaling pathway. Deregulation of PI3K/AKT/mTOR signaling pathway derived from genetic alterations such as PIK3CA/PIK3C2B mutation/amplification, PTEN deletion/mutation, DEPTOR amplification, SGK mutation/amplification and FOXO deletion has been shown to correlated with poor clinical outcomes and found almost 100% of metastatic prostate cancer (68), suggesting that the pleiotropic function of IFITM3 potentially involved in the development of prostate cancer via TGF-β/MAPK and PI3K signaling pathway needs to be investigated.

CONCLUSION

It is now clear that an excessive inflammatory response plays a crucial role in carcinogenesis. In addition to inflammation caused by extrinsic factors such as infection, intrinsic factors such as activation of oncogenes, including members of the RAS family and MYC, which are the most frequently mutated oncogenes in cancer, including B-cell malignancies, could be the source of inflammation (69). Expression of an antiviral protein, IFITM3, is regulated by both intrinsic and extrinsic factors, and affects cancer proliferation, metastasis, and EMT signaling pathways. It is also known as a biomarker to predict poor clinical outcomes in various cancer types. Until today, IFITM3 has primarily been studied in relation to viral immunity, but further research is needed to understand its oncogenic function as a PIP3 scaffold protein.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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