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Non-coding RNAs-Mediated Regulation of Tumor Innate Immunity and Its Clinical Application Prospects

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Abstract. Tumors severely threaten human health, and traditional therapies often struggle with immune escape and drug resistance. Non-coding RNAs (ncRNAs), which do not encode proteins, can regulate tumor innate immune cell functions and related signaling pathways, becoming a research focus. This study explores ncRNAs' mechanisms in tumor innate immunity and clinical prospects. It first sorts out ncRNAs' classification and characteristics, then analyzes their roles in remodeling immune cell functions (regulating immune cell differentiation, polarization, etc., to affect tumor progression) and regulating immune signaling pathways. It also elaborates that ncRNAs interact with cells/factors via exosomes in the tumor microenvironment to modulate immune cells, cytokines, and the extracellular matrix, noting ncRNAs' potential as therapeutic targets and biomarkers. Unlike previous studies that mostly focused on a single type of ncRNA or a single mechanism, this article constructs a comprehensive regulatory network by analyzing the synergistic and antagonistic effects among miRNAs, lncRNAs, and circRNAs, providing a more systematic perspective for related research. Despite challenges, with advances in single-cell sequencing and nano-delivery, ncRNAs are expected to advance tumor innate immunity research and clinical translation.

Keywords: Non-Coding RNA; Tumor Innate Immunity; Tumor Microenvironment; Biomarker.

1. Introduction

Tumors pose a severe threat to human health, and traditional treatment methods often fail to achieve ideal outcomes. For instance, some lung cancer patients still experience recurrence after postoperative chemotherapy [1], which makes exploring new therapeutic directions an urgent priority [2]. A large number of studies have confirmed the close association between non-coding RNAs (ncRNAs) and tumor occurrence and development. Among them, Herbst et al. pointed out in their research on non-small cell lung cancer that the limitations of traditional therapies are closely related to the disorder of intracellular regulatory networks, and ncRNAs may be key molecules to fill this regulatory gap. Subsequently, Song et al. further verified in colon cancer studies that ncRNAs can participate in tumor progression by regulating immune-related pathways, laying a foundation for exploring ncRNAs as new therapeutic targets. Numerous studies indicate a close ncRNA-tumor link; non-protein-coding ncRNAs regulate cellular processes (notably tumor innate immunity) and mediate its regulation via pathways affecting immune cells [3], signaling, and tumor microenvironment [4].

Although these studies have initially revealed the regulatory potential of ncRNAs in tumor innate immunity, there are still many unsolved mysteries in this field. Previous studies mostly focused on a single type of ncRNA or a single mechanism of action: for example, Michaela Kafida et al. only explored the regulatory role of long non-coding RNAs (lncRNAs) in the transcription process [5]. Research on the interactions, synergistic effects, and overall regulatory networks among different types of ncRNAs is relatively scarce [6], in addition, Giuseppina et al. also emphasized that there are even more significant research gaps in the field of ncRNA research related to rare cancers, which limits the universality of ncRNA-based therapeutic strategies [7].

The article explores ncRNAs' tumor innate immunity role (mechanism, clinical prospects), details three ncRNA types' features (immune cell/tumor regulation), key pathway participation (e.g., JAK-STAT) and exosome-mediated tumor microenvironment interaction, notes their

therapeutic/biomarker potential, and aids immunotherapy, clinical translation and prognosis via a comprehensive ncRNA regulatory network.

2. Exploration on Classification and Analysis of Characteristics of ncRNAs

Cellular molecular regulation is complex; as key players, ncRNAs have diverse characteristics, so clarifying ncRNA types is fundamental to understanding their functions. Specifically, ncRNAs are defined as RNA molecules that do not encode proteins yet still exert crucial regulatory effects in various biological processes [8], among them, the primary categories include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs).

MiRNA is a type of single-stranded RNA molecule. It induces gene silencing through complementary base pairing with the 3' untranslated region of target mRNAs, thereby playing a crucial role in post-transcriptional gene regulation [9]. The main focus is on immune cell activity: miR-9 promotes M1 polarization by inhibiting PPARδ, while miR-124 promotes M2 polarization by inhibiting STAT3 and TNF-α converting enzyme, thereby influencing tumor progression [10].

LncRNA is a type of RNA molecule with a conserved secondary structure transcribed by RNA polymerase, and its length exceeds 200 nucleotides [11]. Similar to miRNAs, lncRNAs regulate tumor innate immunity (mainly influencing immune cell vitality); custom arrays identified hundreds of lncRNAs in human/mouse splenic CD8+ T cells [12].

CircRNA is a unique type of exosomal ncRNA. It lacks a 5' cap structure and a 3′ polyadenylated tail, thus possessing excellent stability and a longer half-life [13]. Breast tissue-associated circKIF4A can act as a miR-375 sponge to regulate KIF4A expression, thereby modulating triple-negative breast cancer cell proliferation and migration [14]. Figure 1 presents the characteristics, sources and action sites of the above ncRNAs.

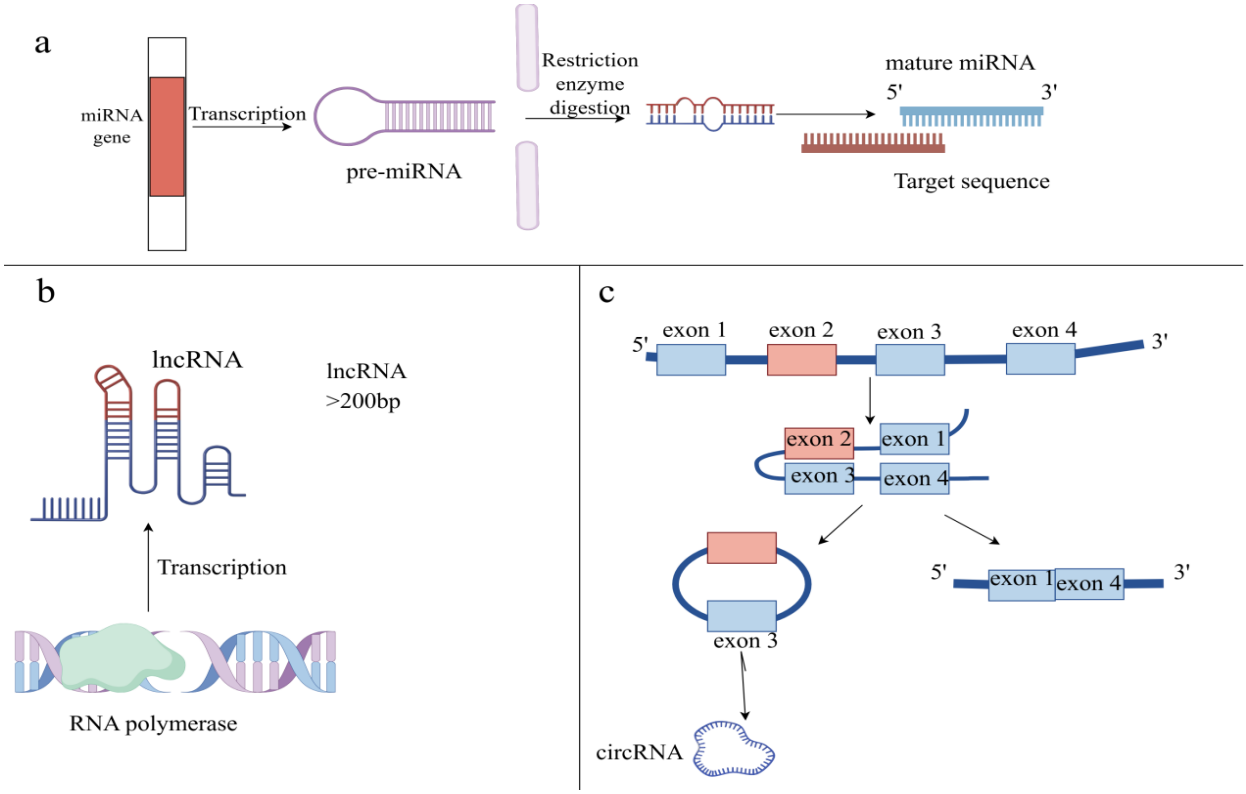

Figure 1. Characteristics, Sources, and Action Sites of NcRNAs by Figdraw

The above outlines ncRNAs' main types/characteristics and further details their significance and research status in tumor innate immunity; critical are their characteristic differences: miRNAs (short linear, easily degraded, low fluid stability) are for clinical targeted therapy via delivery systems,

circRNAs (circular closed, degradation-resistant, high fluid stability) are for early diagnosis biomarkers, and their stability difference directly defines clinical application focuses.

3. NcRNAs Remodel the Functions of Tumor Innate Immune Cells

After clarifying the types of ncRNAs, we can further explore how these different types of ncRNAs exert precise and crucial regulatory effects on the functions of immune cells through their unique molecular structures and modes of action. The immune cells that play a role in cancer mainly include macrophages, dendritic cells, natural killer cells, and T cells [15].

3.1. Mechanism of miRNA-Mediated Regulation of Tumor Innate Immune Cell Functions

To elaborate on the mechanism of miRNA - mediated regulation of tumor innate immune cell functions, it's essential to first grasp how miRNAs exert their regulatory effects at the molecular level. MiRNAs regulate immune cells mainly by regulating gene expression at the post - transcriptional level (inhibiting mRNA translation or promoting mRNA degradation) [16]. Based on this, the expression levels of related factors change, affecting the differentiation, maturation, polarization, and other processes of immune cells.

3.1.1. MiRNA-Mediated Regulation of Macrophage Polarization and Tumor Impact.

Macrophages play a crucial role in the body's physiological and pathological processes, with polarization into M1 and M2 subtypes that exert distinct effects on tumor progression [17]. For instance, miRNAs regulate macrophage polarization through multiple pathways: they can promote inflammation by inhibiting DINPP5D, or regulate M1 polarization by inhibiting SOCS1/BCL6 [18]; specifically, miR-155 blocks M2 polarization (silences IL-13RA, stabilizes TNF, targets CEBP/β), exosomal let-7a promotes M2 polarization (hypoxic tumor), miR-149 impairs M2 macrophage infiltration, miR-214 inhibits M2 polarization (suppresses JAK2/STAT3) [19]. These findings suggest that regulating miRNAs can guide the polarization direction of macrophages, thereby effectively inhibiting tumor progression.

3.1.2. MiRNA-Mediated Regulation of Dendritic Cell Maturation and Immune Functions.

Dendritic cell (DC) function is linked to multiple factors. As key components of immunity, DCs perform antigen presentation, immune activation, regulation, and surveillance [20]. MiRNAs affect DC maturation: miRNA-146a regulates DC maturation and proinflammatory cytokine secretion by targeting CD40L, TRAF6, and IRAK1, reducing NF-κB signaling; miR-17-5p overexpression inhibits DC surface molecule expression and enhances DC endocytosis. MiR-221 silencing increases p27kip1 protein levels and moderate apoptosis in immature DCs, indicating miR-221 supports immature DC survival after monocyte differentiation [21].

3.1.3. MiRNA-Mediated Regulation of NK Cell Development and Cytotoxic Functions.

Natural killer (NK) cells are crucial in the tumor immune system and have dual functions: directly recognizing and killing tumor cells, and secreting cytokines to regulate immune responses [22], miRNAs exert a significant impact on both the development and functions of NK cells [23].

MiR-186-5p can target DAP10, a key adaptor protein of NKG2D, and inhibit NKG2D-DAP10-mediated activation signals to suppress NK cell cytotoxicity [24]. MiR-186-5p targets DAP10 (NKG2D adaptor) to inhibit NKG2D-DAP10 signals and NK cell cytotoxicity; PCR shows miR-181a-5p/miR-223-3p decrease in NK cells of aged/aging mice [25]. These findings suggest that different miRNAs can be selected as markers for patients of different age groups, providing a reference for precise tumor diagnosis and personalized treatment.

3.2. Mechanism of lncRNA-Mediated Regulation of Tumor Innate Immune Cell Functions

After exploring miRNA-mediated immune cell regulation, we turn to lncRNAs—they share similarities with miRNAs in influencing immune cell differentiation, polarization, and infiltration but

differ in targets (miRNAs focus on macrophage polarization/DC maturation; lncRNAs on macrophage expression/DC differentiation/infiltration).

Similar to miRNAs, lncRNAs also regulate macrophage polarization [26]. LncRNA MAGI2-AS3 is abnormal in various cancers; as a molecular scaffold, it recruits chromatin complexes for polarization regulation (KDM1A-mediated H3K4me2 demethylation/RACGAP1 downregulation, EZH2-mediated H3K27 trimethylation/HOXB7 inhibition), altering gene networks, cell polarization and correlating with tumor malignant phenotypes [27]. LncRNAs can regulate DC differentiation/maturation: HOTAIRM1 binds miR-3960 to promote HOXA1, preventing DC differentiation [28]. LncRNAs also affect immune cell infiltration: prostate cancer study shows PCAT14 expression is negatively correlated with DC infiltration [29].

T cells include subsets (cytotoxic, helper, regulatory T cells) with surface receptors for antigen recognition [30]. In cancer, cytotoxic T cells kill tumor cells, helper T cells assist immune activation [31]. LncRNAs affect T cell differentiation and infiltration. Colon cancer: exosomal lncRNA CRNDE-h binds RORγt' s PPXY motif to block its degradation, boost RORγt/IL-17 promoter activity and promote Th17 differentiation [32]. In breast cancer, GSEA/TIMER analysis shows lncRNA TCL6 may correlate with immune cell infiltration [33].

Collectively, these findings indicate that screening lncRNA-targeted agents to regulate immune cell function-related lncRNA activity, or directly modulating lncRNA expression to alter immune cell differentiation, polarization, and infiltration, could enhance the body’s anti-tumor immunity and inhibit tumor progression.

3.3. Mechanism of circRNA-Mediated Regulation of Tumor Innate Immune Cell Functions

After examining miRNAs and lncRNAs, we now focus on circRNAs—unlike the two, they use unique mechanisms, targets, and modes to regulate immune cells: miRNAs regulate post-transcriptional genes, lncRNAs regulate differentiation, and circRNAs involve protein regulation, miRNA interaction, and cytokine modulation.

In addition to regulating T cell differentiation and maturation, circRNAs also play a role in regulating macrophage polarization, just like other ncRNAs. Tumor-expressed PD-L1 binds PD-1, inhibiting T cell activation [34]. CircRNAs impact T cell activity via PD-L1: circ-CPA4 inactivates CD8+ T cells by boosting exosomal PD-L1 and sponging miR-let-7; circRNA_104889 modulates activity T cells through the miR-34a/miR-28-5p/PD-L1/PD-1 axis [35].

CircRNAs—like miRNAs and lncRNAs—are also involved in inducing macrophage polarization: circN4bp1 sponges miR-138-5p to regulate polarization via EZH2; circRNAPLCE1, circITGB6, circ_0001142, hsa_circ_007485 mediate M2 polarization; circRNACdyl, circPrkcsh, circPPM1F drive M1 polarization [36]. Developing drugs to inhibit protumor circRNA function or enhance antitumor circRNA activity can precisely regulate macrophage status for tumor therapy.

Key ncRNAs' roles in Table 1.

Table 1. Core Regulatory Roles of ncRNAs in Tumor Innate Immunity

Type	Core Regulatory Targets	Key Roles and Tumor Associations
MiRNA	Immune cell polarization, signaling pathways	Regulates macrophage M1/M2 polarization, DC maturation, NK cytotoxicity; affects tumor progression
LncRNA	Immune cell differentiation, cell infiltration	Regulates T cell/DC differentiation, correlates with TME immune infiltration; modulates tumor malignancy
CircRNA	Immune escape, cell function maintenance	Regulates PD-L1/PD-1-mediated T cell inactivation, macrophage polarization, NK functions; serves as stable biomarkers

Summary: The three ncRNAs exert synergistic or antagonistic effects—lncRNA synergizes with miRNA to regulate macrophage polarization, circRNA antagonizes miRNA in the context of T cell activation (with lncRNA also aiding this regulatory process), and miRNA inhibits NK cell signals (while circRNA complements by influencing cytotoxicity) to maintain NK cell function and affect tumor innate immunity. As for the table content, it systematically lists the specific regulatory roles of each of these three ncRNAs (lncRNA, circRNA, and miRNA) and the nature of their interactions (whether synergistic or antagonistic) in different immune-related processes, such as macrophage polarization, T cell activation, and NK cell function modulation. This summary integrates and elaborates on the relationships and mechanisms that are presented in the table.

4. NcRNAs and Tumor Innate Immune Signaling Pathways

Immune cell function hinges on signaling networks (ncRNA immune regulation is linked to these); exploring ncRNAs in tumor innate immunity pathways (JAK-STAT, NF-κB, TLR) holds the key to mechanisms, immune escape and novel therapies.

The JAK-STAT pathway is a crucial intracellular signal transduction pathway [37]. STAT proteins bind phosphorylation sites via SH2 domains, are phosphorylated by JAK kinases, dissociate to form dimers, enter the nucleus through nuclear localization signals, and bind specific DNA in the nucleus to regulate gene transcription [38].

The TLR (Toll-like receptor) pathway is critical for defending against pathogens and maintaining immune homeostasis [39]. Pathogen-associated factors activate TLRs by binding and recruiting MyD88-like adaptors; IRAK's cascade (TRAF6, TAK1, IKK) degrades IkB, releases NF-κB, and NF-κB enters the nucleus for immune gene transcription and immune-inflammatory responses [40].

NF-κB is a nuclear protein factor that specifically binds to the κB sequence in the immunoglobulin κ light chain gene enhancer [41]. It enters the nucleus via nuclear localization signal, binds to κB site in target gene promoters to initiate transcription, and triggers inflammation-like responses [42].

The three pathways are not isolated; their transduction routes and interactions are in Figure 2.

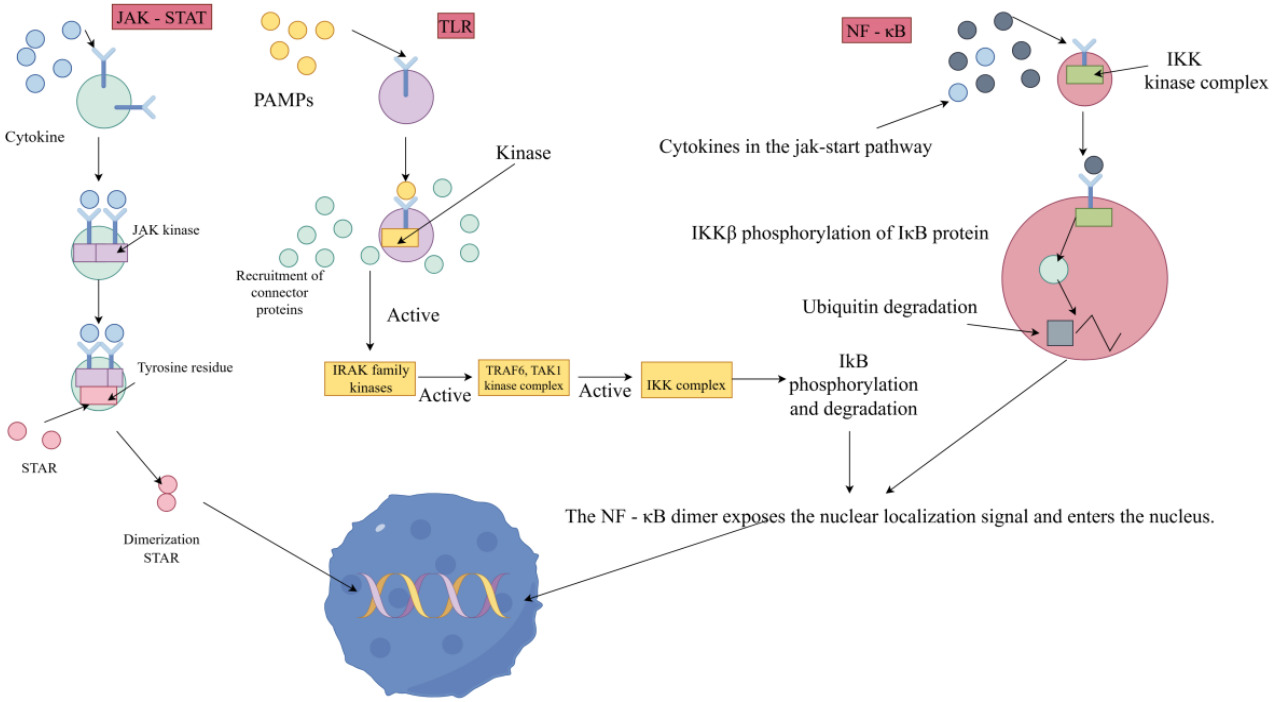

Figure 2. Tumor Signaling Pathway Diagram. By Figdraw

NcRNAs regulate above pathways by inhibiting/promoting signal transduction: lncRNA-IL7R/lncRNA-EPS activate TLR pathway; miR-9 modulates TLR pathway (suppresses inflammation), miR-139 activates RIG-I (induces IFN-β); miR-3570/122/125a/125b/22/3470b

inhibit MAVS post-transcriptionally, MAVS-related antiviral lncRNA inhibits miR-122 (as ceRNA); [43]; miR-23b [44] and miR-146a [45] both inhibit IRF3/7. MiRNAs/lncRNAs roles in Figure 3.

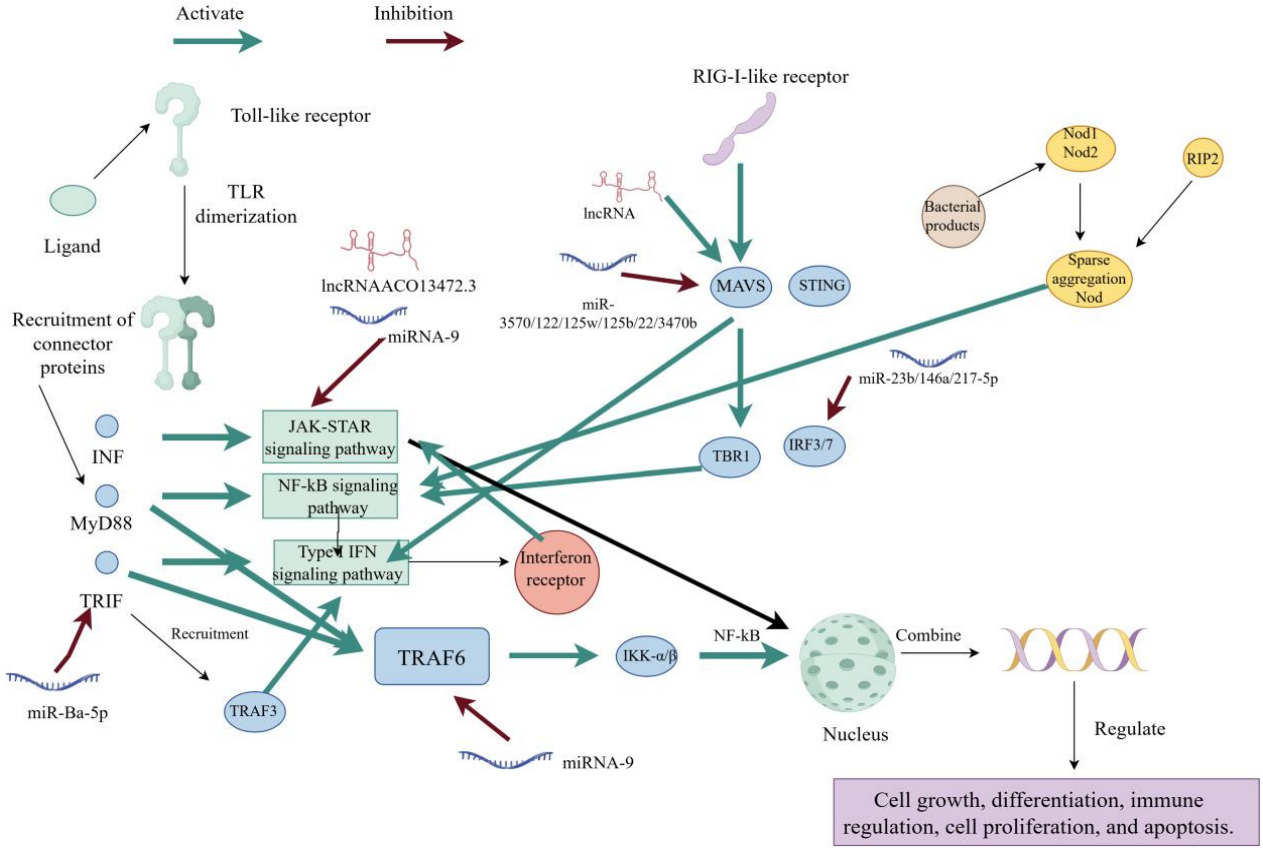

Figure 3. Schematic of ncRNA Effects on Tumor Signaling Pathways. By Fig draw

The above studies explored ncRNA interactions: in the TLR pathway, lncRNA-IL7R etc. promote activation while miR-9 suppresses inflammation; miR-3570 etc. inhibit MAVS, yet MAVS-related antiviral lncRNA binds miR-122 to inhibit its activity. These ncRNAs antagonize to co-regulate immune cell function and responses.

5. NcRNAs in the Tumor Microenvironment: Key to Intercellular Communication

Building on the previous discussion about ncRNAs regulating immune signaling pathways, during tumor progression, these key regulatory ncRNAs further interact with cells and factors in the tumor microenvironment (TME) to regulate the TME itself. As a core site for tumor cell growth, proliferation, and metastasis, the TME mainly consists of tumor cells, immune cells, extracellular matrix, and soluble molecules [46].

This section focuses on the exosome-mediated pathway: prostate cancer exosomes containing miRNA let-7a-5p downregulate integrin-β3 (inducing M2 polarization and PCa cell migration), and CRC cell exosomes are high in miR-21-5p [47]. Exosomes derived from renal cell carcinoma also deliver overexpressed circSAFB2 to TAMs, inducing M2 polarization [48]. During tumor development, ncRNA-enriched exosomes impact progression through target sites; using exosomes as biomarkers or intervening in their pathways helps inhibit tumors.

NcRNAs regulate cytokines in the microenvironment: miR-155 targets and inhibits SOCS1 expression [49]; circRNA-002039 sequesters miR-29b to relieve its suppression on target genes, altering cytokine (e.g., interleukin-10) expression and facilitating cancer cell immune escape [50]. Clearly, ncRNAs have a broad range of effects, offering multiple perspectives for exploring tumor suppression methods.

Additionally, ncRNAs shape the extracellular matrix: miR-29 downregulation promotes myocardial fibrosis (excessive extracellular matrix synthesis/deposition); lncRNA NEAT1 upregulation in degenerated human nucleus pulposus cells affects ERK/MAPK pathway for extracellular matrix degradation [51].

To summarize, the three ncRNAs exert synergistic/antagonistic effects in the tumor microenvironment—miRNAs and circRNAs synergistically regulate immune cell polarization and antagonize each other (with examples), while all three together maintain its balance (e.g., miR-29 and lncRNA NEAT1 affect extracellular matrix synthesis and degradation respectively).

6. Potential of non-coding RNAs as Targets for Tumor Innate Immune Therapy

Exploring ncRNAs' tumor effects aims to open avenues: identifying ncRNA-mRNA interactions as therapeutic targets and using ncRNA enrichment as biomarkers for tumor diagnosis and treatment efficacy; taking MAVS (in tumor immune signaling pathways) as an example, its protein network (Fig. 4a) and node centrality (Fig. 4b) were analyzed, and TAAF6, DDX58, and TBK1 (with high centrality) may be key therapeutic targets, which helps develop related approaches and outlines the prospects of targeted therapy.

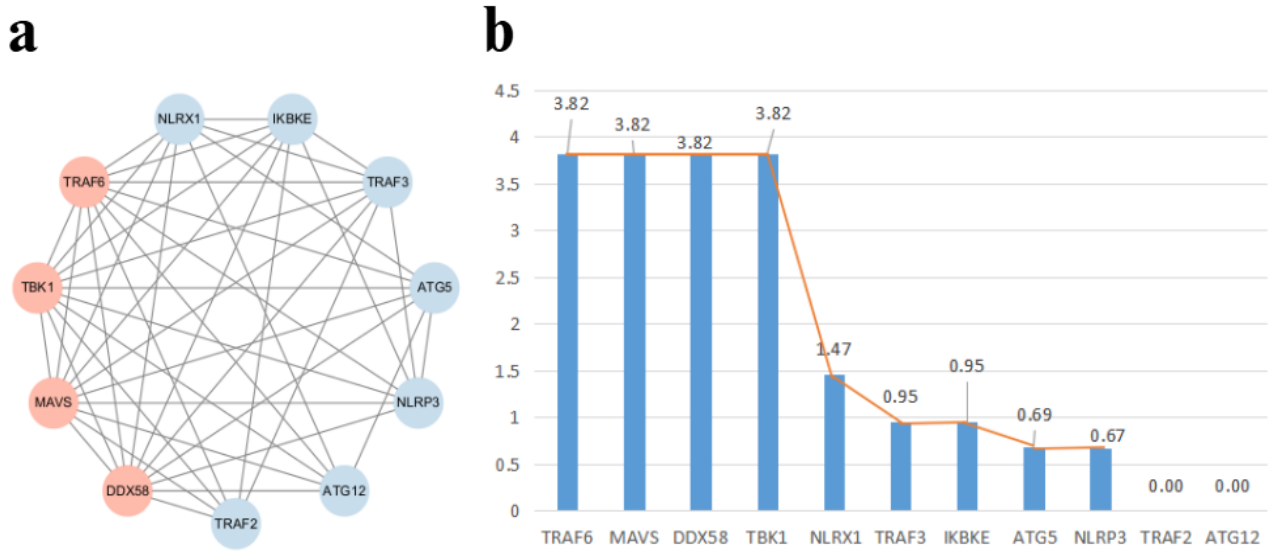

Figure 4. MAVS Network and Betweenness Centrality

Note (a) MAVS Protein Network (b) Node Betweenness Centrality

Acting as key biomarkers, NcRNAs are indispensable for early disease detection. Three core attributes underpin this significance: their expression alterations occur earlier than both clinical symptoms and shifts in traditional biomarkers; they are closely associated with disease progression; and their monitoring supports prognosis evaluation and treatment planning.

7. Conclusions and Prospects

This article systematically reveals that ncRNAs mainly include miRNAs, lncRNAs, and circRNAs, each with unique structural and functional traits. In remodeling tumor immune cell functions, they precisely regulate the differentiation, polarization, maturation, and activity of macrophages, DCs, NK cells, and T cells, thereby affecting tumor progression. In immune signaling pathway regulation, ncRNAs participate in key pathways like JAK-STAT, NF-κB, and TLR, and influence immune cell activation and immune response intensity by inhibiting or promoting signal transduction. In the tumor microenvironment, ncRNAs interact with cells and cytokines via exosome mediation, regulating immune cell functions, cytokine secretion, and extracellular matrix state—exerting a notable impact on tumor growth, invasion, and metastasis. Additionally, ncRNAs hold potential as tumor therapeutic targets and biomarkers, offering new directions and insights for tumor treatment and diagnosis.

Looking ahead to the future, although research on ncRNAs has made certain progress, there are still many challenges, such as the relatively limited focus on rare cancers. With the continuous advancement of single-cell sequencing technology, it has become possible to deeply analyze the expression patterns and functions of ncRNAs at the single-cell level, which helps identify more tumor-related ncRNA biomarkers. Nanotechnology can be used to develop more efficient ncRNA delivery systems, improving the efficacy and safety of ncRNAs as therapeutic agents. Gene editing technologies such as the CRISPR/Cas system can precisely regulate the expression and function of ncRNAs, providing a powerful tool for studying the mechanism of action of ncRNAs and developing targeted therapeutic strategies. By comprehensively applying these technologies to conduct in-depth research on the role of ncRNAs in tumor innate immunity, it is expected to open up new avenues for tumor immunotherapy, significantly improve the prognosis of tumor patients, and bring new hope for overcoming cancer, a major disease.

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