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REVIEW

Unraveling the Biology of Interferon-Stimulated Genes: Mechanisms, Functions, and Clinical Implications

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Abstract: Interferon-stimulated genes (ISGs) constitute a central component of host defense, orchestrating antiviral, antibacterial, immunoregulatory, and cell fate–modulating responses. Traditionally recognized for their roles in restricting viral replication through well-characterized effectors such as Mx proteins, OAS, PKR, and the IFIT/IFITM families, ISGs are now understood to possess broader biological functions. Emerging evidence reveals their involvement in host–microbe interactions, tumor immunosurveillance, metabolic regulation, autophagy, and tissue repair. These diverse activities position ISGs as context-dependent immune regulators rather than mere antiviral effectors. This review synthesizes current knowledge on the canonical and noncanonical functions of representative ISG families, highlights their regulatory networks and evolutionary origins, and discusses their relevance to infectious, inflammatory, and malignant diseases. We further examine the therapeutic potential of targeting ISG pathways and explore their utility as biomarkers for diagnosis, prognosis, and treatment stratification. By integrating mechanistic insights with translational perspectives, this review provides a comprehensive understanding of ISGs as dynamic mediators at the interface of immunity, infection, and disease.

Keywords: interferon, interferon-stimulated genes, antiviral, biomarkers, immune response

Introduction

Interferon (IFN), first identified in 1957 as a biologically active molecule that inhibits viral replication, initiates antiviral and immunomodulatory responses through interaction with specific cell surface receptors.[1] This interaction activates downstream signaling pathways, ultimately inducing the expression of hundreds of interferon-stimulated genes (ISGs).[2] These ISGs are primarily regulated by IFN-activated transcription factors, especially members of the STAT family, and encode classical antiviral effectors (such as MX1, OAS, PKR, ISG15), modulators that maintain the antiviral state, and regulators of immune signaling.[3,4]

The kinetics and magnitude of ISG induction differ among IFN subtypes: type I IFNs (eg, IFN-α/β) typically induce rapid and robust ISG expression, whereas type III IFNs (eg, IFN-λ) elicit a slower and more localized response. Moreover, different cell types display unique ISG expression profiles following IFN stimulation, reflecting cell-type-specific antiviral strategies and functional specialization.[5,6]

Beyond their well-established antiviral functions, recent research indicates that ISGs also participate in antibacterial defense, tumor immunosurveillance, metabolic regulation, and autoimmune diseases. These findings highlight ISGs not merely as antiviral effectors, but as context-dependent regulators of host immunity and cellular homeostasis.

This review summarizes the canonical and noncanonical functions of major ISG families, delineates their regulatory networks and evolutionary context, and discusses their implications in infectious, inflammatory, and malignant diseases, with emphasis on their potential as biomarkers and therapeutic targets.

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The Origin of ISGs in Evolution

The evolution of the interferon system is characterized by the diversification of both interferon receptors and interferon-stimulated genes (ISGs). Approximately three decades after the initial discovery of interferons (IFNs), researchers identified a membrane-bound receptor complex that binds IFNs, subsequently named the interferon receptor. In 1984, it was determined that IFN-α and IFN-β interact with a specific receptor known as the type I interferon receptor (IFNAR), whereas IFN-γ associates with the type II interferon receptor (IFNGR).[7] More recently, a third receptor complex, the type III interferon receptor (IFNLR), has been identified. The expression of IFNLR is primarily restricted to epithelial cells, hepatocytes, and certain leukocyte subsets.

Comparative genomic analyses indicate that approximately 10% of human genes may be regulated by interferon (IFN) signaling pathways.[8] Upon ligand engagement, IFNs initiate JAK–STAT signal transduction cascades, leading to the transcriptional activation of downstream ISGs.[9] The proteins encoded by ISGs fulfill a diverse array of biological functions, encompassing antiviral, antibacterial, and immunomodulatory activities. These proteins can operate independently or synergistically to disrupt various stages of the viral lifecycle, including entry, genome replication, assembly, and egress. Furthermore, certain products of ISGs provide feedback regulation of the IFN signaling pathway itself, thereby modulating immune responses.[10]

Phylogenetic and functional analyses of ISGs families have revealed substantial variations in signaling characteristics among different IFN subtypes. Although IFN receptors are ubiquitously expressed, the induction of ISGs demonstrates notable specificity to particular cell types. A subset of "robust" ISGs consistently responds to all IFN subtypes and is activated even at low IFN concentrations. Conversely, "tunable" ISGs exhibit subtype-specific induction, requiring higher IFN doses and often displaying restricted expression to specific cell types. Recent single-cell RNA sequencing studies have identified a core ISG signature, comprising genes that are broadly expressed across various cell types and encode essential antiviral effectors.[11–13]

Classification and Function of ISGs

ISGs Family Classification

The proteins encoded by ISGs exhibit significant diversity in both structure and function. DNA microarray analyses of cells treated with interferons have uncovered a comprehensive transcriptional response involving over 300 ISGs,[14,15] rendering an exhaustive classification based on simple structural or functional criteria impractical. In this review, we focus on key members of the ISG family, elucidating both their well-established and recently identified roles. ISGs can be broadly categorized based on their contributions to innate immunity and the molecular mechanisms they employ. These categories include antiviral effectors, such as members of the large GTPase, OAS, protein kinase, four-repeat protein, and TRIM families, along with various other antiviral molecules; metabolic and immunoregulatory factors, exemplified by PLSCR1; and ubiquitin-like modifiers and de-modifiers, such as ISG15 (Table 1).

Functions of ISGs Family

Antiviral Effector Proteins

The antiviral Mx proteins were among the first ISGs to be characterized, initially identified for their role in conferring resistance to inhaled influenza A virus.[16] Mx genes are conserved across vertebrates, ranging from fish to primates, and encode dynamin-like GTPases that act as critical effectors of the type I/III interferon system by inhibiting the early stages of viral replication, thereby preventing genome amplification. In humans, two paralogs, MxA and MxB, are expressed, whereas mice possess the Mx1 and Mx2 counterparts.[17] Mx proteins demonstrate broad-spectrum antiviral activity against a variety of RNA and DNA viruses, including HIV-1, HBV, HCV, and HSV-1.[18–21] Beyond their classical antiviral functions, recent studies have expanded the role of Mx proteins into oncology and immunology. Mx1 has been shown to regulate apoptosis and autophagy in prostate cancer cells,[22] while immunohistochemical detection of MxA surpasses conventional markers in diagnosing dermatomyositis.[23] Furthermore, MxA expression in juvenile dermatomyositis correlates with disease activity and autoantibody status.[24]

Table 1 Classification and Signal Transduction of ISGs

Type	Members	Signaling Pathway
Antiviral effectors	Large GTPases: GBP1, Mx1 (MxA)	RIG-I/MDA5-MAVS-TBK1-IRF3/7
	OAS Family: OAS1, OAS2, OAS3	cGAS-STING-TBK1-IRF3
	Protein Kinase: PKR (EIF2AK2)	PKR-eIF2α phosphorylation
	IFIT Family: IFIT1, IFIT2, IFIT3, IFIT5	NF-κB activation
	TRIM Family: TRIM5, TRIM22, TRIM25	JAK1/TYK2-STAT1/STAT2
Metabolic and Immunoregulatory Factors	PLSCR1, NO2, IDO1, SAMHD1, CD74	JAK–STAT (STAT1/STAT2)
		SREBP/LXR (cholesterol metabolism)
		Aryl hydrocarbon receptor (AhR) signaling
		NF-κB
Ubiquitin-like Modification Enzymes	ISG15, USP18 (UBP43), UBE1L, HERC5	ISGylation of target proteins (eg, RIG-I, IRF3, STAT1)
		USP18-mediated negative feedback on IFNAR signaling
		JAK-STAT modulation
		NF-κB/IRF pathways

Note: "-": Signaling axis.

And, in pre-treatment biopsies of rectal cancer, combined assessment of tumor-infiltrating CD8+ lymphocytes and MxA+ cell density stratifies neoadjuvant therapy response more effectively than standard immunoscores[25] (Figure 1).

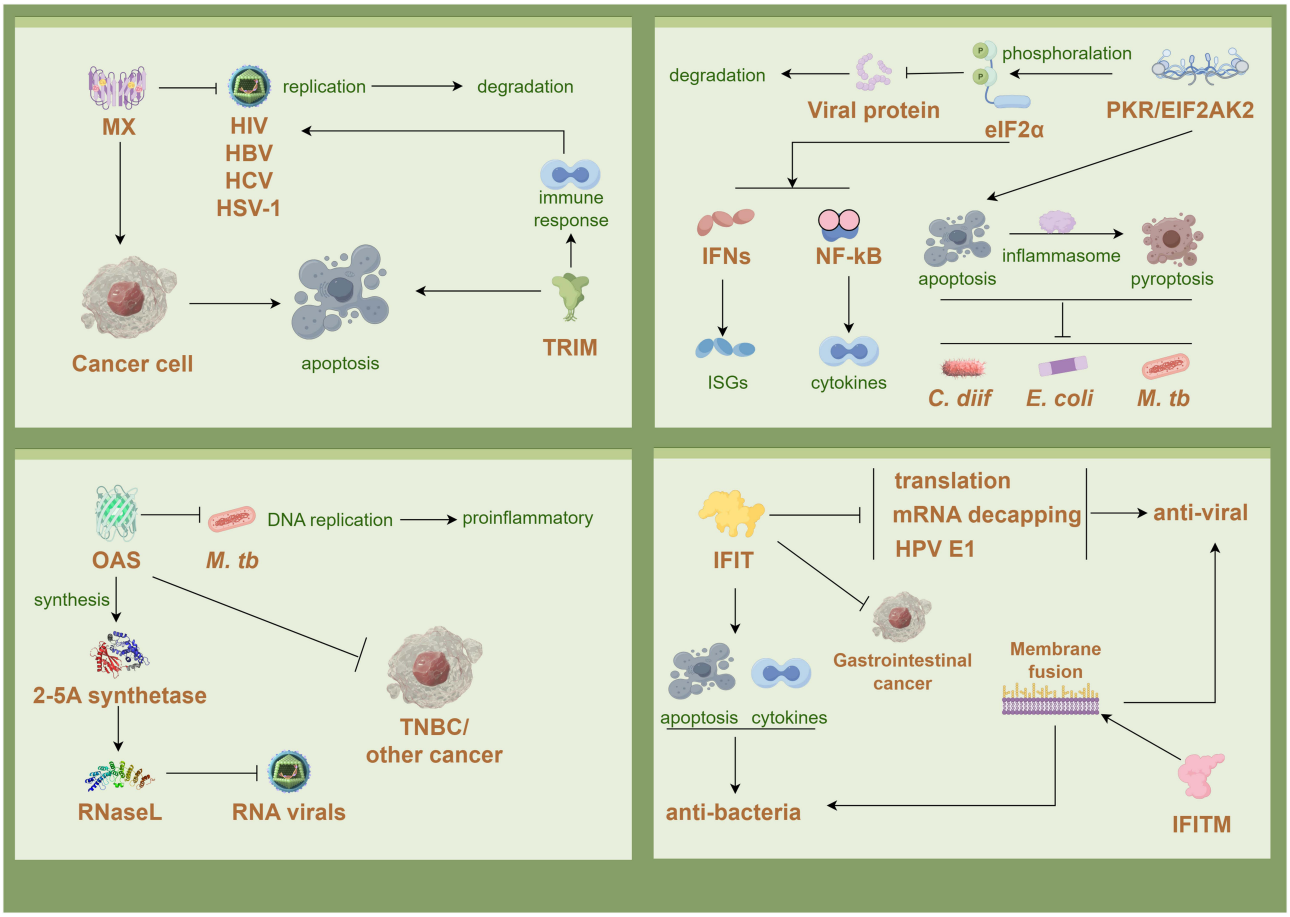

Figure 1 Schematic of the Antiviral and Antibacterial Mechanisms of Key ISGs. MX–TRIM–mediated antiviral and pro-apoptotic pathway. KR/eIF2AK2-dependent translation inhibition and inflammatory signaling. OAS–2-5A synthetase–RNase L antiviral and antibacterial pathway. IFIT and IFITM Dual-Layer defense.

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The 2′–5′ oligoadenylate synthetases (OAS) constitute an evolutionarily conserved family of interferon-induced nucleotidyltransferases, comprising four functional genes (OAS1, OAS2, OAS3, and OASL) situated on chromosome 12.[26] Within the cytosol, OAS enzymes facilitate the synthesis of 2′–5′ oligoadenylates, which in turn activate RNase L, thereby conferring broad-spectrum antiviral activity against a wide array of RNA viruses and certain DNA viruses, most notably the hepatitis C virus (HCV) and related hepatic pathogens.[27] Genetic polymorphisms in OAS1 have been associated with the severity of COVID-19,[28] and population-specific variants of OAS influence the progression of endemic infectious diseases in Africa. In oncological research, variations in OAS expression are utilized as prognostic and immunological biomarkers across diverse cancer types.[29,30] For instance, elevated OAS expression in basal-like, immune-activated triple-negative breast cancer is associated with improved overall survival (OS), disease-free survival (DFS), and distant metastasis-free survival (DMFS).[31] Furthermore, OAS proteins are implicated in restricting the intracellular replication of *Mycobacterium tuberculosis* (*M. tuberculosis*) and in promoting cytokine secretion in infected cells,[32,33] with the OAS1 rs1131454 G allele providing a protective effect against tuberculosis in the Han Chinese population.[34]

Protein kinase R (PKR; EIF2AK2) is an interferon-induced serine/threonine kinase that is activated by double-stranded RNA, as well as by cytokines, growth factors, and various cellular stresses.[35] Upon activation, Protein Kinase R (PKR) phosphorylates eukaryotic initiation factor 2 alpha (eIF2α), thereby inhibiting the initiation of translation and subsequently suppressing viral protein synthesis. Concurrently, PKR activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), resulting in the upregulation of interferons and ISGs. Beyond its antiviral role, PKR is implicated in the regulation of metabolic processes, inflammatory responses, tumorigenesis, and neurodegenerative conditions. While PKR's ability to inhibit hepatitis C virus (HCV) replication suggests a potential tumor-suppressive function, paradoxically, its overexpression in cirrhotic liver tissue facilitates the progression of hepatocellular carcinoma via the mitogen-activated protein kinase (MAPK) pathway and other mechanisms. In the context of acute myeloid leukemia, the nuclear localization of PKR disrupts the DNA damage response, correlating with poor prognosis and accelerated disease progression in NHD13 mouse models.[36] In chemoresistant ovarian cancer, PKR influences mitotic processes and suppresses the Bcl-2 pathway, thereby enhancing sensitivity to paclitaxel. Preclinical studies indicate that the Bcl-2 inhibitor venetoclax can overcome this resistance.[37] Moreover, PKR facilitates apoptosis and inflammasome activation, leading to pyroptosis and exerting antibacterial effects against both Gram-positive and Gram-negative bacteria, as well as *Mycobacteria*.[38–41] It also modulates key cytokines involved in antibacterial defense.[42] The antimicrobial agent nitazoxanide promotes PKR phosphorylation and has shown in vivo efficacy against *Clostridioides difficile, Escherichia coli, Mycobacterium leprae*, and *M. tuberculosis*,[43–46] presenting a novel strategy for addressing bacterial infections.

The IFIT family, comprising IFN-induced proteins with tetratricopeptide repeats (namely IFIT1, IFIT2, IFIT3, and IFIT5), together with the IFITM proteins (interferon-induced transmembrane proteins), constitutes a crucial group of ISGs that impede viral entry or replication through various mechanisms. These proteins are effective against a wide array of pathogens, including the Japanese encephalitis virus (JEV), influenza virus, hepatitis B virus (HBV), human papillomavirus (HPV), hepatitis C virus (HCV), West Nile virus (WNV), and adenovirus.[47–52] Although typically expressed at low basal levels, IFITs and IFITMs are significantly upregulated in response to type I and III interferons and the pattern recognition receptor (PRR)–JAK/STAT signaling pathways. The transcription of these proteins is initiated by viral RNA or DNA, and their functions encompass the inhibition of translation initiation, sequestration of uncapped RNA, and cytosolic entrapment of viral proteins, such as the E1 protein of HPV.[53] Recent studies have also implicated IFITs in antibacterial defense mechanisms; for instance, IFIT1 expression is upregulated during Vibrio parahaemolyticus infection,[54] and miR-645 has been shown to promote gastric cancer progression associated with Helicobacter pylori by targeting the tumor suppressor IFIT2. IFIT3, originally identified as IRG2 in endotoxin studies,[55] is upregulated in response to a wide array of viral infections, including those caused by JEV, cytomegalovirus (CMV), polyomavirus, herpes simplex virus type 1 (HSV-1), HCV, human parainfluenza virus (HVJ), vesicular stomatitis virus (VSV), Kaposi's sarcoma-associated herpesvirus (KSHV), respiratory syncytial virus (RSV), and SARS-CoV-2.[56–58] And, by modulating immune molecules, exerting direct antimicrobial activity, enhancing host defenses, and inducing apoptosis, can distinguish active from latent tuberculosis in PBMCs with an AUC of 0.918, highlighting its biomarker potential.[59]

In the context of tumor immunosurveillance, IFIT2 expression is reduced in lung adenocarcinoma and squamous cell carcinoma, where its diminished expression serves as an independent predictor of poor prognosis in non-small cell lung cancer (NSCLC). Similar correlations with disease progression and adverse outcomes have been reported in gastric, oral, and esophageal cancers.[60–63] Comprehensive bioinformatics analyses have identified IFIT1, IFIT2, IFIT3, ISG15, MX1, and RSAD2 as central genes for the early diagnosis of tuberculosis.[64] In the realm of bacterial infections and inflammation, key ISGs identified in rheumatoid arthritis patients with *Staphylococcus aureus* (*S. aureus*) bacteremia include RSAD2, IFIT3, GBP1, RTP4, IFI44, OAS1, IFI44L, ISG15, and HERC5, with IFI44, OAS1, IFI44L, ISG15, and HERC5 acting as common markers across rheumatoid arthritis, COVID-19, and *S. aureus* bacteremia. Notably, IFI44 facilitates pathogen immune evasion by negatively regulating interferon signaling.[65] In a model of *S. aureus* osteomyelitis, interferon beta released by osteoblasts initiates autocrine and paracrine induction of ISGs—including IFIT1, IFIT3, SLFN2, IRGM2, MX2, PLSCR1, IFI205, and IGTP—to reduce intracellular bacterial load and mitigate infection.[66]

Interferon-induced transmembrane proteins, specifically IFITM1, IFITM2, and IFITM3, represent a vital category of ISGs-encoded effectors. These proteins exert antiviral effects by modifying membrane lipid composition and biophysical properties, thereby impeding viral entry and egress during the membrane fusion phase, which culminates in broad-spectrum antiviral activity.[67] IFITM1 is predominantly localized at the plasma membrane, and its overexpression has been demonstrated to inhibit infections by enveloped viruses that fuse at the cell surface, including paramyxoviruses such as respiratory syncytial virus (RSV) and mumps virus, pneumoviruses like human metapneumovirus (HMPV), and enveloped DNA viruses such as herpes simplex virus type 1 (HSV-1).[68] In contrast, IFITM3 is particularly critical for the in vivo control of influenza A virus.[69] Beyond their antiviral roles, IFIT family proteins are also involved in antibacterial defense and host immunity. For example, in a murine model of Staphylococcus aureus-induced osteomyelitis, osteoblasts upregulate IFIT1 and IFIT3 to combat bacterial infection.[66]

Members of the tripartite motif (TRIM) family, distinguished by a conserved RBCC domain, have been recognized as significant ISGs with robust immunomodulatory and antiviral capabilities. Noteworthy members such as TRIM5, TRIM19, TRIM22, and TRIM25 are involved in various cellular processes, including differentiation, apoptosis, and innate immune signaling. Recent research has identified TRIM14 as a pivotal regulator of type I interferon (IFN) responses. TRIM14 inhibits hepatitis C virus (HCV) replication by modulating pattern-recognition receptor signaling and directly targeting the viral NS5A protein. Elevated expression of TRIM14 is associated with rapid viral clearance, indicating its potential role in preventing hepatocellular carcinoma.[70] Furthermore, TRIM14 has been shown to suppress the replication of hepatitis B virus (HBV) and influenza A virus[71,72] and serves as a crucial factor in restricting *M. tuberculosis* during bacterial infection.[73]

Metabolic and Immune Regulatory Factors

Phospholipid scramblase 1 (PLSCR1) is a calcium-binding protein that is induced by interferons and growth factors, enhancing the antiviral efficacy of interferons, partly through the upregulation of specific antiviral ISGs.[74] PLSCR1 exhibits a broad-spectrum antiviral activity, restricting various viruses such as hepatitis C virus (HCV),[75] hepatitis B virus (HBV),[76] human T-cell leukemia virus type 1 (HTLV-1),[77] human immunodeficiency virus type 1 (HIV-1),[78] influenza A virus, Epstein-Barr virus (EBV),[79] and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[80] through multiple mechanisms. In murine lung tissue, PLSCR1 modulates innate type-2 immune responses via a chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2)-dependent pathway, demonstrating therapeutic potential in chronic inflammatory conditions such as asthma.[81] During Staphylococcus aureus infection, PLSCR1 facilitates interferon-mediated protection against staphylococcal α-toxin.[82] Beyond its antiviral roles, PLSCR1 enhances granulocyte responsiveness to growth factors and interferons, regulates hematopoietic differentiation and apoptosis, and its elevated expression is associated with improved prognosis in patients with acute myeloid leukemia (AML).[83] In human AML models, the PLSCR1–inositol 1,4,5-trisphosphate receptor type 1 (IP_3R1)–calcium (Ca^2+) axis is implicated in baicalin-induced myeloid differentiation, suggesting a potential mechanism for antileukemic therapies. PLSCR1 is frequently overexpressed in colorectal and hepatocellular carcinomas[84,85] and exhibits oncogenic properties in pancreatic ductal adenocarcinoma. However, its pro-tumor activity is suppressed by miR-628-5p, which targets PLSCR1 and IRS1 to inhibit the AKT/NF-κB signaling pathway.[86] In breast cancer, the upregulation of PLSCR1

mediated by STAT3 enhances STAT1 activity, thereby promoting tumor survival, metastasis, and resistance to therapy. Conversely, in ovarian epithelial carcinoma, PLSCR1 demonstrates antiproliferative and antitumor effects through the SnoN/SkiL pathway.[87]

Inducible nitric oxide synthase (iNOS or NOS2) is an enzyme stimulated by IFNs that plays a pivotal role in immune responses and inflammatory processes. While initial research underscored its antitumor immune functions, recent findings suggest that NOS2 is overexpressed in more than 50% of various cancers, including estrogen receptor-negative breast cancer, gliomas, melanoma, cervical cancer,[88] hepatocellular carcinoma,[89] ovarian cancer, and pancreatic cancer.[90] In these contexts, elevated NOS2 levels are generally associated with poor survival outcomes. Thus, NOS2 emerges as both a significant prognostic biomarker and a promising therapeutic target.[91] Furthermore, NOS2 exhibits both direct and indirect antiviral properties: it can alter viral proteins and the RNA-dependent RNA polymerases of RNA viruses, thereby disrupting viral replication and assembly.[92] Additionally, its reactive nitrogen intermediates can damage viral capsid proteins, diminishing their binding affinity for host receptors.[93] In certain infection models, NOS2-mediated apoptosis of infected cells serves to limit viral dissemination[94] (Figure 2).

Ubiquitin-Like Modification and Demodification Factors

ISG15 (interferon-stimulated gene 15; also referred to as UCRP, G1P2, IP17, IMD38, IFI15, and IMD3) was among the earliest identified ubiquitin-like proteins and is considered one of the most robustly induced ISGs during viral infections.[95,96] ISG15 is covalently attached to substrate proteins via an enzymatic process known as ISGylation, which modulates both inflammatory and antiviral responses. Under normal physiological conditions, ISG15 is expressed

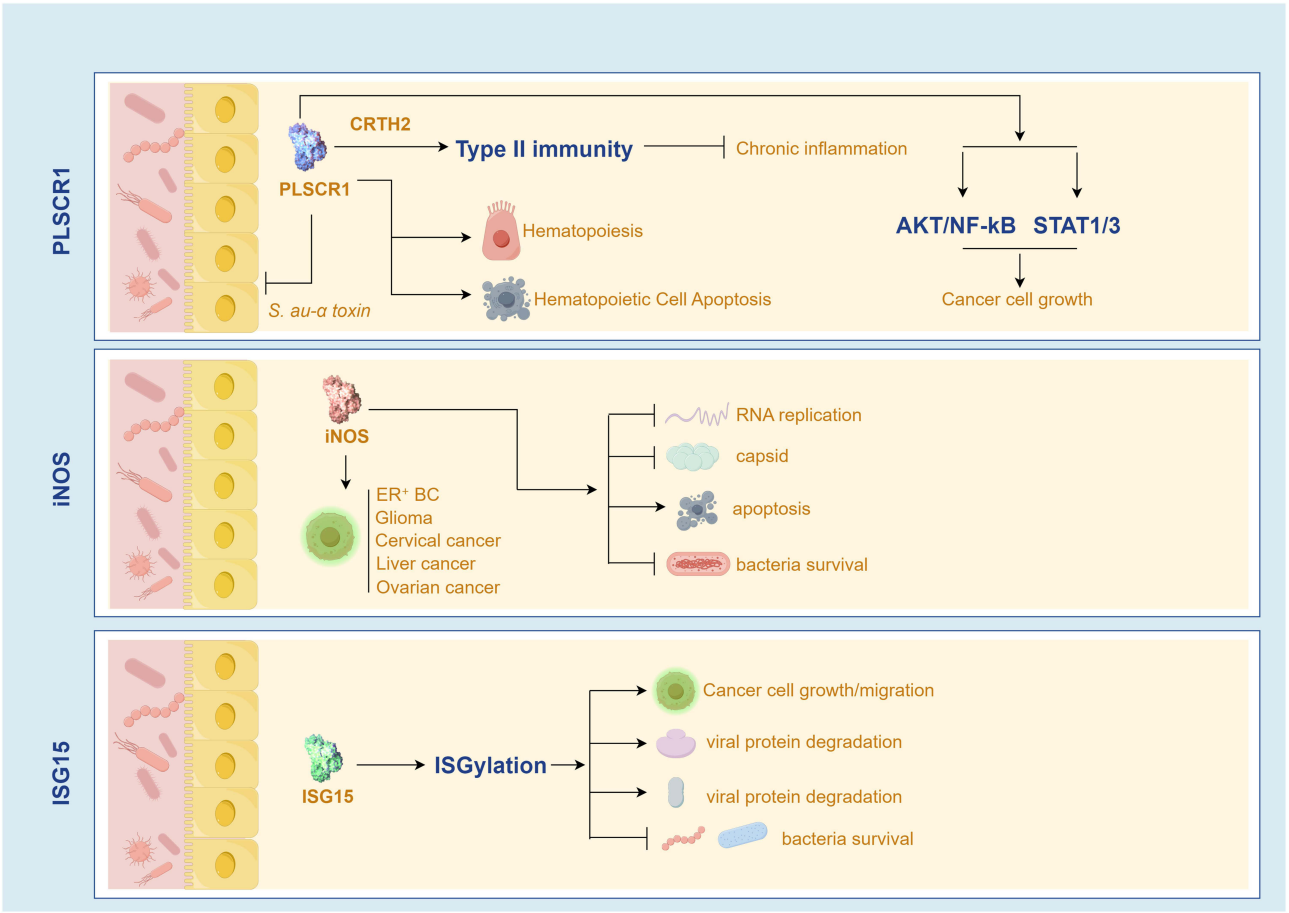

Figure 2 Multifaceted roles of PLSCR1, iNOS, and ISG15 in host defense and cancer. PLSCR1 regulates type II immunity, hematopoiesis, inflammatory signaling, and cancer cell growth. iNOS influences viral replication, apoptosis, bacterial survival, and is implicated in multiple cancer types. ISG15 functions through ISGylation to modulate cancer cell behavior and promote viral protein and bacterial degradation.

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at low levels, but its IFN-dependent expression becomes dysregulated in several pathological states, including breast cancer. In mammary carcinoma, hyperactivation of the ISG15/ISGylation pathway facilitates tumor cell migration and invasion by destabilizing cytoskeletal structures and stabilizing oncogenic proteins,[97–100] a phenomenon also observed in other tumor types.[101,102]

Beyond these classical roles, recent studies have further emphasized the context-dependent functions of ISG15 in cancer and immunity. Cohort-based pan-cancer and experimental analyses have shown that high ISG15 expression correlates with increased PD-L1 levels, enrichment of immunosuppressive tumor-associated macrophages, and features of an exhausted T cell phenotype, supporting a role for ISG15 in shaping an immune-evasive tumor microenvironment.[103] In addition, ISGylation has been linked to mitochondrial function and metabolic reprogramming in innate immune cells and tumor cells, influencing oxidative phosphorylation, glycolysis, and autophagy in response to infection or stress.[104,105] These findings suggest that ISG15 is not only an antiviral and antibacterial effector but also a broader regulator of immune metabolism and checkpoint signaling, with important implications for tumor progression and therapeutic resistance.[106,107]

In the context of antiviral defense, ISG15 plays a dual role: it can label viral proteins for proteasomal degradation to limit infection, while also protecting key host antiviral factors from degradation, enhancing their stability.[108,109] Although traditionally considered antiviral, ISG15 has recently been shown to affect host responses to intracellular pathogens through regulation of metabolic signaling, inflammasome activation, and autophagy rather than solely through direct antimicrobial effects. These multifaceted roles support the concept of ISG15 as a dynamic regulator at the intersection of immunity, infection, and tumor biology.

Intracellularly, ISG15 mitigates excessive IFN-α/β signaling and prevents autoinflammation; individuals deficient in functional ISG15 experience recurrent infections with low-virulence mycobacteria and exhibit type I interferonopathies, neurodegeneration, and inflammatory disease phenotypes. In the context of antibacterial immunity, inherited ISG15 deficiency in humans causes Mendelian susceptibility to mycobacterial disease, largely because leukocytes fail to secrete free ISG15, which normally acts as an extracellular cytokine to promote IFN-γ production by NK and T cells and is therefore essential for optimal anti-mycobacterial responses.[110–112] In murine models of *Listeria monocytogenes* infection, ISGylation of endoplasmic reticulum and Golgi proteins reshapes secretory pathways, enhances cytokine release, modulates autophagy and cellular metabolism, and collectively restricts intracellular bacterial replication in vivo.[113] Recent work also suggests that ISG15 expression induced by intracellular bacteria such as *Chlamydia* can limit bacterial proliferation while tuning inflammatory cytokine production, further underscoring its context-dependent antibacterial functions.[114] By directing proteins toward degradation or stabilization, modifying their subcellular localization, disrupting complex assembly, and fine-tuning immune signaling, ISG15 thus functions as a contextual "double-edged sword", rendering its pathway a promising target for therapeutic intervention.[115]

Clinical Relevance and Therapeutic Potential

The upregulation of type I interferons is a characteristic feature of systemic autoimmune diseases, including primary Sjögren's syndrome (pSS), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc).[116] The expression of IFN-I is induced by the activation of Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and DNA-sensing receptors (DSRs), with subsequent integration by TANK-binding kinase TBK1. Inhibition of TBK1 significantly diminishes ISGs expression in peripheral blood mononuclear cells from IFN-I–positive patients, underscoring TBK1 as a potential therapeutic target.[117] Deng et al further demonstrated that neutrophils and low-density granulocytes (LDGs) from the blood and kidneys of SLE patients exhibit the highest ISGs activity. This finding suggests that targeting these granulocyte subsets may prevent excessive downstream pathway activation. Consequently, the C5a receptor antagonist avacopan shows potential clinical efficacy for SLE and lupus nephritis.[118] In the context of chronic hepatitis B virus (HBV) infection, Xu et al demonstrated an upregulation of IFIT3 in patient sera and elucidated that IFIT3 enhances the anti-HBV efficacy of IFN-α in human hepatocytes and hepatoma cells through the JAK–STAT signaling pathway. This study identifies IFIT3 as a potential target for optimizing IFN-α therapy.[119]

Prospective

Recent research on ISGs increasingly employs methodologies that capture their dynamic and context-dependent biological roles, moving beyond the traditional view of ISGs as isolated antiviral factors. The advancement of single-cell and spatial omics technologies now enables the examination of ISG expression with precise spatial and temporal resolution across diverse immune cell subsets and tissue microenvironments. These datasets are beginning to elucidate the coordination of ISG programs in vivo and their variations between physiological and pathological states. Despite significant advancements, the functions of numerous ISGs remain inadequately characterized. Further mechanistic investigations are essential to elucidate how these genes integrate with established antiviral and inflammatory signaling pathways. High-throughput experimental platforms and computational modeling are anticipated to facilitate the identification of ISG-related regulatory circuits with therapeutic potential, including pathways amenable to intervention via small molecules or biologics.

From a clinical standpoint, a more precise evaluation of ISG expression patterns and ISGylation status in patient samples could facilitate the development of biomarkers for early diagnosis and treatment stratification. A deeper understanding of ISG activity in tumor immunity, metabolic regulation, and neuroinflammatory conditions may expand the clinical contexts in which these pathways are deemed relevant. As fundamental discoveries increasingly intersect with clinical research, ISG-associated networks are well-positioned to contribute to future antiviral, antitumor, and immunomodulatory therapeutic strategies.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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