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Review

Non-coding RNAs, another side of immune regulation during triple-negative breast cancer

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ABSTRACT

Triple-negative breast cancer (TNBC) is considered about 12–24 % of all breast cancer cases. Patients experience poor overall survival, high recurrence rate, and distant metastasis compared to other breast cancer subtypes. Numerous studies have highlighted the crucial roles of non-coding RNAs (ncRNAs) in carcinogenesis and proliferation, migration, and metastasis of tumor cells in TNBC. Recent research has demonstrated that long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) play a role in the regulation of the immune system by affecting the tumor microenvironment, the epithelial-mesenchymal transition, the regulation of dendritic cells and myeloid-derived stem cells, and T and B cell activation and differentiation. Immune-related miRNAs and lncRNAs, which have been established as predictive markers for various cancers, are strongly linked to immune cell infiltration and could be a viable therapeutic target for TNBC. In the current review, we discuss the recent updates of ncRNAs, including miRNAs and lncRNAs in TNBC, including their biogenesis, target genes, and biological function of their targets, which are mostly involved in the immune response.

1. Introduction

The incidence and morbidity rate of breast cancer has continuously increased worldwide [1]. Triple-negative breast cancer (TNBC), characterized by the absence of progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2) expression, is by far the most malignant subtype of breast cancer [2]. TNBC accounts for about 12–24 % of all breast cancer cases. Patients experience poor overall survival (OS), high recurrence rate, and distant metastasis compared to other breast cancer subtypes [3,4]. Great strides have been made to uncover the underlying mechanisms of TNBC carcinogenesis, particularly by focusing on non-coding RNAs (ncRNAs) [5].

ncRNAs are a cluster of RNAs that generally exist in eukaryotes and have non-protein-coding properties. As described, approximately 98 % of the genome is composed of ncRNAs [6], including circular RNAs (circRNAs), microRNAs (miRNAs), and long non-coding RNAs (lncRNAs) [7]. Previously, ncRNAs, because of the non-coding features, were described as "junk RNAs". However, with emerging data, the specific roles of ncRNAs in different tumors, particularly in TNBCs, have been explained [8]. ncRNAs have critical roles in numerous biological processes, including transcription, energy conversion, cell division, molecular transport and intercellular signaling transduction. In addition, the correlation between ncRNAs and their target genes creates a vast gene regulatory network, which mediates cell behavior [9].

ncRNAs are involved in cellular processes, including pre-transcription, mRNA transcription, post-transcription modification, and translation. If they do not act properly, it interferes with cellular function, subsequently resulting in uncontrolled cell proliferation and genomic instability, triggering carcinogenesis. lncRNAs are involved in tumorigenesis, invasiveness, and drug resistance [10]. Moreover, most previous studies have demonstrated deregulated tumorigenic lncRNAs

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resulting in cancer cell proliferation, metastasis, and tumor progression in TNBC patients [11]. In the current review, we discuss the recent updates of ncRNAs, including miRNAs and lncRNAs in TNBC, including their biogenesis, target genes, and biological function of their targets, which are mostly involved in the immune response.

2. TNBC

TNBC is a subtype of breast cancer that may be identified by the fact that it does not express PR, ER, or HER2 [12]. TNBCs account for 9–20 % of breast cancers and are especially prevalent in younger women who are bearers of the BRCA (breast cancer gene) mutation. Poor disease-free survival (DFS), a high recurrence rate, and a shortened overall survival (OS) time are all characteristics of this aggressive type breast cancer. These characteristics are linked with clinicopathologic and biological features, such as high histological grade, high nuclear grade, genomic instability, loss of suppressor genes, and sometimes TP53 mutations, as well as the acquisition of stem cell-like and migratory ability of tumor cells [13,14]. In addition to the identification of breast cancer based on its molecular subtypes, such as luminal A, luminal B, HER2+, and TNBC, a classification of TNBC subtypes based on gene expression analysis has been described [15,16]. This classification includes basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), and luminal AR (LAR). Molecular subgrouping of TNBC highlights in a noticeable way the association of mesenchymal properties as well as interactions among extracellular matrix (ECM) and tumor cells in the aggressive ability of TNBC tumor cells [17]. Molecular subgrouping of TNBC highlights in a noticeable way the association of mesenchymal properties as well as interactions among extracellular matrix It has been shown that breast cancer growth and metastasis are both connected to alterations in the ECM. Overexpression of matrix metalloproteinases (MMPs), heparanases, cysteine cathepsin, urokinase, and other related enzymes has been seen in malignancies [18]. Cross-linking between collagen and elastin molecules is catalyzed by lysyl oxidase (LOX) and lysine hydroxylase, which also encourage modifying the behavior of tumor cells by controlling the elasticity and strength of ECM. Any modification or addition of a cross-linked matrix makes the tumor tissue more rigid, stimulates cell proliferation, and bolsters the signaling pathways that are involved in migration and metastasis [19]. ECM components make it possible for tumor cells to proliferate, migrate, and metastasize by activating a number of signaling pathways, including Janus kinase 2 (JAK2)/Signal transducer and activator of transcription 5 (STAT5), Phosphoinositide 3-kinase (PI3)/AKT kinase (AKT), AKT/mechanistic target of rapamycin (mTOR), Src, and Extracellular signal-regulated kinases (ERK)1/2 and JNK [17,20,21]. Recent research has shown that noncoding RNAs, in particular miRNAs and lncRNAs, may affect several genes and signaling pathways, hence increasing the likelihood of the development of tumors and immunological responses. These are the topics that are covered in the following sections.

3. miRNAs alteration in TNBC progression

miRNAs (21–23 nucleotides) are short, non-coding, single-strand RNAs [22]. They are involved in the regulation of gene expression post-translationally [23,24]. miRNAs make up 1–5 % of the total human genome; they act as a regulator of approximately 30 % of protein–coding genes [25,26]. In miRNA biogenesis, primary miRNAs (pri-miRNAs) are transcribed by RNA polymerase II/III. To produce precursor miRNAs (pre-miRNAs), post-transcriptional changes such as 7-methylguanosine capping and polyadenylation on pri-miRNAs are performed. After that, pre-miRNAs (stem-loop secondary structure) binding to Exportin 5 is transported from the nucleus into the cytoplasm, which evolved by Drosha, Dicer (RNase III), RNA polymerase III, and other associated molecules. At the final step, mature miRNAs, together with the RNA-induced silencing complex (RISC), form a functional complex that can attach to the 3′-untranslated regions (3′-UTRs) of target mRNA molecules and mediate the degradation of target mRNA or suppress of translation process [25,27,28].

Numerous studies have emphasized the importance of microRNAs in TNBC carcinogenesis, proliferation, migration, and metastasis. Based on their oncogenic or oncosuppressive properties, microRNAs have a dual function in tumor promotion and suppression [29]. Table 1 lists the most reported miRNAs that are associated with TNBC. Typically, miRNA dysregulation is the consequence of genomic and epigenetic alterations, which are commonly related with chromosomal abnormalities including the deletion, amplification, or translocation of miRNAs. These chromosomal abnormalities have the potential to lead to the development and progression of tumors [29]. Of oncogenic miRNAs involved in TNBC, several are of major interest. For example, miR-135b. miR-135b overexpression in TNBC is associated with cancer cell proliferation. miR-135b expression is independent of hormones and is considered an oncomiR. It is demonstrated that Androgen Receptor (AR), as a protein target of miR-135b, serve as a poor prognosis factor [30]. A microRNA known as miR-150-5p can be found on chromosome 19q13. In some hematologic disorders as well as head and neck, liver, cervical, colorectal, and ovarian carcinomas, miR-150-5p expression is reduced, which is indicative of a tumor suppressive activity in these tumors. On the other hand, miR-150-5p expression is increased in lung and gastric cancers, which promotes the development of tumors. In a recent study, results have indicated; that miR-150-5p expression levels are significantly related to high tumor grades and the Caucasian ethnicity in TNBC. Moreover, miR-150-5p regulates cell growth, clonogenic capacity, drug resistance, and migration [31]. Autophagy plays an important role in maintaining cancer stem cells (CSCs). The results of a study indicated that autophagy flux was inhibited in TNBC cancer stem cells. Moreover, miR-181a expression is upregulated in TNBC cancer stem cells. miR-181a targets autophagy-related 5 (ATG5) and autophagy-related 2B (ATG2B), which are involved in the development of autophagosomes. Suppression of miR-181a expression resulted in reduced TNBC stemness and an elevated autophagy flux. Autophagy prevents cancer stemness by a miR-181a-regulated mechanism in TNBC [32]. Some members of the let-7 family linked with miR-100, miR-34a-1/2, and miR-125b-1 were discovered at fragile locations on human chromosomes (11q23-q24-D) that are associated with aberrant

Table 1
Immune-related ncRNAs studied in TNBC models.

miRNA/lncRNA	Target	Cell line/model	Ref.
miR-424-5p	PD-L1	MDA-MB-231	[86–88]
miR-34a	PD-L1	MDA-MB-231	[89–91]
miR-138-5p	PD-L1	MDA-MB-231	[92]
miR-570–3p	PD-L1	MDA-MB-231, MDA-MB-468	[93]
miR-200c-3p	PD-L1, PD-L2, HMOX-1, GDF15	MDA-MB-231, BT549, Hs578T, SUM159PT, MDA-MB-453	[94,95]
miR-383-5p	PD-L1	MDA-MB-231	[96]
miR-3609	PD-L1	MDA-MB-231, MDA-MB-468	[97]
miR-195-5p	PD-L1	MDA-MB-231	[98]
miR-497-5p	PD-L1	MDA-MB-231	[98]
DRAIC	IL-17	Bioinformatics	[99]
irlncRNA	PD-L1	Bioinformatics	[100]
MALAT1	MICA/B, ULBP2, CD155, ICAM-1, TNF-α, IL-10	Human samples	[101]
LncRNAs RP11-180N14.1, RP11-1024P17.1, RP11-890B15.3	Extreme immune response	Bioinformatics	[102]
HEIH	MICA/B, PD-L1	MDA-MB-231	[103]
GATA3-AS1	GATA3, PD-L1	MDA-MB-468, MDA-MB-436, MDA-MB-231, HCC1937	[73]
OSTN-AS1	PDCD1, CTLA-4	Bioinformatics	[53]

miRNA expression in breast cancer [33]. MiR-17/92 and the miR-200 cluster were elevated, but let-7b and let-7c were downregulated among the 116 unregulated miRNAs in primary TNBC and normal tissue samples, according to a separate research [34]. Kim et al. identified dysregulated miRNAs in TNBC patients. Overexpression of miR-371b-5p substantially inhibited TNBC cell proliferation, migration, and invasion. In addition, the expression of cold shock domain-containing protein E1 (CSDE1), a direct target gene of miR-371b-5p, was shown to be elevated in TNBC cells. Furthermore, they discovered that suppressing the expression of CSDE1 reduced the proliferation of TNBC cells by regulating the transcription of Rac Family Small GTPase 1 (RAC1). CSDE1, the phosphorylated C-terminal domain (p-CTD) of RNA polymerase II (RNAPII), and Cyclin-dependent kinase 7 (CDK7) form a complex. In CSDE1-deficient TNBC cells, downregulation of CSDE1 results in a weak connection between RNAPII p-CTD and CDK7, a drop in RNAPII p-CTD expression, and a decrease in RAC1 transcript levels. miR-371b-5p has been identified as a tumor-suppressing microRNA that influences the CSDE1/Rac1 axis. In addition, this miRNA has the potential to function as a biomarker for predicting TNBC [35].

4. lncRNAs alteration in TNBC progression

LncRNA is a form of RNA molecule with longer than 200 nucleotide transcripts. In the form of RNA, they serve a crucial function in controlling gene expression at several levels (epigenetic, transcriptional, or post-transcriptional regulation). lncRNA is a novel gene regulator associated with the beginning, development, and prognosis of human illnesses such as cancer [36]. LncRNAs may have a role in cancer progression by controlling cell proliferation, apoptosis, migration, invasion, and stemness [37,38]. Furthermore, due to their high efficiency, tissue specificity, and stability, lncRNAs may be used as potential therapeutic targets and biomarkers for diagnosis, prognostic evaluation, and treatment [39]. As oncogenes and/or tumor suppressors, lncRNAs may play a role in epigenetic alterations. Recent research has implicated many lncRNAs, including SOX21 Antisense Divergent Transcript 1 (SOX21-AS1), Human ovarian cancer-specific transcript 2 (HOST2), HUMT, X-inactive specific transcript (XIST), FAM83H-AS1, and LINC00173, in the initiation and development of TNBC through a variety of routes and mechanisms [40–43]. Han et al. studied the function and modulation of FAM83H-AS1 during TNBC progression. FAM83H-AS1 expression is elevated in TNBC cells and tissues, and it stimulates TNBC cell proliferation, migration, and invasion through modulating miR-136-5p and metadherin expression [42]. Also, Fan et al. proposed LINC00173 as a novel TNBC driver. They demonstrate that LINC00173 increases TNBC cell proliferation and invasion by inhibiting miR-490–3p. As a result, targeting LINC00173 could be a possible treatment method for TNBC [44]. Another study revealed that the lncRNA Plasmacytoma Variant Translocation 1 (PVT1) induces TNBC carcinogenesis by promoting Kruppel Like Factor 5 (KLF5)/β-catenin signaling. PVT1 expression is increased in clinical TNBC cancers. PVT1 depletion decreased cell proliferation, colony formation, and orthotopic xenograft tumor growth when genetic methods targeting PVT1 in TNBC cells were used [45]. Moreover, It is revealed that LncRNA MIR100HG supports cell proliferation in TNBC via triplex formation with p27 loci [46]. In the instance of chemosensitivity, researchers compared the expression levels of lncRNA H19 in paclitaxel-resistant and paclitaxel-sensitive cell lines. lncRNA H19 expression was much greater in paclitaxel-resistant cells than in paclitaxel-sensitive cells, and taking down lncRNA H19 might restore chemosensitivity in paclitaxel-resistant TNBC [47]. Through the miR-199b-5p/paxillin axis, the lncRNA DLX6 Antisense RNA 1 (DLX6-AS1) increased cell proliferation, epithelial-mesenchymal transition (EMT), and cisplatin resistance in TNBC [48]. Additionally, downregulation of HLA Complex P5 (HCP5) contributed to cisplatin resistance in TNBC, although HCP5 overexpression restored the resistance through upregulating the Phosphatase and tensin homolog (PTEN) level [49]. In order to investigate the role of lncRNAs in TNBC stemness, Shin et al. introduced Nuclear Enriched Abundant Transcript 1 (NEAT1) as a central lncRNA associated with cancer stem cell property in this cancer [50]. Also, lncRNA Colon Cancer Associated Transcript 2 (CCAT2) supports oncogenesis in TNBC through stemness regulation of cancer cells [51]. In TNBC cells, Lung Cancer Associated Transcript 1 (LUCAT1) is overexpressed, and inhibiting LUCAT1 reduced cell stemness. LUCAT1 interacts with ELAV Like RNA Binding Protein 1 (ELAVL1) protein through SOX2 and stabilizes Lin-28 Homolog B (LIN28B) expression, affecting cell stemness in TNBC by altering SOX2 expression [52]. Several studies examined the role of lncRNAs in TNBC apoptosis. It is revealed that up-regulated lncRNA Growth Arrest Specific 5 (GAS5) stimulates apoptosis of TNBC [53]. Hepatocellular Carcinoma Up-Regulated EZH2-Associated Long Non-Coding RNA (HEIH) is an oncogenic lncRNA that regulates TNBC apoptosis via the miR-4458/SOCS1 axis and is overexpressed in TNBC and linked with clinical progression [54]. In addition, XIST is down-regulated in TNBC, and overexpression of XIST inhibits TNBC cell proliferation and EMT, induces apoptosis in vitro, and inhibits tumor development in vivo [55].

5. immune-related non-coding RNAs in TNBC

The ability of an organism to establish powerful immunity to pathogens while avoiding autoimmunity to self-antigens depends on precise regulation of immune system gene expression [56]. The majority of research has so far concentrated on the role of proteins in this process, notably cell-surface receptors, released cytokines, and transcription factors. However, RNA's contribution is less well understood. Non-coding RNAs, such as lncRNA and miRNA, are pervasive genes that regulate a wide range of biological processes, including immune response control (Fig. 1) [57–59].

The importance of miRNA is not restricted to cancer cells; it has also been linked to immune cell activation and immune response modulation. According to the findings of a recent study, the microRNA known as miR-149–3p possesses the capability to target the inhibitory receptors known as Programmed cell death 1 (PD-1), T-cell immunoglobulin mucin-3 (TIM-3), and B- and T-lymphocyte attenuator (BTLA) when it comes to breast cancer. It is possible to improve the CD8+ T-cell-mediated immune response and reverse T-cell fatigue by improving the number of T-cell cytokines that are related with and facilitate T-cell activation, promoting T-cell proliferation and reducing T-cell death, and downregulating Forkhead box protein 1 (FOXP1). This work further showed the function that miR-149-3p plays in modulating antitumor immunity and altering T-cell fatigue both directly and indirectly [60]. In a recent research, it was shown that miRNA-141 had an anti-cancer impact on breast cancer through cytotoxic CD4+ T cells and Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4) expression [61]. Zhang et al. proposed new immunotherapy for breast cancer treatment based on miR-5119 mimic-engineered dendritic cells (DCs). Engineering DCs with miR-5119 suppressed various negative regulatory factors in DCs, including inhibitory receptor ligands like PD-1 ligand (PD-L1) and Indoleamine 2,3-dioxygenase 2 (IDO2), which stimulated antitumor immune responses and upregulated cytokine secretion while lowering inhibitory receptor expression and T cell apoptosis [62]. Weng et al. demonstrated that miR-34a expression enhances M1 polarization in p53-mutant TNBC cells, implying that miR-34a may influence tumor immunity and heterogeneity. Monocarboxylate transporter 1 (MCT-1) antagonists, in combination with miR-34a expression, may modify immune cell polarity and activity, enhancing TNBC therapeutic efficacy [63]. The miR-200c/PAI-2 axis promoted IL-10 production in TNBC cells, which boosted Tumor-associated macrophage (TAM) polarization towards the M2 phenotype [64]. Also, miR-200c restoration increases the release of cytokines that improve M1 antitumor macrophage polarization [65,66]. miR-519a-3p has been found to enhance cancer cell survival by inhibiting Natural Killer (NK) cell activation, developing resistance to NK

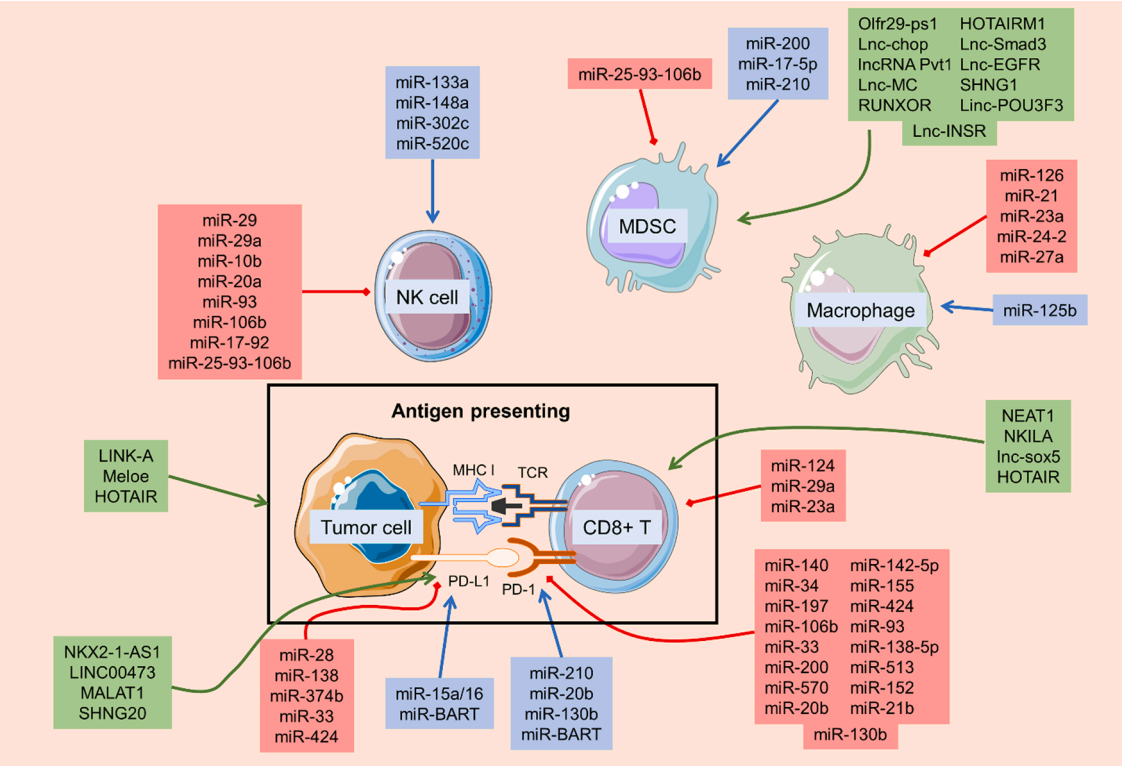

Fig. 1. Immune regulation by ncRNAs. miRNAs and lncRNAs could affect the activity of immune cells and immune checkpoints to trigger or inhibit the stimulation of these immune components.

cell-mediated cytotoxicity, and triggering tumor cell death by regulating functionally related pathways synergistically [67].

Additionally, it has been shown that some immune-related lncRNAs that have been well researched have a regulatory function in the activities of the immune system at an epigenetic level. Studies have shown that lncRNAs are extremely lineage-specific and influence the differentiation and function of innate and adaptive cell types [68]. Recent research found that T Cell Leukemia/Lymphoma 6 (TCL6) regulated tumor-associated B cells, CD8+ T cells, CD4+ T cells, neutrophils, and DCs. The lncRNA TCL6 was also associated with TIL infiltration and the immune checkpoint molecules PD-1, PD-L1, PD-L2, and CTLA-4. As a consequence, lncRNA TCL6 was likely associated with immune infiltration and may be a useful biomarker for breast cancer patients with poor prognosis [69]. lncRNA Small Nucleolar RNA Host Gene 1 (SNHG1) controls Treg cells' differentiation and affects breast cancer's immune escape by regulating miR-448/IDO [70]. Myocardial Infarction Associated Transcript (MIAT), as a lncRNA, plays a vital function in breast cancer immune response and provides new insight into breast cancer immune control [71]. The biological functions of OSTN Antisense RNA 1 (OSTN-AS1) have been revealed to be strongly linked to immunity and metabolism. PD-1, CTLA-4, and CD79, among immune-related genes implicated in T- and B-cell receptor signaling pathways, showed a strong linear connection with OSTN-AS1 expression in TNBC [53]. Moreover, Oncogenic lncRNA LINK-A suppresses antigen presentation and intrinsic tumor suppression [72]. The lncRNA GATA3 Antisense RNA 1 (GATA3-AS1) contributed to TNBC formation and immune evasion by stabilizing PD-L1 protein and degrading GATA3 protein, indicating a potential target for TNBC treatment [73]. HEIH was predominantly upregulated in TNBC tissues, as compared to normal and other breast cancer subtypes. Knocking down HEIH in MDA-MB-231 cells led to a substantial decrease in cellular viability, colony-forming ability, and migratory potential. These results indicate that HEIH is a cancer-causing lncRNA in TNBC. In TNBC cells, HEIH siRNAs induced an upregulation of the key NKG2D ligands MICA and MICB, suggesting an immunomodulatory role. In addition, inhibiting HEIH dramatically decreased the immunosuppressive cytokines Transforming growth factor-beta (TGF-β) and IL-10 [74].

6. Targeting immune-related non-coding RNAs as a therapeutic approach in TNBC treatment

Previous research has found that TNBC is linked to a large number of molecular changes and that specific molecular factors that play key roles in TNBC progression can be addressed to treat TNBC. A growing body of evidence suggests that dysregulated expression of non-coding RNAs is linked to various diseases, including TNBC [75] (Table 1). miRNAs and lncRNAs have recently been shown to have a role in immune system control by influencing tumor microenvironment, epithelial-mesenchymal transition, dendritic cell and myeloid-derived stem cell regulation, and T and B cell activation and differentiation. Immune-related miRNAs and lncRNAs, which have been established as predictive markers for various cancers, are strongly linked to immune cell infiltration and could be a viable therapeutic target for TNBC [76]. There are two approaches to using miRNAs for therapeutic purposes. miRNA antagonists are one technique for inhibiting oncomiRs. The other strategy, miRNA replacement, entails reintroducing tumor suppressor miRNAs to replace those that have lost action [77]. Also, technologies such as antisense oligonucleotides, CRISPR-Cas9 and nanomedicines may be promising strategies to target lncRNAs [78]. A recent study observed that knocking down Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) decreased tumor development and metastasis in vivo. Additionally, patients with a high MALAT1 expression level had a lower overall survival time than those with a low MALAT1 expression level.

Furthermore, the findings revealed a reciprocal negative control link between MALAT1 and miR-1: downregulation of MALAT1 enhanced miR-1 expression, whereas overexpression of miR-1 lowered MALAT1 expression. Slug has been identified as a direct miR-1 target. The miR-1/

slug axis is thought to have played a role in MALAT1's function. As a result, MALAT1 could be a target for TNBC treatment [79]. When miR-5119 mimic-engineered DC vaccinations were delivered via injection, apoptosis of spleen T cells from breast tumor-bearing mice was decreased when compared to T cells from breast tumor-bearing mice treated in vivo with conventional, control miRNA-transfected DC immunization. Based on these data, it seems that treatment with miR-5119 mimic-engineered DCs may reduce apoptosis in T cells in breast cancer rats [62]. GATA3 has recently been identified as a regulator in T helper cell differentiation. In TNBC cells, a recent study looked at the internal association between the lncRNA GATA3-AS1 and GATA3. To prove the effect of GATA3-AS1 on TNBC tumor growth and metastasis, in vivo tests were carried out. It was determined that the GATA3-AS1–downregulated group grew slower, which was reflected in tumor volume and weight [73]. The lncRNA PCAT6 increases TNBC cell proliferation, motility, and angiogenesis both in vitro and in vivo. Furthermore, it was shown that M2 macrophages released VEGF to trigger the overexpression of PCAT6, which may offer new insight into TNBC treatment [80].

LncRNA-targeted therapy may open new possibilities for tumor combination therapy. Antisense oligonucleotide application (ASO) gives lncRNA-targeted therapy its start. ASO targets RNAs, causing co-transcriptional cleavage via RNase H to stop transcription and rapid lncRNA destruction. For instance, it has been discovered that therapeutic targeting of lncRNA PVT1 utilizing PVT1 ASOs can inhibit the development of tumor cells both in vitro and in vivo [81]. It's significant that ASO targeting cancer-causing lncRNA has advanced to the development stage. Additionally, the use of small molecule inhibitors in lncRNA is in its infancy. Some particular molecules can obstruct the connection between lncRNAs and proteins or behave as clones of competing lncRNA structures to obstruct the functions of lncRNAs. Comp34, a curcumin derivative, inhibits the carcinogenic lncRNA NUDT3-AS4 in TNBC and exhibits a strong preclinical anti-tumor activity [82].

It has been demonstrated that non-coding RNAs that control IFN signaling play a role in the development of several cancers and immune-related diseases. IRFs are the molecules that have been studied the most in relation to how non-coding RNAs affect IFN signaling [111–115]. For instance, functional connections between IRF-1 and miR-301a, miR-195, miR-19a, miR-18a, miR-4295, miR-124, and miR-155 have been discovered. IRF-2 also interacts with miR-664, miR-221-3p, and miR-1290. In addition, miR-320, miR-587, miR-19, and miR-18a all interact with IRF-6. The greatest way to evaluate these interactions has been in the context of cancer, which highlights the significance of immune activity in the pathoetiology of cancer [83,84]. Since these miRNAs can influence immune responses against cancer, they become suitable targets for anti-cancer therapy. Future research is required to assess how these miRNA-targeting treatments affect cancer xenograft models [85].

7. Future perspective

Given the intricacy of the immune response, animal models of infection and/or illness would arguably give the greatest evidence to establish a function for ncRNAs. Animal models are, after all, the only way to investigate many elements of the acquired immune response. Future studies will definitely find further and unexpected insights into the activities of ncRNAs in immunity, thanks to rapid scientific advances in studying the mammalian transcriptome. Meanwhile, the following major research problems in the field of immune-regulatory ncRNAs that must be addressed in the future are worth mentioning. For starters, the interaction between miRNAs and lncRNAs in immune regulation is an area of potential interest [104]. miRNAs are a class of post-transcriptional gene expression regulators involved in many aspects of immune responses [105]. A recent discovery indicates that coding and lncRNAs may co-regulate and interact by vying for common miRNA binding.

To put it another way, lncRNAs can operate as a molecular sponge for miRNAs, regulating the expression of protein-coding genes [106]. Furthermore, it has been proposed that lncRNAs can control miRNA processing by base-pairing with the main miRNA, resulting in miRNA maturation inhibition [107]. The novel functions of RNA–RNA interaction between various RNA species will lead to new gene regulatory network discoveries. Further research into the implications of this innovative notion in immunity modulation is required [108]. Altogether, there is growing evidence that lncRNAs, like miRNAs, are essential immune response regulators. There are expected to be many more immune-related lncRNAs found in the future, and these will work in various ways. In further studies, it will be necessary to investigate whether or not incorrect expression of lncRNA is associated with the onset of autoimmune and allergic disorders, as well as inflammation that is associated with a wide variety of chronic diseases. Several studies have found varied patterns of expression of long noncoding RNAs (lncRNAs) in inflammatory illnesses of varying types [109]; while further research is needed to see if they play a role in pathogenesis.

In the long term, (a) immune-related ncRNAs diagnostic and prognosis biomarker studies will need to emphasize serum circulating immune-related ncRNAs and predicting treatment response, such as chemotherapy, radiation, targeted therapy, and immunotherapy [110]. (b) The use of high-throughput next-generation sequencing (NGS) for ncRNA profiling has shown a large number of differences in lncRNAs between TNBC and non-TNBC tissues. However, more detailed functional investigations of the TNBC-related ncRNAs that have been discovered are required. (c) Because immune-related ncRNAs are involved in various processes in TNBC immunology, the mechanism of control of abnormally produced immune-related ncRNAs should be researched in the future; (d) practically all ncRNA studies in TNBC have been conducted on cell lines. Future research might focus further on clinical TNBC patients or animal models.

8. Conclusion

It has been demonstrated in recent years that ncRNAs play a significant role in the regulation of a number of vital cellular and physiological processes, including growth, development, proliferation, oncogenic transformation, tumor suppression, and immunological modulation. Growing evidence has shown and established the crucial role of ncRNAs in influencing the behavior of both effector and immunological suppressor cells in the setting of malignancies. An entirely new layer of post-transcriptional regulatory mechanisms that exist in a cell has been revealed by the pan-cellular role of ncRNAs in regulating targets linked to immune evasion by tumors, targets involved in an efficient immune response by immune cells, or target proteins related to cross-talk between tumor and immune cells. Additionally, a deeper comprehension of the functions of immune-modulatory ncRNAs will aid in the development of more advanced and efficient therapeutic strategies against cancer cells as well as enhance the efficacy of already available medications.

In the current review, we discussed the recent updates of ncRNAs, including miRNAs and lncRNAs in TNBC immunology, biogenesis, target genes, and the biological function of their targets in the immune response. miRNAs and lncRNAs have recently been shown to have a role in immune system control by influencing TME, EMT, DC and myeloid-derived stem cell regulation, and T and B cell activation and differentiation. For starters, the interaction between miRNAs and lncRNAs in immune regulation is an area of potential interest, especially in TNBC treatment.

CRediT authorship contribution statement

All authors contributed to the study conception and design. Data collection and analysis were performed by Maha Waleed Alghazali,

Hussein Riyadh Abdul Kareem Al-Hetty, Zahraa Muhsen M. Ali and Abduladheem Turki Jalil. The first draft of the manuscript was written by Marwan Mahmood Saleh, Maha Waleed Alghazali, and Ahmed AbdulJabbar Suleiman all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Consent to participate

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Consent to publish

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