

ISG20: The multifaceted ‘molecular star’ in cancer research (Review)

XINHUI ZHU^{1*}, SHIHAO JIANG^{1*}, LIPENG ZHANG^{1*}, SHAOJIAN ZOU^{2*},
HOUQIN ZHANG³, JINGYU ZHANG¹, LIYU CHEN¹, HUI LI⁴ and ZHEN ZONG¹

¹Department of Gastrointestinal Surgery, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China; ²Huan Kui Academy, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China; ³The Second Clinical Medical College of Nanchang University, Nanchang, Jiangxi 330006, P.R. China; ⁴Department of Rheumatology and Immunology, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China

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Abstract. IFN-stimulated gene (ISG)20 is a key member of the ISG family, serving a central role in antiviral defense, immune regulation and cell metabolism through its exonuclease activity. ISG20 is markedly dysregulated in various malignancies, including clear cell renal cell carcinoma, glioma, breast cancer and hepatocellular carcinoma, and it is associated with tumor proliferation, metastasis, angiogenesis and immune evasion. Its dual regulatory roles, such as promoting tumor progression via the MMP9/CCND1 signaling axis or enhancing antitumor immunity by activating the IFN- β pathway, highlight its complex involvement in tumor biology. The present review aimed to summarize the discovery, structural characteristics and physiological functions of ISG20, and its multifaceted roles in tumor development. Moreover, the potential of ISG20 as a novel biomarker, immunoadjuvant and therapeutic target is discussed, offering theoretical insight and translational directions for precision oncology.

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1. Introduction

IFN-stimulated genes (ISGs) are a group of genes upregulated in response to IFN stimulation (1). IFNs are cytokines classified into three main types: Type I, II and III (2). Type I IFNs have a broad range of biological functions including modulation of innate and adaptive immune responses, anti-proliferative function and antiviral activity (3). Type II IFN is IFN- γ , which is primarily produced by immune cells (activated T cells, natural killer cells and macrophages) and has been described as an immunomodulatory cytokine, but it also shows responses to viruses, bacteria, and parasites (4,5). Type III IFNs are uniquely chemotactic, with signaling and function largely restricted to epithelial cells, and these interferons are as key players in mucosal immunity (6,7). Following viral infection, pathogenic invasion or other stimuli, pattern recognition receptors (PRR) in host cells detect pathogen-associated molecular patterns, triggering an immune response. This induces IFN production, which then binds to specific cell surface receptors and activates intracellular signaling cascades, leading to the transcriptional induction of ISGs (8).

ISG20 is an RNA exonuclease belonging to the Rex4 subfamily, a homolog of yeast RNA exonuclease 4 and a member of the DEDDh exonuclease family, comprising four conserved acidic residues, three aspartates (D), and one glutamate (E), distributed among three separate sequence motifs (Exo I-III) (9,10) and with a fifth conserved residue of histidine (H). It has the ability to degrade single-stranded (ss)RNA and DNA, and encodes a 20 kDa protein (11). Under physiological conditions, ISG20 primarily contributes to the antiviral defense of the host. It directly degrades viral RNA

Correspondence to: Professor Zhen Zong, Department of Gastrointestinal Surgery, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, 1 MinDe Road, Nanchang, Jiangxi 330006, P.R. China
E-mail: ndefy16133@ncu.edu.cn

Professor Hui Li, Department of Rheumatology and Immunology, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, 17 Yongwaizheng Road, Nanchang, Jiangxi 330006, P.R. China
E-mail: ndyfy04408@ncu.edu.cn

*Contributed equally

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and modulates intracellular antiviral signaling pathways, such as inducing type I IFN responses, thereby inhibiting viral replication and spread (12). In addition, ISG20 may regulate immune cell functions and cytokine signaling (13). Previous advances have further revealed the complex role of ISG20 in tumorigenesis, attracting increasing interest (14-18).

A growing body of research has demonstrated that ISG20 expression is significantly dysregulated in various types of cancer (19-22). In clear cell renal cell carcinoma (ccRCC), ISG20 is markedly upregulated at both the mRNA and protein levels, and is positively associated with advanced clinical stage. Elevated ISG20 levels are associated with worse overall survival (OS) and disease-free survival (DFS), suggesting its potential as a diagnostic and prognostic biomarker (23). In glioma, ISG20 mRNA expression is also significantly upregulated compared with that in normal brain tissue, with differential expression observed across clinical subgroups. High ISG20 expression is associated with poor prognosis, and immunohistochemical and immunofluorescence analyses have revealed stronger expression in high-grade glioma, predominantly localized to M2 macrophages (24). Furthermore, aberrant ISG20 expression has been reported in other malignancies, including cervical and oral cancer, hepatocellular carcinoma, breast cancer and acute myeloid leukemia, where it may be upregulated, associated with specific tumor-promoting factors or predictive of unfavorable outcomes (19,25,26).

Although considerable progress has been made in elucidating the role of ISG20 in cancer, the number of publications remains limited compared with other ISGs (13,27,28). Therefore, a comprehensive summary of the functions of ISG20 in tumorigenesis is key. The present review outlines the historical discovery of ISG20, and elaborates on its molecular structure and physiological functions, as well as the role of ISG20 in cancer and its therapeutic potential.

2. Discovery and molecular characterization of ISG20

ISG20 was first identified in 1997 by Gongora *et al* (29); this study employed differential display techniques to screen IFN-regulated genes in human Daudi lymphoblastoid cells treated with IFN- α/β (29). Among these genes, one was notably inducible by both type I and II IFNs, and was designated as ISG20, encoding a 20 kDa protein. In 1998, Pentecost (30) identified a transcript with low baseline expression in multiple cell lines that was significantly upregulated by estradiol in estrogen receptor (ER)-positive breast cancer cells. This transcript, discovered via differential display PCR in ER-transfected human cervical carcinoma cells (UP1), was named HeLa estrogen-modulated 45 kDa band (HEM45). Subsequent studies have confirmed that HEM45 and ISG20 are the same gene product; as a result, ISG20 is also referred to as HEM45 (29,30).

In 2000, Gongora *et al* (31) demonstrated that ISG20 transcription is induced by both type I (α/β) and II (γ) IFNs through a unique IFN-stimulated response element located in its promoter, regulated by IFN regulatory factor 1 (IRF1) (31). In 2001, Nguyen *et al* (32) revealed that the ISG20 protein shares homology with members of the 3'-5' exonuclease superfamily, including RNase T and D and the proofreading domain of *Escherichia coli* DNA polymerase I. The catalytic

site consists of four conserved acidic residues arranged within three characteristic exonuclease motifs, classifying it under the DEDDh subfamily of 3'-5' exonucleases (32). In 2003, Espert *et al* (33) revealed the antiviral activity of ISG20; HeLa cells overexpressing ISG20 were resistant to RNA viruses such as vesicular stomatitis virus (VSV), influenza and encephalomyocarditis virus, even in the absence of IFN treatment. This antiviral effect was attributed to the exonuclease activity of ISG20, which also partially contributed to IFN-mediated anti-VSV effects, demonstrating IFN-driven antiviral mechanisms (33). ISG20 expression is directly induced by synthetic double-stranded RNA (dsRNA) via activation of NF- κ B and IRF1; this induction is more rapid and robust than that triggered by IFN (34). Moreover, ISG20 translocates to the nuclear matrix upon induction. Its site of action is different from the cytoplasmic functional region of PKR (dsRNA-activated serine-threonine protein kinase, a member of the IFN-induced antiviral signaling pathway, which together with the 2',5'-oligoadenylate synthetase/RNase L pathway constitutes the core antiviral mechanism of the IFN system), suggesting its involvement in the cell antiviral response, potentially through a PKR-independent innate antiviral and anti-apoptotic pathway (34). Horio *et al* (35) resolved the crystal structure of human ISG20 in complex with two Mn^{2+} ions and uridine 5'-monophosphate (UMP) at a resolution of 1.9 Å. The structure revealed marked similarity to DEDDh family DNases, suggesting a shared catalytic mechanism. Unique residues within ISG20 may confer its substrate preference for RNA, providing structural insights into its antiviral function (35). Espert *et al* (36) further demonstrated, using immunofluorescence, that ISG20 primarily localizes to the nucleolus and Cajal bodies, and associates with complexes containing nuclear survival of motor neuron protein. As its structure and regulatory mechanisms have become clearer, investigations into the physiological roles of ISG20 under various conditions have expanded (Fig. 1) (37-39).

3. Structural features and physiological functions of ISG20

ISG20 is located on chromosome 15q26 in humans and encodes a protein consisting of 181 amino acids with a molecular weight of ~20.4 kDa (29). ISG20 belongs to the 3'-5' exonuclease superfamily (32). The catalytic site of this superfamily consists of four conserved acidic residues (Asp-Glu-Asp-Asp) distributed across three exonuclease motifs (ExoI, ExoII and ExoIII) (10,40). These residues coordinate two metal ions necessary for hydrolyzing the terminal phosphodiester bond of RNA or DNA, thereby facilitating an enzymatic reaction. Crystal structure analysis has revealed that ISG20 contains a five-stranded β -sheet core flanked by two clusters of α -helices ($\alpha 3$, $\alpha 4$ and $\alpha 1$, $\alpha 2$, $\alpha 5$, $\alpha 7$) (35). At the active site, specific amino acid residues, such as Asp11, Glu13 and Asp154, participate in coordinating metal ions (such as Mn^{2+}), enabling catalytic activity (35). *In vitro*, ISG20 exhibits exonucleolytic activity against ssRNA and ssDNA, with a marked preference for RNA substrates. This substrate preference may be due to residues such as Met14 and Arg53, which directly interact with the ribose 2'-OH group of UMP (35). However, the precise molecular mechanism underlying this specificity remains to be elucidated (Fig. 2).

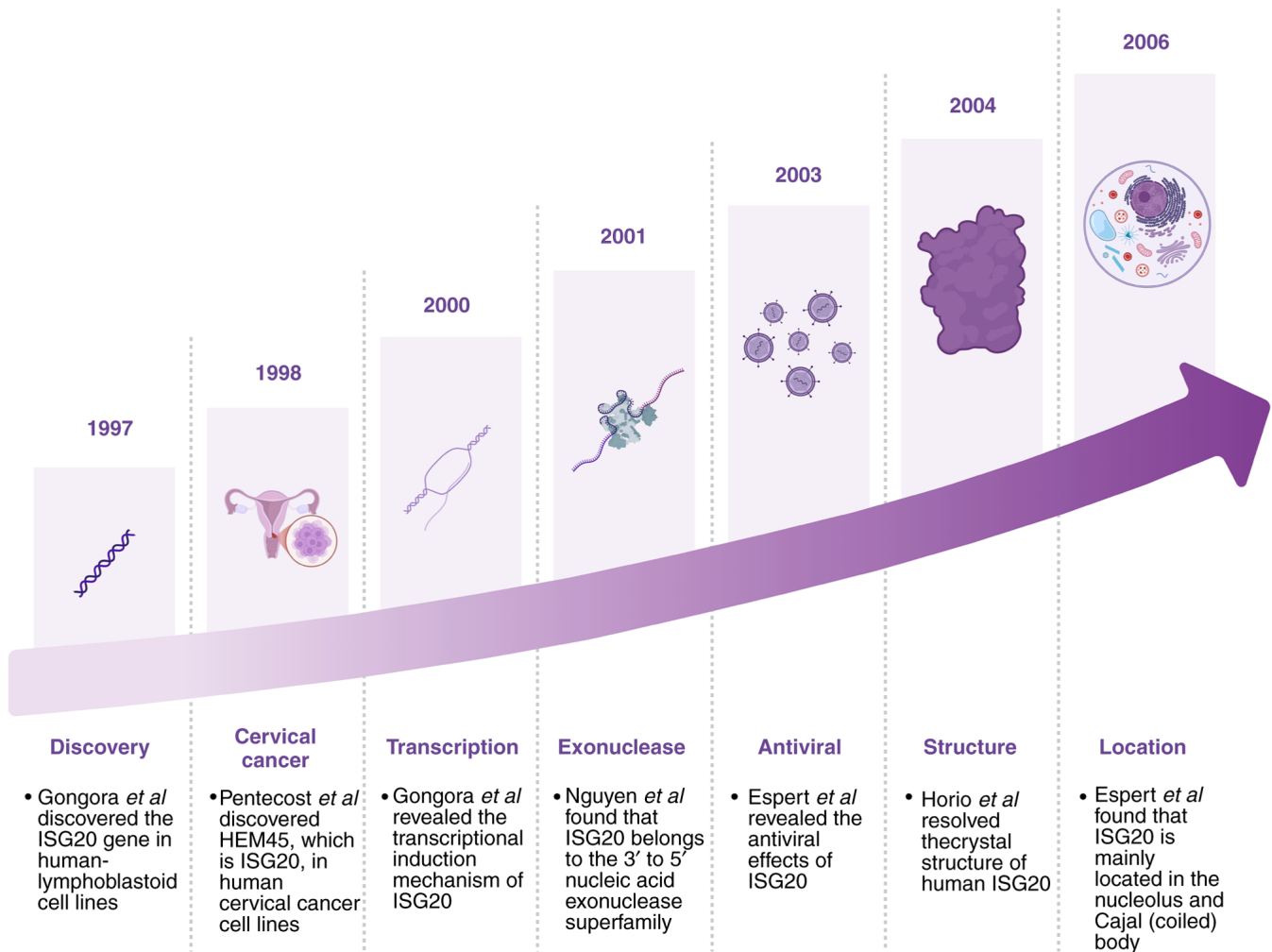


Figure 1. Timeline for ISG20/HEM discovery. ISG, IFN-stimulated gene ;HEM, HeLa estrogen-modulated.

Although purified ISG20 primarily cleaves ssRNA *in vitro*, it may exhibit resistance to substrates with 3' structures. For example, Liu *et al* (41) found that the encapsidation signal ϵ RNA of hepatitis B virus (HBV) exhibits resistance to ISG20 (41). The ϵ RNA is located near the 5' end of the HBV pre-genomic RNA and features a unique secondary structure, including a long 13-bp basal stem, a 6-nt bulge region (initiator loop), an 11-bp upper stem and a terminal hexaloop (42). It has been shown that ISG20 specifically binds the lower stem of ϵ RNA, with binding stability requiring a lower stem of >9 RNA bps (41). However, despite tight binding, ISG20 is unable to effectively cleave the ϵ RNA substrate. Notably, deletion of the C-terminal ExoIII motif of ISG20 results in complete loss of RNA binding, suggesting that the ExoIII motif may harbor an RNA-binding domain, or that the coordination of MnA by Asp154 is key for RNA binding (41). In addition to its role in nucleic acid degradation, ISG20 is involved in other key cellular processes. ISG20 has been reported to mediate estrogen signaling, serving a role in regulating cell proliferation and differentiation (41). Its expression is significantly upregulated in response to IFN or estrogen, further highlighting its key role in hormone-regulated cell networks (43-45).

The antiviral effects of ISG20 have been extensively studied (12,45,47). These include direct degradation of

viral RNA, deamination of viral DNA, IFN-induced and IFIT1 (IFN-induced protein with tetratricopeptide repeats1)-mediated suppression of viral RNA translation and non-IFN-induced inhibition of non-self RNA translation (Fig. 3) (48). ISG20 exhibits RNase activity, capable of degrading viral ssRNA and ssDNA. As aforementioned, ISG20 can degrade HBV RNA by directly binding the ϵ -stem-loop structure of viral RNA, thereby inhibiting HBV replication. Additionally, Kang *et al* (49) studied the inhibitory mechanism of ISG20 on bluetongue virus (BTV), and found that mutating Asp94 to Gly in ISG20 to create a nuclease-deficient mutant significantly decreased its inhibitory effect on BTV replication, suggesting that ISG20 may directly degrade viral RNA through its exonuclease activity during BTV infection (49). However, there remains controversy regarding whether ISG20 directly degrades viral RNA and its antiviral mechanism and specificity are not fully understood (11,41,50).

Some studies have suggested that ISG20 may exert its effects more through translational inhibition than RNA degradation (12,46). For example, in mouse embryonic fibroblasts, overexpression of mouse ISG20 indirectly suppresses viral translation by inducing an IFN response and IFIT1, without involving viral RNA degradation (12). However, ISG20 is an IFN regulatory protein, and the mechanism by which it induces

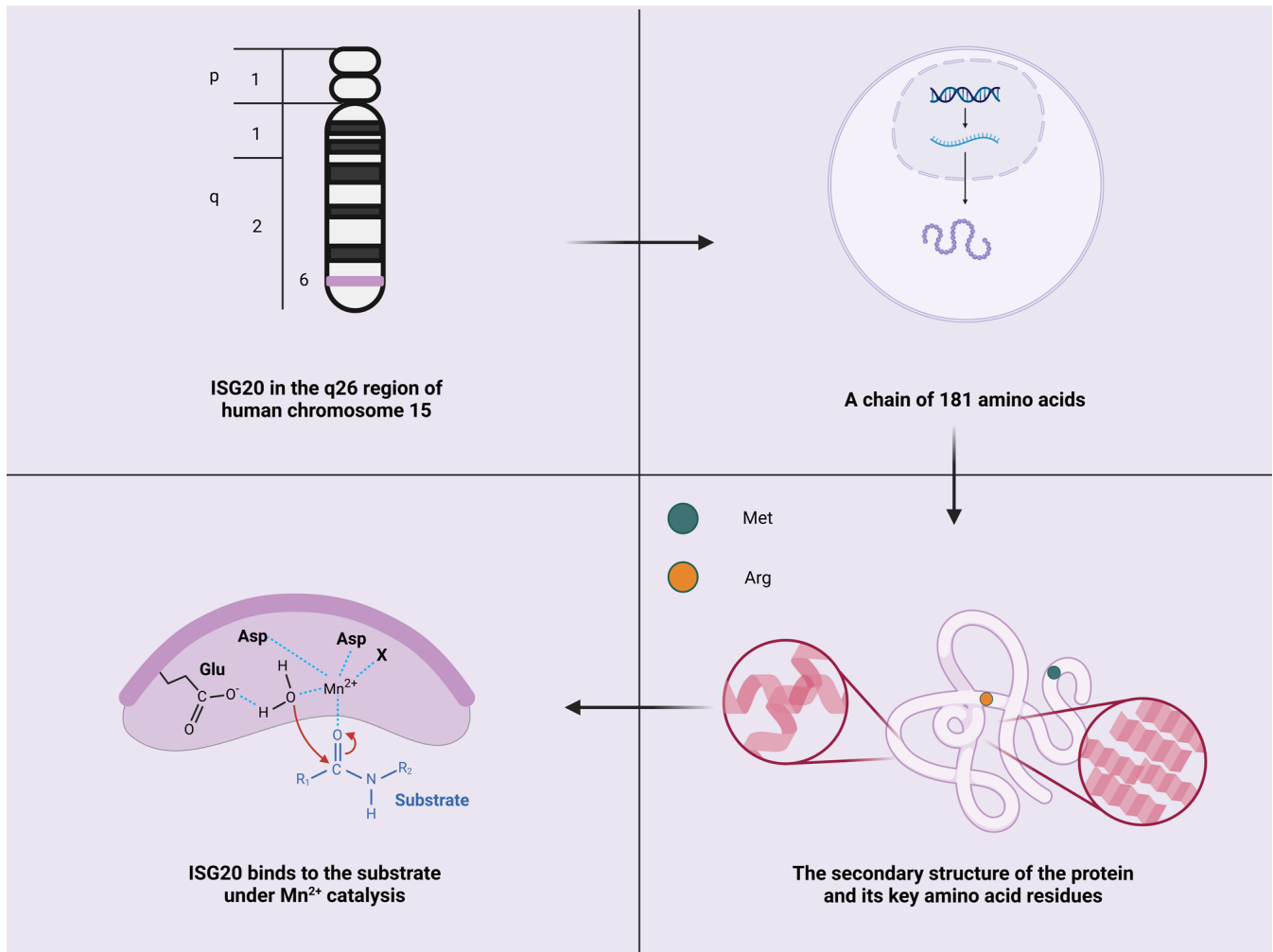


Figure 2. Schematic representation of the structure of ISG20. ISG, IFN-stimulated gene.

IFN, as well as how it mediates suppression of a range of viruses, remains unclear. Additionally, the source of the RNA (cellular or viral) targeted by ISG20 during IFN induction has yet to be determined. Furthermore, it has been demonstrated that the subcellular localization and dynamic changes of ISG20 may influence its antiviral function (36,46,51). For example, under uninfected conditions, ISG20 is predominantly localized in the nucleus, associated with nuclear structures such as promyelocytic leukemia bodies, nucleoli and Cajal bodies, and potentially involved in RNA processing and transcriptional regulation (48). After viral infection, a fraction of ISG20 translocates to processing bodies (P bodies) in the cytoplasm, which serve a crucial role in RNA degradation and translational regulation. The localization of ISG20 in P bodies may aid degradation of viral RNA or the suppression of viral RNA translation, thereby contributing to its antiviral activity (11).

ISG20 not only serves a key role in antiviral responses but also participates in the immune regulation processes, affecting numerous aspects of the immune system (52,53). In innate immunity, ISG20 may serve as an important effector molecule, participating in the responses of immune cells such as macrophages and dendritic cells to pathogens (54). ISG20 serves a key role in macrophages resisting *Listeria* infection, and in dendritic cells responding to *Mycobacterium tuberculosis*

and *Toxoplasma gondii* infection, suggesting it may enhance innate immune defense by regulating immune cell function (54,55). ISG20 may also play a role in adaptive immunity. For example, Rodríguez-Galán *et al* (56) reported that the ISG20 family member ISG20L2 specifically binds uridylylated microRNAs (miRs), is upregulated in T lymphocytes under T cell receptor and type I IFN stimulation, and participates in regulating T cell function. Knockout of this gene may lead to delayed T cell proliferation, increased apoptosis, abnormal expression of activation-associated molecules, increased IL-2 secretion and impaired immunological synapse formation and dynamics, indicating that ISG20 may influence T cell activation and function, thereby indirectly affecting the adaptive immune response (56).

The role of ISG20 in immune regulation may also be associated with its impact on the interaction between immune and tumor cells. In the tumor microenvironment (TME), the functional state of immune cells markedly influences tumor initiation, progression and the effectiveness of immunotherapy. Studies have indicated that ISG20 may affect the immune balance in the TME by regulating immune cell infiltration, modulating immune signaling pathways and adjusting chemokines, thereby influencing tumor cell proliferation and metastasis (14,43).

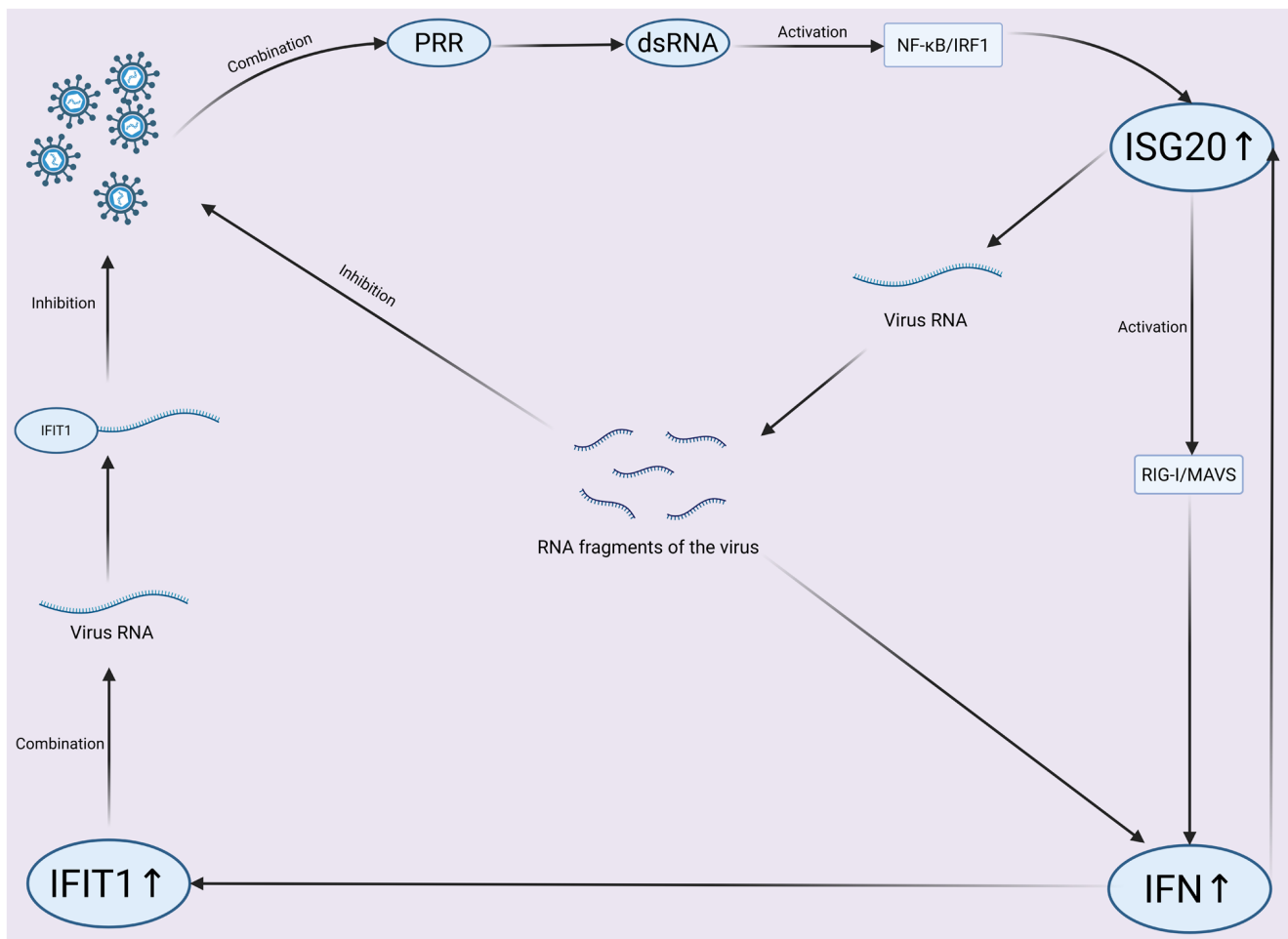


Figure 3. Mechanistic pathway of ISG20 antiviral activity. Viral dsRNA is recognized by PRR, activating NF-κB/IRF1 to upregulate ISG20. ISG20 degrades viral RNA and activates RIG-I/MAVS for IFN production. IFN-induced IFIT1 binds viral RNA, inhibiting replication and viral-PRR interaction. Viral RNA fragments modulate the response, forming a coordinated innate immune network. ISG, IFN-stimulated gene; IFIT, Interferon-induced protein with tetratricopeptide repeats; IRF, IFN regulatory factor; PRR, Pattern recognition receptor; ds, double-stranded; RIG-I, Retinoic Acid-Inducible Gene I; MAVS, Mitochondrial Antiviral Signaling Protein.

4. Role of ISG20 in cancer

ISG20 exhibits opposing mechanisms of action in tumors, necessitating further research. From an immunological perspective, when tumor cells successfully evade immune responses, cancer progression occurs (57). IFNs are a family of secreted proteins, also known as key drivers of inflammation in the TME, that have a crucial role in triggering immune responses in immune cells (57-59). As the second protein induced by IFNs or dsRNA, ISG20 exhibits differential expression in healthy individuals and certain types of tumors, but its precise mechanism remains to be explored (Fig. 4).

Impact on tumor cell proliferation. In certain types of cancer, such as RCC, breast and cervical cancer, glioblastoma (GBM) and hepatocellular carcinoma, ISG20 promotes tumor cell proliferation (Fig. 5). In ccRCC, Xu *et al* (23) conducted Gene Set Enrichment Analysis and revealed that high ISG20 expression notably contributes to the 'cell cycle pathway', promoting tumor cell proliferation. The aforementioned study also revealed that silencing ISG20 leads to significant down-regulation of MMP9 and CCND1 expression in ccRCC, both

of which are typically upregulated in ccRCC (23). Therefore, ISG20 may accelerate the cell cycle progression and promote rapid tumor cell proliferation by positively regulating the expression of the cell cycle-associated proteins MMP9 and CCND1. Furthermore, ISG20 has been identified as a potential prognostic target in ccRCC. Rajkumar *et al* (18) used microarray technology to analyze samples from various stages of cervical cancer, cervical intraepithelial neoplasia and normal cervical tissue; the findings initially indicated a potential expression difference for ISG20, which was validated by reverse transcription-quantitative PCR and calibrated to normal samples, confirming high ISG20 expression in cervical cancer tissue. These results suggested that ISG20 may serve an important role in the progression of cervical cancer (18).

By contrast, in ovarian cancer, ISG20 inhibits tumor cell proliferation both *in vivo* and *in vitro* (45). ISG20 overexpression can significantly inhibit the proliferation of Caov3 cells *in vivo*. Additionally, xenograft tumor assays in nude mice revealed that stable overexpression of ISG20 in Caov3 cells using pLVX-ISG20-IRES-Neo slows tumor growth. These results suggested that ISG20 may suppress tumorigenesis *in vivo* (45).

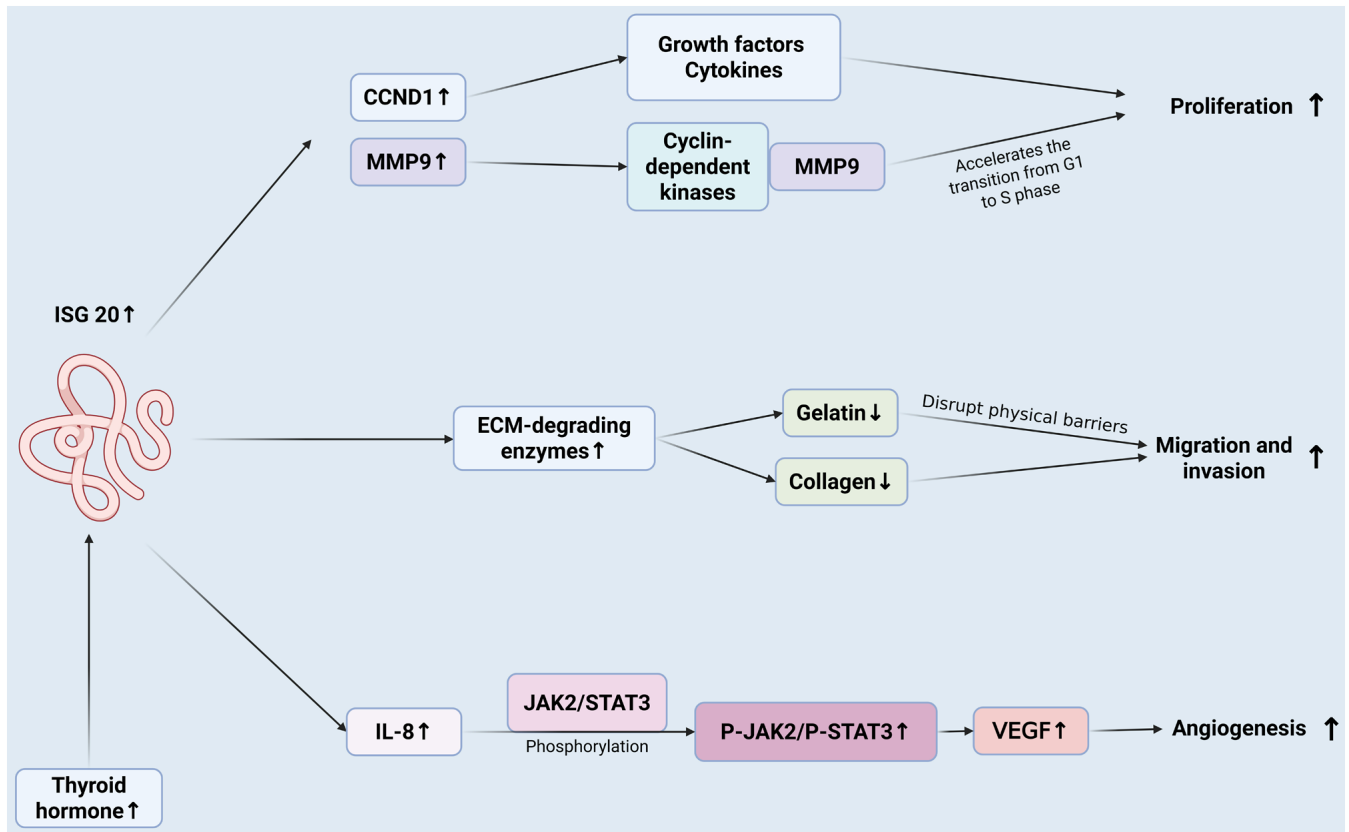


Figure 4. Mechanism of ISG20 in promoting tumor cell proliferation, migration, invasion and angiogenesis. ISG20, induced by thyroid hormone, promotes cancer cell proliferation, migration, invasion and angiogenesis. It acts via pathways like CCND1/MMP9 for proliferation, ECM-degrading enzymes for migration/invasion, and IL-8-JAK2/STAT3-VEGF for angiogenesis. ISG, IFN-stimulated gene; CCND, cyclin D1; P, phosphorylation.

Effect on tumor cell migration and invasion. Tumor migration and invasion are regulated by multiple factors, including genetic mutation, signaling pathway activation, TME remodeling and phenotypic plasticity. ISG20 exhibits heterogeneity in its effect on tumor migration and invasion. Alsheikh *et al* (43) reported that the NMI (N-Myc and STAT interactor protein)-STAT5A signaling axis inhibits ISG20 expression via miR-20a, maintaining normal breast epithelial differentiation and suppressing tumor metastasis. Clinical samples revealed that in 70% of patients with metastatic breast cancer, NMI protein levels are lower than those in primary tumor samples, whereas ISG20 expression is significantly higher in metastatic than in primary sites. Functional assays, including Transwell, Matrigel and lung metastasis experiments, confirmed that ISG20 overexpression enhances migration, invasion and lung metastasis potential in breast cancer cells (43).

Additionally, ISG20 may promote the expression of certain extracellular matrix (ECM)-degrading enzymes, leading to the breakdown of collagen and gelatin components in the ECM, thereby disrupting physical barriers around tumor cells and facilitating migration and invasion (23). Notably, in ccRCC, high ISG20 expression may promote MMP9 activity, thereby enhancing tumor migration and invasion (23). MMP9, a key ECM-degrading enzyme, disrupts the basement membrane and ECM, providing a physical passage for tumor cell migration (60). ISG20 knockdown inhibits cell invasion, confirming its role in ECM remodeling through an MMP9-dependent mechanism (23).

However, in ovarian cancer, Yu *et al* (45) employed Transwell assays to assess the invasion and migration of Caov3 cells *in vitro*, finding that ISG20 overexpression significantly inhibited cell invasion and migration compared with the control group, however, the underlying mechanism remains unclear (45).

ISG20 upregulation induces tumor angiogenesis. Tumor formation is typically driven by the proliferation and metastasis of tumor cells, which depend on the ability of tumor cells to recruit their own blood supply. Angiogenesis is the key pathway by which tumors acquire nutrients and oxygen and achieve distant dissemination, and is therefore key for the development of human cancer (61). In the intricate regulatory network of angiogenesis, the positive regulator vascular endothelial growth factor and the negative regulator thrombospondin-1 form a dynamic balance (62,63).

Previous studies have shown that ISG20 overexpression does not inhibit angiogenesis, whereas its dominant negative mutation ExoII (lacking exonuclease activity) inhibits angiogenesis by 43% (64,65). In addition, fibrin gel assay suggested that the exonuclease activity of ISG20 may be essential for angiogenesis (64). In hepatocellular carcinoma, Lin *et al* (65) reported that thyroid hormone (triiodothyronine) upregulates ISG20, which promotes hepatocellular carcinoma angiogenesis by regulating IL-8 and activating the phosphorylated (p-) JAK2/p-STAT3 signaling pathway, providing therapeutic targets and a theoretical basis for liver cancer treatment. *In vitro*,

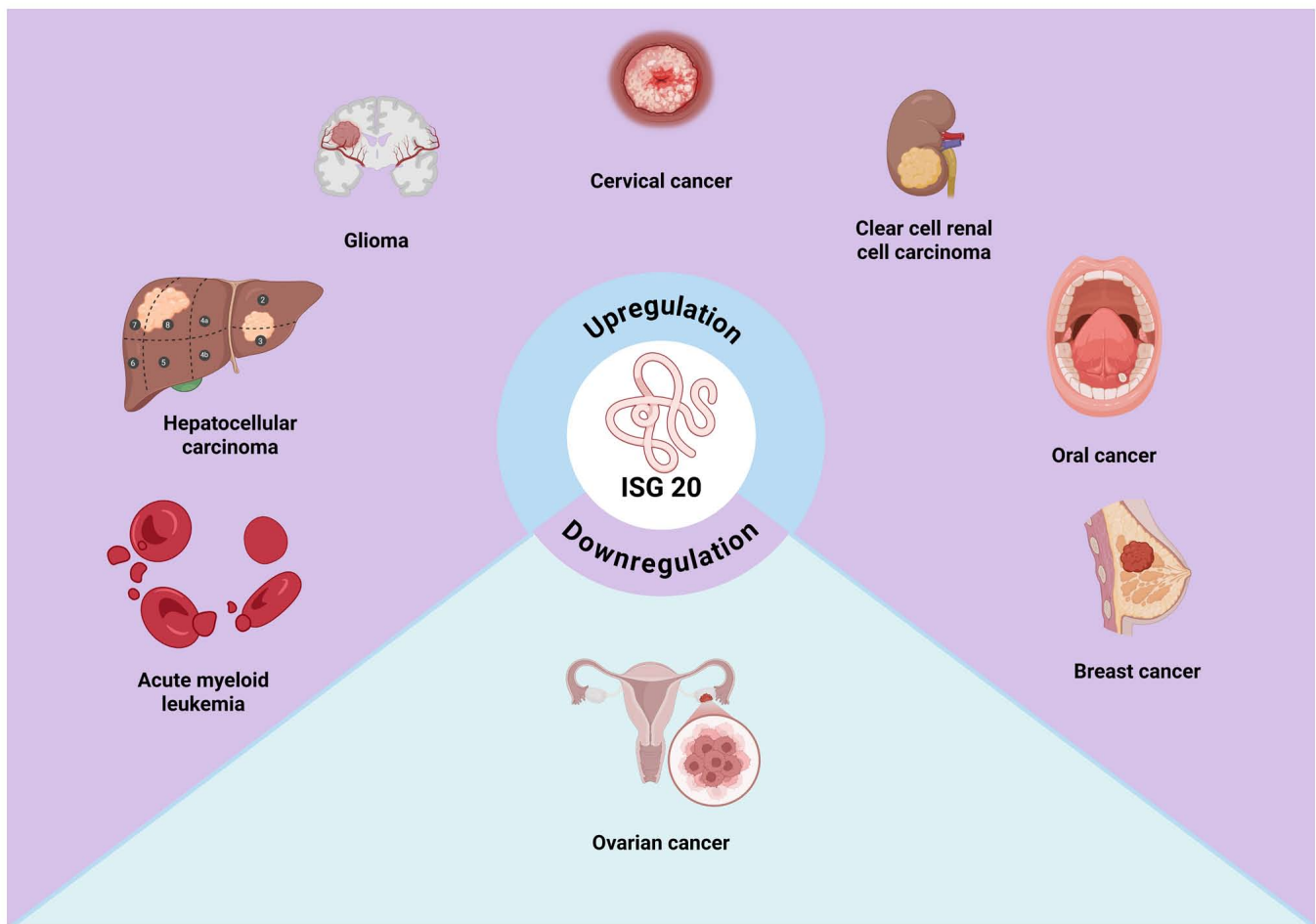


Figure 5. ISG20 is up- or downregulated in different cancers. ISG, IFN-stimulated gene.

conditioned medium from ISG20-overexpressing hepatocellular carcinoma cells significantly promotes the formation of lumen-like structures by human umbilical vein endothelial cells (HUVECs), whereas ISG20 knockdown may inhibit thyroid hormone-induced HUVEC tube formation (65). *In vivo*, experiments using the Matrigel plug and chicken embryo chorioallantoic membrane (CAM) models have confirmed that ISG20-overexpressing cells enhance angiogenesis, as evidenced by increased hemoglobin content in the Matrigel plugs, more CAM blood vessel branches and elevated expression of the endothelial marker CD31 (65). Knockdown of ISG20 decreases these effects. Clinical analysis has also revealed that ISG20 expression in liver cancer tissue is positively associated with angiogenesis-associated clinical parameters, such as vascular invasion and tumor size (65). Additionally, patients with high ISG20 expression have shorter recurrence-free survival, providing evidence that ISG20 promotes angiogenesis in hepatocellular carcinoma (65,66). Furthermore, human angiogenesis chip assays have revealed that ISG20 overexpression significantly upregulate the angiogenic factor IL-8 and activates the p-JAK2/p-STAT3 signaling pathway in HUVECs (65). By contrast, knockdown of IL-8 or the use of IL-8 neutralizing antibodies inhibits ISG20-induced tube formation *in vitro* and angiogenesis *in vivo*. Treatment with JAK2/STAT3 inhibitors also significantly blocks ISG20-mediated angiogenesis, confirming the key role of this pathway (65).

Regulation of TME. The TME refers to the local environment that supports the survival and development of tumor cells, encompassing various cells, molecules and the ECM, including tumor and immune cells (67). These components form a complex ecosystem that serves a key role in tumor initiation, growth, metastasis and response to treatment (68). The regulatory mechanisms of ISG20 expression in the TME involve numerous signaling pathways and molecular mechanisms, with its effect on tumor cells varying depending on tumor type and microenvironment. In some tumors, it may suppress tumor progression by enhancing immune responses, whereas in others, it may promote tumor progression by fostering immune suppression or enhancing tumor invasiveness (Fig. 6) (14,22,23).

Chen *et al* (22) revealed that ISG20 stimulates antitumor immunity in ovarian cancer through a dsRNA-induced IFN response (22). Specifically, through protein-protein interactions and survival analysis, ISG20 was identified as the only gene significantly associated with OS in patients with ovarian cancer. Comparison of the high and low ISG20 subgroups in The Cancer Genome Atlas (TCGA) ovarian cancer dataset revealed that high ISG20 expression is associated with increased CD8⁺ T-cell infiltration and enhanced tumor immunogenicity. Functional experiments demonstrated that ISG20 degrades endogenous long dsRNA into shorter fragments through its exonuclease activity, activating the

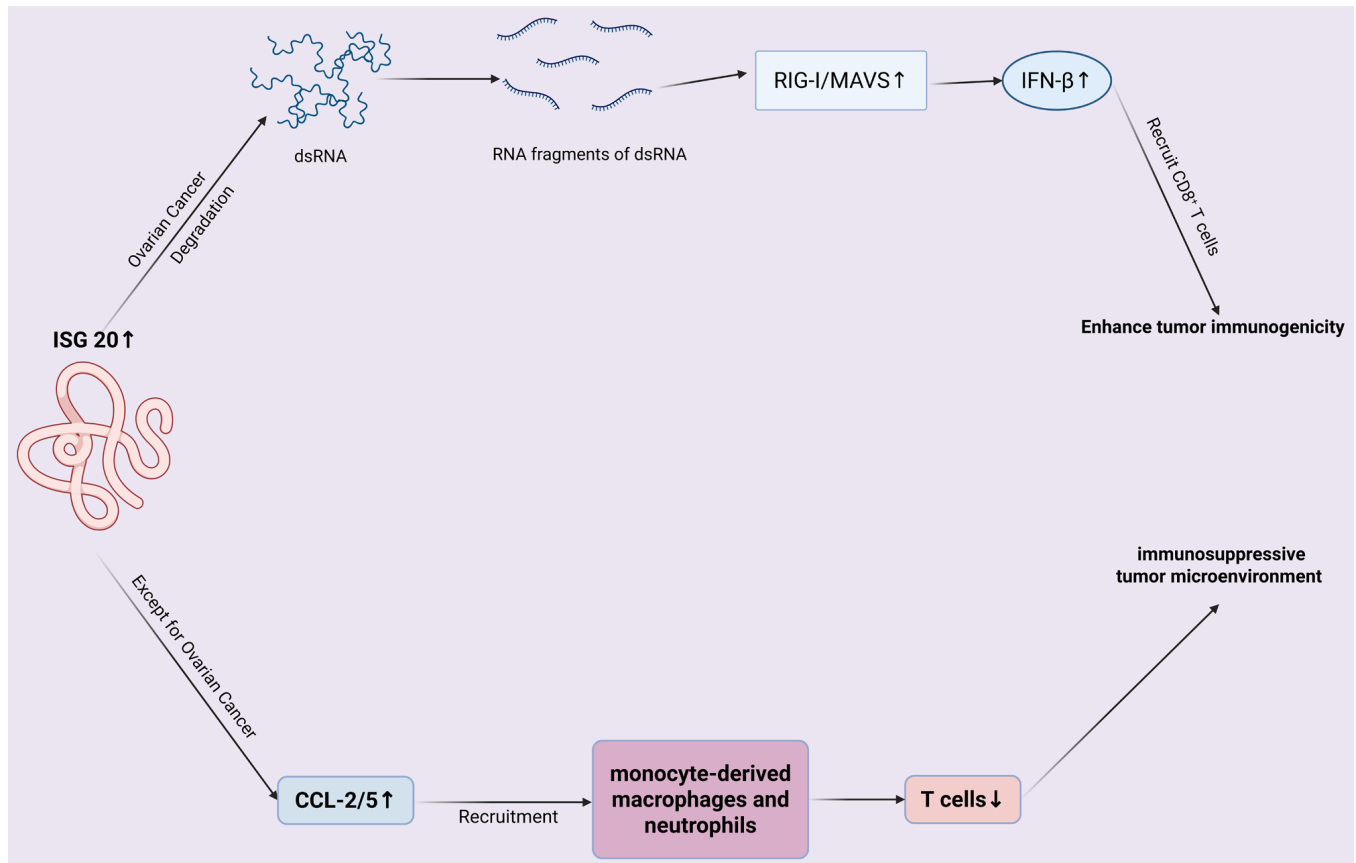


Figure 6. Mechanism of ISG20 regulating tumor immune microenvironment. In ovarian cancer, ISG20 degrades dsRNA into fragments, activating RIG-I/MAVS to induce IFN- β , which recruits CD8⁺ T cells and enhances immunogenicity. In other cancers, ISG20 upregulates CCL-2/5, recruiting monocyte-derived macrophages/neutrophils, reducing T cells and forming an immunosuppressive tumor microenvironment. ISG, IFN-stimulated gene; ds, double-stranded; RIG-I, retinoic Acid-Inducible Gene I; MAVS, Mitochondrial Antiviral Signaling Protein.

RIG-I/MAVS (retinoic acid-inducible gene I/Mitochondrial antiviral-signaling protein) signaling pathway and promoting IFN- β secretion. IFN- β upregulates ISGs, such as CXCL10 and CXCL11, enhancing tumor cell immunogenicity and CD8⁺ T cell infiltration. The aforementioned study identified the critical role of the RIG-I/MAVS signaling pathway, dependent on ISG20 exonuclease activity, in ovarian cancer. Enhancing the ISG20/RIG-I pathway (through dsRNA agonists) or use of immune checkpoint inhibitors (such as anti-PD-1) may offer novel therapeutic strategies for ovarian cancer immunotherapy.

In glioma, ISG20 has been shown to promote local tumor immunity (14). Gao *et al* (14) used functional enrichment and correlation analysis to reveal that ISG20 recruits monocyte-derived macrophages and neutrophils by upregulating chemokines such as CCL2/5, while inhibiting the infiltration of antitumor T cell subsets, including central memory and follicular helper T cells. This expression pattern is positively associated with immune checkpoint molecules such as PD-1/PD-L1 and CTLA4 and JAK/STAT pathway activation, thus shaping an immune-suppressive microenvironment (14). Although the aforementioned study revealed the key role of ISG20 in the glioma immune microenvironment, its specific molecular mechanisms, such as direct target interactions and signaling pathway regulation, require further investigation. Another study using large TCGA cohorts and

meta-analysis demonstrated that higher ISG20 expression is associated with poor prognosis in patients with glioma (24). The aforementioned study further revealed that ISG20 is expressed in tumor-associated macrophages, influencing immune cell infiltration and immune checkpoint regulation, thereby participating in the regulation of the glioma immune microenvironment (24). ISG20 is primarily expressed in M2-type tumor-associated macrophages, with high expression positively associated with M2 macrophage and regulatory T cell (Treg) infiltration, and negatively associated with plasma and naïve T cells (24). It was also positively associated with immune checkpoint molecules such as PD-1 and CTLA4, suggesting that it promotes tumor immune escape by shaping an immune-suppressive microenvironment (24). Immunofluorescence confirmed the co-localization of ISG20 with CD163, indicating its predominant expression in M2-type tumor-associated macrophages. Furthermore, enrichment analysis showed that ISG20-associated genes are directly involved in pathways such as IL6/JAK/STAT3 (cell proliferation), PI3K/AKT/mTOR (survival signaling) and ECM remodeling (invasion and metastasis) (24). This suggested that ISG20 may serve as a novel biomarker for malignant phenotype and prognosis in glioma. It influences tumor progression by regulating the immune microenvironment and pro-cancer pathways, offering a target for immunotherapy aimed at M2 macrophages.

A previous study investigated the precise effect of ISG20 on macrophage polarization in GBM (69). The results demonstrated that FOSL2 (Fos-like 2), a potential transcription factor, may activate ISG20 transcription through DNA hypomethylation, inducing macrophage polarization towards the M2 phenotype. This can lead to the secretion of immunosuppressive cytokines, such as IL-10 and TGF- β , which suppress T cell function and establish an immune-suppressive microenvironment, thus promoting tumor progression. The aforementioned study reveals the critical role of the FOSL2/ISG20 pathway in GBM progression, providing new targets for therapies aimed at M2 macrophage polarization and FOSL2/ISG20-associated treatment strategies. However, the aforementioned study did not elucidate the mechanism by which ISG20 induces M2 macrophage polarization in the GBM TME.

In ccRCC, ISG20 promote the infiltration of suppressive immune cells, enhances immune checkpoint signaling and regulates disulfide metabolism, thereby constructing an immune-suppressive TME that enables tumor cells to evade host immune surveillance and attack (70). Specifically, in the C2 subtype (high-risk group) with high ISG20 expression, tumor-infiltrating immune cells, including Tregs and myeloid-derived suppressor cells, are significantly enriched (70).

Single-cell and spatial transcriptomic analyses (70) have revealed that ISG20 is highly expressed in Tregs and exhausted CD8⁺ T cells, co-localizing with T cell exhaustion markers such as lymphocyte activation Gene 3). This suggests that ISG20 may maintain the immunosuppressive phenotype of Tregs and the functional decline of exhausted T cells, thus inhibiting effector T cell activity (70). Furthermore, high ISG20 expression is significantly associated with the upregulation of immune checkpoint proteins, such as PD-1, CTLA-4 and T cell Immunoglobulin and ITIM Domain), which transmit inhibitory signals leading to T cell inactivation (70). The high-risk group exhibits significantly higher T cell exhaustion and dysfunction scores, further confirming that ISG20 contributes to the inhibitory TME, hindering T cell attacks on tumors (70). ISG20 is also positively associated with the disulfide death core gene SLC7A11 at the protein level, and their co-expression may regulate intracellular disulfide bond metabolism and redox homeostasis, influencing ferroptosis and shaping a microenvironment that supports tumor survival (70).

In summary, ISG20 exhibits a dual role in the TME, driving anti-tumor immunity while promoting immunosuppression and tumor progression. This functional heterogeneity is shaped by a series of key determinants of tumor type specificity. In-depth investigation of these factors is essential for understanding the biological role of ISG20 and developing precision targeting strategies. Cellular localization of ISG20 action is a key factor. In ovarian cancer, Chen *et al* (22) clarified that its function mainly originates from the expression of tumor cells, which activates the RIG-I/MAVS/IFN- β pathway through degradation of endogenous dsRNA in tumor cells, which in turn recruits CD8⁺ T cells. By contrast, in glioma and ccRCC, key evidence (co-localization with CD163, expression in Tregs/depleted CD8⁺ T cells) suggests that the pro-tumorigenic effect of ISG20 stems primarily from its expression in specific immune cell subsets (especially M2-type tumor-associated macrophages and Tregs), which are the key

components of the immune-suppressive TME. Downstream pathways and effector molecules activated by ISG20 show functional shifts due to differences in the molecular composition of the TME. The abundant endogenous dsRNA in ovarian cancer provides ISG20 with a substrate to activate the RIG-I pathway, which produces chemokines such as CXCL10/11 that recruit effector T cells. In glioma, high expression of ISG20 (potentially activated by FOSL2 transcription) is associated with the sustained activation of the JAK/STAT pathway, leading to the upregulation of chemokines such as CCL2/5 that recruit suppressor myeloid cells and promoting the expression of immune checkpoints such as PD-1/PD-L1. Renal cancer studies (22,23). have further revealed ISG20 synergy with disulfide death-related genes (such as SLC7A11) and its spatial co-localization with T cell depletion markers, suggesting that it may shape the suppressive TME by regulating cell metabolism and directly participating in the maintenance of the depletion phenotype. Finally, the 'functional output' of ISG20 is dependent on the composition and activation status of the immune cell network in which it operates. CCL2/5 may recruit different cell types in different TMEs; ISG20-induced production of IFN- β may enhance immunogenicity in ovarian cancer, whereas it may promote immune tolerance or depletion in the context of chronic inflammation or in the presence of other suppressive signals. The association of high ISG20 expression with decreased infiltration of specific T cell subsets (central memory and follicular helper T) observed in glioma studies (14,24) and with Tregs/myeloid-Derived Suppressor Cells) enrichment and elevated T cell dysfunction score in renal carcinoma (70) is a manifestation of this network dependence. Thus, ISG20 functions are affected by the cellular ecological niche, molecular signaling network and immune context of specific tumor types. Understanding the determinants of tumor specificity, such as cellular localization, microenvironmental molecular context (substrate, pathway coupling) and immune cell network composition and status, is a fundamental prerequisite for resolving its dual roles, evaluating its value as a biomarker and designing effective targeted intervention strategies. Furthermore, in terms of potential molecular mechanisms between ISG20 and immune checkpoint regulation, existing studies (14,24) have primarily provided correlation evidence (co-expression, co-localization) and pathway associations (JAK/STAT), but lack conclusive molecular mechanistic models (key transcription factor complexes, direct substrate-product association, specific protein interactions) and in-depth experimental validation such as chromatin and RNA immunoprecipitation followed by Sequencing, reporter gene analysis, effects of conditional knockout/overexpression in specific cell types. In glioblastoma (69), the transcription factor FOSL2 activates ISG20 transcription through DNA hypomethylation, induces macrophage polarization towards M2 type and secretes inhibitory factors such as IL-10 and TGF- β . M2 type macrophages may further upregulate PD-L1 expression through the JAK/STAT pathway, creating an immunosuppressive microenvironment. In ccRCC (70), high ISG20 expression was positively associated with the phosphorylation of STAT3, a key transcriptional activator of PD-L1, which is enhanced by direct binding to the PD-L1 promoter. In addition, ISG20 is positively correlated with the disulfide death core gene SLC7A11 in renal cancer,

which regulates intracellular redox homeostasis. SLC7A11 enhances PD-L1 transcription by stabilizing hypoxia-inducible factor 1 α , and ISG20 may indirectly support this process through metabolic reprogramming (70). Future studies are needed to characterize these factors in more tumor types and explore the precise molecular mechanisms of their interaction.

5. Potential application of ISG20 in cancer therapy

As a tumor-associated antigen. Due to marked dysregulation of the IFN signaling pathway in various tumors, ISG20 is upregulated in tumors of the brain, uterus, breast, cervix, esophagus, kidney, liver, pancreas, skin and testes (24). In ovarian cancer, ISG20 enhances type I IFN signaling, increasing the immunogenicity of tumor cells and promoting immune cell infiltration and antitumor immune responses (22). This suggests that ISG20 gene delivery via viral vectors (including lentiviruses) may directly increase ISG20 expression in tumor cells, promoting dsRNA fragmentation and IFN- β secretion, thereby activating both innate and adaptive immune responses. Alternatively, drugs specifically activating ISG20 RNase activity, or alleviating ISG20 inhibitors (protein modification regulation), may be developed to induce endogenous dsRNA accumulation and IFN pathway activation for ovarian cancer treatment. However, ISG20 has a tumor-promoting role in most types of cancer, including glioma and ccRCC (23,24). In the future, ISG20 could be used as a tumor-associated antigen to design vaccines (such as peptide, DNA/RNA or dendritic cell vaccines) to activate specific immune responses targeting tumor cells for antitumor effects. However, due to the complex and potentially risky mechanisms of ISG20 in different tumors, the development of ISG20-based vaccines requires further research and validation. Future research should focus on clarifying the specific mechanisms of ISG20 in different types of disease, optimizing vaccine design and evaluating their safety and efficacy.

As a potential biomarker. Biomarkers are typically defined as objective indicators that can be measured to reflect physiological or pathological processes, as well as biological effects following exposure to treatment or intervention. As aforementioned, ISG20 is upregulated in various tumors, and is significantly associated with disease progression and prognosis. Therefore, ISG20 is increasingly recognized as a potential biomarker for certain types of tumor (14,23,71). For example, Xu *et al* (23) reported that ISG20 is highly upregulated in ccRCC tumors, where it enhances tumor cell proliferation and metastasis by modulating the MMP9/CCND1 signaling pathway. ISG20 has been identified as a potential predictive target for ccRCC, with high ISG20 expression associated with poorer OS and DFS (23). In cervical cancer tissue, Rajkumar *et al* (29) observed high expression of ISG20, which may be associated with the onset and progression of cervical cancer (18). In ovarian cancer (72), a significant decrease in ISG20 levels has been observed, which may be associated with ethnicity, advanced clinical stage, higher pathological grade and poor prognosis. Lower ISG20 mRNA expression is detected in cisplatin-resistant ovarian cancer compared with in a cisplatin-sensitive group (25). Furthermore,

Lin *et al* (65) reported that ISG20 upregulation in patients with hepatocellular carcinoma is positively associated with clinical factors such as vascular invasion and tumor size, and poorer relapse-free survival (65). Additionally, in radioresistant oral cancer cells, the mRNA and protein expression levels of ISG20 are higher than those in corresponding parental cells, suggesting that ISG20 upregulation may be essential for the radioresistant phenotype in oral cancer (26). In summary, ISG20 may serve as a potential biomarker for early tumor diagnosis, prognostic assessment and treatment response prediction.

As an immunological adjuvant. An immunoadjuvant is a non-specific immune enhancer, typically administered with an antigen to enhance the immune response to a specific antigen or alter the type of immune response. Its primary function is to improve vaccine efficacy and immune response strength by altering the physical properties of the antigen, promoting antigen processing and presentation and stimulating immune cell activation (73). Tumor neoantigen vaccines and PD-L1 inhibitors are promising immunotherapeutic approaches to the clinical treatment of various types of tumor, but show limited efficacy in patients with tumors lacking functional T cell infiltration (74,75). As aforementioned, ISG20 has been shown to enhance tumor immunogenicity in ovarian cancer, recruiting various immune cells, including CD8⁺ T cells, to infiltrate tumor tissue and enhance antitumor immune responses (22). This suggests that ISG20 may serve as an immunoadjuvant when combined with tumor antigens to achieve antitumor immune effects. However, studies have shown that ISG20 promotes tumor immune evasion in glioma, indicating that its use as an immunoadjuvant should be selected based on the specific tumor type and microenvironment (14,24).

6. Conclusion

ISG20 is an insufficiently explored molecular target in cancer. It is upregulated in various types of tumor tissue, and influences processes such as tumor cell proliferation, migration, invasion, angiogenesis and immune modulation in the TME through complex mechanisms. ISG20 may serve as a tumor antigen, biomarker and immunoadjuvant. However, prior to clinical application, further research is needed to clarify its structure and functional sites as a tumor antigen, evaluate its role as a biomarker and explore its precise application as an immunoadjuvant across different tumor types and microenvironments.

Future research should focus on elucidating the molecular mechanisms underlying the roles of ISG20 in various tumors and further investigating its regulatory network in the TME, particularly its impact on immune cells. Leveraging advanced technology to analyze its three-dimensional structure and protein-protein interaction sites may accelerate the development of small-molecule drugs or biologics targeting ISG20. Additionally, large-scale, multicenter clinical studies should be conducted to validate its value in tumor precision diagnosis and personalized treatment, facilitating its efficient translation from basic research to clinical application, and providing novel strategies and approaches for cancer treatment.

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Availability of data and materials

Not applicable.

Authors' contributions

XZ and SJ designed the study. LZ and SZ wrote the manuscript. HZ, JZ and LC constructed the figures. HL and ZZ performed the literature review. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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