Long non-coding RNAs (lncRNAs) are involved in fundamental biochemical and cellular processes. The neighbor of BRCA1 gene 2 (NBR2) is a long intergenic non-coding RNA (lincRNA) whose gene locus is adjacent to the tumor suppressor gene breast cancer susceptibility gene 1 (BRCA1). In human cancers, NBR2 expression is dysregulated and correlates with clinical outcomes. Moreover, NBR2 is crucial for glucose metabolism and affects the proliferation, survival, metastasis, and therapeutic resistance in different types of cancer. Here, we review the precise molecular mechanisms underlying NBR2-induced changes in cancer. In addition, the potential application of NBR2 in the diagnosis and treatment of cancer is also discussed, as well as the challenges of exploiting NBR2 for cancer intervention.

Keywords: long non-coding RNA, neighbor of BRCA1 gene 2, cancer, metabolism, epithelial-mesenchymal transition, autophagy

INTRODUCTION

Presently, it is believed that nearly 87.3% of the human genome is actively transcribed, but <3% of the genome encodes functional proteins (1, 2). Transcripts devoid of protein-coding capacity are termed as non-coding RNAs (ncRNAs) (3, 4). LncRNAs, which were previously recognized as “transcription noise”, represent a class of ncRNAs consisting of >200 nucleotides (5–7). To date, more than 10,000 manually annotated lncRNA genes that produce more than 15,000 lncRNAs have been identified, and their total number continues to grow rapidly, which is due to advancements in RNA sequencing, epigenomic technologies, and computational prediction techniques (2, 8, 9). Furthermore, the increasing numbers of lncRNAs have drawn increased attention to understanding their roles in biology. The lncRNA family is heterogeneous, and individual members can be classified according to their location, structure, function, and transcription orientation (10–12). For instance, based on their location in reference to protein-coding messenger RNAs (mRNAs), lncRNAs can be classified as antisense lncRNAs, lincRNAs, bi-directional lncRNAs, sense lncRNAs, and intronic lncRNAs (6, 13). Similar to mRNAs, the transcription of most lncRNAs is induced by RNA polymerase II, which is accompanied by 5′-capping, 3′-polyadenylation, and splicing (14–16). Although not translated, lncRNAs are emerging as essential modulators of cellular processes through the regulation of chromatin dynamics, gene expression, and protein function (7, 17–20). Functions of lncRNAs are closely associated with their intracellular distribution. LncRNAs in the...
cytoplasm can interact with mRNAs and proteins, thereby regulating the translation, degradation, and splicing of mRNAs, and inducing changes in protein activity and stability. LncRNAs can also function as “sponges” of microRNAs (miRNAs) in the cytoplasm, leading to the overexpression of miRNA target molecules. For lncRNAs localized in the nucleus, they can recruit transcription activators/repressors to the target gene promoter, thereby facilitating transcriptional activation/silencing. Nuclear lncRNAs can also decoy transcription factors (TFs), resulting in transcriptional inactivation. Moreover, nuclear lncRNAs can induce epigenetic modifications of target genes to regulate their expression (15, 21–25).

Cancer is a complicated disease that associates with a variety of genetic mutations, epigenetic alterations, and chromosomal translocations/deletions/amplifications (26–30). Numerous lncRNAs have been identified as oncogenes or tumor suppressors in a wide range of solid tumors and hematological malignancies, implying that lncRNAs are master regulators in cancer (11, 31, 32). LncRNAs are involved in the regulation of cancer cell proliferation, survival, invasion, and metastasis, as well as the antitumor immune response (33–40). Furthermore, the dysregulated expression of lncRNAs in cancer is associated with the clinical outcome and prognosis of cancer patients (41–44). Among these lncRNAs, NBR2 is a newly defined lncRNA whose expression is induced by energy stress in the tumor microenvironment (TME) and participates in cancer development (45). Here, we review the role of lncRNA NBR2 in cancer biology, as well as emphasize its clinical application.

IDENTIFICATION OF THE NBR2 GENE

NBR2 is a non-protein-coding gene on human chromosome 17q21 that spans ~30 kb of genomic DNA and resides adjacent to the BRCA1 gene (45, 46). BRCA1 is a tumor suppressor gene which encodes a nuclear protein that can maintain genome integrity, and germline mutations of the BRCA1 gene are responsible for most familial cases with breast and ovarian cancer (46–50). To date, more than 100 distinct germline mutations in the coding region of the BRCA1 gene have been confirmed (51–53). Different from other tumor suppressor genes with both germline and somatic mutations, there are rare somatic mutations in the BRCA1 gene in breast and/or ovarian cancers. Therefore, BRCA1 mutations in the coding region are not involved in the development of sporadic cancers, and alternative inactivating mechanisms, such as promoter mutation and DNA hypermethylation, may be involved in the dysregulation of the BRCA1 gene in sporadic human cancers. Thus, studies aimed at determining the regulation of the BRCA1 gene are warranted (46, 51, 53). Previous studies, which investigated the 5′ region of the BRCA1 gene in considerable detail, have revealed the transcription start sites for both BRCA1 and neighbor of BRCA1 gene 1 (NBR1) genes. The genomic region housing the 5′ ends of BRCA1 and NBR1 genes is duplicated, as a partial copy of the genomic region encompassing exons 1A, 1B, and 2 of the BRCA1 gene lies head-to-head with the NBR1 gene. Meanwhile, a partial copy of the NBR1 gene, consisting of exons 1A, 1B, and 3, resides adjacent to the transcription start site of the BRCA1 gene, and this partial copy is identified as a part of the NBR2 gene that is situated in the genomic region between BRCA1 and pseudo-BRCA1 (BRCA1P1) genes and lies head-to-head with the BRCA1 gene (Figure 1) (46, 54, 55). Despite high sequence homology at the 5′ ends of NBR1 and NBR2 genes, the remaining sequence regions show low homology. The NBR1 gene has been identified to encode a protein of 966 amino acid residues, which acts as a receptor for the selective autophagosomal degradation of ubiquitinated targets (56, 57). NBR1 is also associated with endosomal membranes by mediating the delivery of certain cargoes. In terms of expression, NBR1 is expressed in all tissues with the highest level in thyroid and testis. There has been little information about the role of NBR1 in cancer. The expression of NBR1 mRNA shows low cancer specificity, and there are weak to moderate NBR1 protein level in cytoplasm of different cancer cells. Decreased NBR1 mRNA level is associated with a poor clinical outcome in patients with clear cell renal carcinoma, indicating NBR1 mRNA level is negatively related with the prognosis of cancer patients. However, other findings revealed the properties of NBR1 in promoting cancer migration and metastasis, and in inducing tumor immune escape by
distributing major histocompatibility complex-I (MHC-I) on the cell surface. Therefore, the role of NBR1 in cancer is complicated and needs further investigations (58). Different from the NBR1 gene, the transcript encoded by the NBR2 gene is an lncRNA, and its expression has been identified in most examined tissues, including the spleen, thymus, prostate, testis, ovary, small intestine, colon, and peripheral blood leukocytes (46, 59, 60). A previous study has reported that there is an open reading frame (ORF) of 112 amino acid residues in the NBR2 DNA that was predicted to encode a ~12-kDa protein. However, a strong Kozak signal has not been observed within this ORF, and the stop codon is located >55 bp upstream of the last splicing site for the putative predicted to encode a ~12-kDa protein. Therefore, these findings suggest that the NBR2 transcript may have been degraded by nonsense-mediated mRNA decay, although it is subjected to protein synthesis (46, 51).

**REGULATION OF NBR2 EXPRESSION IN CANCER**

The NBR2 gene, which is located between BRCA1 and BRCA1P1 genes, shows less conservation across species, as it has only been identified in primates but not in other species, including mice. Consistent with the BRCA1 gene, NBR2 expression is usually down-regulated in cancer. In a single-strand conformation polymorphism (SSCP) analysis, it was revealed that the NBR2 gene shows no mutations in both breast and ovarian cancers, suggesting that the involvement of the NBR2 gene in these cancers is not concerned with gene mutations (46). Sequence analysis of the NBR2 gene reveals that it contains five exons, in which the last exon is alternatively used and is transcribed in the opposite direction from that of the BRCA1 gene. The transcription of two distinct BRCA1 transcripts α and β, in which exon 1A and exon 1B are the first exons, respectively, is achieved by their respective promoters α and β. Promoter α of the BRCA1 gene is defined to be bi-directional, and cis-control elements in the intergenic region of BRCA1 and NBR2 genes dominate promoter α activity, as promoter α-induced transcription of both BRCA1 and NBR2 genes is regulated by enhancers and silencers located in the region between nucleotide positions 1 and 1357. Moreover, the TF binding sites in the BRCA1/NBR2 promoter have been delineated. Therefore, the expression of BRCA1 and NBR2 genes can be affected by different TFs, dominated by cis-elements in the intergenic region, and regulated by the availability of these TFs during development and tumorigenesis (54, 61, 62).

The analysis of the DNA sequence homology in the region that encompasses both the bi-directional promoter and the BRCA1 promoter β (nucleotide positions 1191 to 2052) indicates a role for the CCAAT element in the coordinated activation of both BRCA1 and NBR2 genes (62). Other elements that can modulate the transcription of BRCA1 and NBR2 genes have also been identified (63–65). In the intergenic region between BRCA1 and NBR2 genes, a minimal 56-bp EcoRI–HaeIII fragment has been delineated to act as a bi-directional promoter and it induces transcription in the NBR2 gene direction 2–4-fold higher than that in the BRCA1 direction in all tested cell lines (including cervical carcinoma, colon carcinoma, and mammary carcinoma cells). Within this sequence, the potential binding sites for TFs of the E-twenty-six (ETS) family, Sp1 transcription factor (SP1) family, and cAMP-responsive element-binding protein (CREB) have been defined. In addition, a specific protein–DNA complex was identified when this 56-bp EcoRI–HaeIII minimal promoter was incubated with nuclear extracts from cancer cells. Moreover, the 56-bp minimal promoter can be further divided into 38-bp EcoRI–MspI and 18-bp MspI–HaeIII fragments, and tissue-specific factor binding to MspI–HaeIII is required for BRCA1 transcription (65). Another 36-bp BstNI–BseRI fragment, which is 575-bp into the first intron of the BRCA1 gene, exhibits non-tissue-specific transcriptional suppressor activity by interacting with specific nuclear proteins. However, this putative negative regulatory element (NRE) only blocks transcription in the BRCA1 direction, although the promoter is shared by the divergently transcribed NBR2 gene (63). For the NBR2 gene, an 18-bp transcriptional repressive element, which resides 948-bp into its first intron, was recently identified. The interaction between nuclear proteins and this 18-bp HaeIII–HaeIII repressive element was confirmed by electrophoretic mobility shift assays (EMSA), and functional suppression was conferred to the heterologous thymidine kinase promoter by this element. In addition, this repressive element had no effect on the BRCA1 direction in the context of its native genomic organization (64). Therefore, a model of the BRCA1–NBR2 bi-directional transcription unit is established, in which the minimal 56-bp DNA region functions to drive the transcription in both directions and the uni-directional transcription is controlled by distinct repressors binding to elements in the first intron of respective genes (Figure 2A).

Specific molecules that regulate NBR2 transcription by interacting with corresponding regulatory elements have been identified. For instance, methyl-CpG binding domain protein 2 (MBD2) specifically binds to the methylated region of the repeated LTR12c element at the BRCA1–NBR2 locus, which leads to the silencing of the NBR2 gene (66). MBD2 is a member of the MBD protein family, which are key molecules that participate in the interpretation of DNA methylation, leading to gene silencing (67). In the study by Auriol E et al., MBD2 was found to bind to the methylated region of the CpG island flanking the bi-directional BRCA1–NBR2 promoter in HeLa cells, but not the unmethylated region. Meanwhile, the methylated region of the BRCA1 island was not bound by other MBD proteins, such as methyl-CpG binding protein 2 (MeCP2) and MBD1, implying that the binding of MBD2 is specific. The BRCA1–NBR2 locus-bound MBD2 induced the specific methylation-dependent repression of NBR2, whereas it did not affect the transcription of BRCA1 (Figure 2B) (66). In addition to the regulation of NBR2 expression at the transcriptional level, the modulation of the expression of this lncRNA at the post-transcriptional level has also been identified. In acute liver failure (ALF), increased miR-19a expression is accompanied by
decreased NBR2 expression. MiR-19a can interact with NBR2 and protein kinase AMP-activated catalytic subunit alpha 1 (PRKAA1) (the gene encodes adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)), and down-regulate the levels of both NBR2 and AMPK in injured hepatocytes, thereby inhibiting autophagy in hepatocytes (Figure 2C) (59).

In addition to these endogenous regulatory patterns, NBR2 expression can also be mediated by exogenous factors such as TME conditions and antitumor drugs. TME is a complex network consisting of a variety of cell types and factors, which is essential for tumor progression (68). Hypoxia, which is a common feature of TME and critical for the evolution of malignant cells, can affect BRCA1 and NBR2 expression differently. Hypoxia results in histone modifications at the endogenous BRCA1 promoter in human breast cells, thereby repressing BRCA1 transcription, whereas it induces the activation of NBR2 transcription from the bi-directional BRCA1 promoter. Different regulatory elements drive the hypoxia-induced repression of BRCA1 and the activation of NBR2 in cancer cells. It has been reported that hypoxia-induced silencing of the 218-bp minimal promoter is responsible for BRCA1 down-regulation, whereas elements that control NBR2 expression are beyond this minimal promoter and remain to be determined (69, 70). In addition, glucose starvation in TME can also induce the expression of lncRNA NBR2 in cancer cells through the liver kinase B1 (LKB1)–AMPK pathway, and the precise mechanism will be discussed in the next section (45). Several antitumor drugs, such as phenformin and...
curcumin, have been reported to induce NBR2 expression in cancer, although the precise regulatory mechanisms remain unknown (Figure 2D) (71, 72). NBR2 is involved in cancer progression based on its ectopic expression. Therefore, we place an emphasis on the NBR2-induced regulatory mechanisms in tumorigenesis in the following section.

FUNCTIONS OF NBR2 IN CANCER BIOLOGY

In consideration of the high mutation/deletion rate of the BRCA1 gene in human breast and ovarian cancers, the NBR2 gene, which is proximal to the BRCA1 gene, was initially presumed to be co-deleted/mutated with BRCA1 in certain cancers. Thus, NBR2 may also play a role in tumor suppression similar to BRCA1. However, NBR2 was later confirmed to be a lncRNA, and its complicated roles in tumor biology are being revealed gradually (45, 51, 73).

Dual Role of NBR2 in Regulating Glucose Metabolism

The study by Liu X et al. identified the role of lincRNA NBR2 in tumor suppression for the first time, and it was confirmed that energy stress-induced NBR2 interacts with AMPK and potentiates AMPK activity under a condition of energy stress (45, 51, 73). Glucose deprivation in TME can subsequently result in increased cell apoptosis and decreased cell migration and invasion. However, to resist energy stress-induced apoptosis, cancer cells can adjust to the nutrient-limited environment and develop compensatory ways through metabolic reprogramming. Different from normal cells, cancer cells exhibit increased glucose uptake, aerobic glycolysis, enhanced glutamine uptake and malate dehydrogenase, and increased cell apoptosis and decreased cell migration and invasion. Therefore, to resist energy stress-induced apoptosis, cancer cells can adjust to the nutrient-limited environment and develop compensatory ways through metabolic reprogramming.

AMPK, a heterotrimeric complex containing a catalytic α subunit and two regulatory β and γ subunits (75). Stress-induced NBR2 interacts with AMPKζ of the AMPK complex through its first exon and enhances the activity of AMPK kinase, which is parallel to LKB1-induced AMPK activation. NBR2 was not required for initial energy stress-induced AMPK activation. Therefore, the feedback mechanism responsible for NBR2-AMPK regulation in both breast and kidney cancer cells under glucose-starvation conditions was revealed. AMPK is a crucial checkpoint of metabolism. Under conditions of energy stress, AMPK signaling is activated to facilitate catabolic processes (such as autophagy, fatty acid oxidation, and glycolysis) and suppress anabolic processes (such as sterol/lipid/protein synthesis), thereby leading to restored energy balance. Mammalian target of rapamycin complex 1 (mTORC1)-induced protein synthesis and cell growth are major anabolic processes inhibited by AMPK in response to energy stress (76, 77), and energy stress-induced AMPK can also promote autophagy by directly activating the Unc-51 like autophagy activating kinase 1 (ULK1) through the phosphorylation of serine (Ser) 317 and Ser 777 (78). Therefore, the AMPK pathway functions to suppress cancers, as anabolic processes are necessary for tumor progression. Consistent with this finding, NBR2 led to decreased cell cycle progression, but increased autophagy, which down-regulated apoptosis under energy stress and inhibited the progression of breast and kidney cancers, suggesting that NBR2 is a tumor suppressor that regulates AMPK activity. Accordingly, the NBR2 level was decreased in breast and kidney cancer patients and was negatively correlated with poor prognosis (45, 51, 73). In colorectal cancer (CRC), the NBR2–AMPK pathway is involved in curcumin-mediated CRC progression. It has been reported that glucose starvation induces the expression of NBR2 in CRC cells, at least partly through an AMPK-dependent manner. NBR2 overexpression results in the activation of the AMPK–mammalian target of rapamycin kinase (mTOR) pathway under glucose-starvation conditions, thereby affecting CRC progression (72). Curcumin, a compound isolated from the rhizomes of Curcuma longa, has been approved for the intervention of human cancers, including CRC (79). Curcumin shows a synergistic effect with glucose starvation in regulating the AMPK–mTOR pathway. Similar to glucose deficiency, curcumin induces NBR2 expression in CRC cells. The increased NBR2 enhances the curcumin-mediated suppression of the proliferation and clone formation of CRC cells through the activation of the AMPK–mTOR pathway, providing new insights for CRC therapy (Figure 3) (72).

In addition to affecting the activation of the AMPK pathway, lncRNA NBR2 can mediate the glucose metabolism of cancer cells by other mechanisms. In breast and kidney cancer cells, NBR2 regulates cancer cell sensitivity to phenformin through glucose transporter 1 (GLUT1). Phenformin is an inhibitor of mitochondrial respiratory chain complex I, and its antitumor effect is more potent than that of metformin. Phenformin induces NBR2 expression in breast and kidney cancer cells, and NBR2 deficiency renders cancer cells more sensitive to phenformin-induced apoptosis. Thus, NBR2 expression may function as an adaptive response to maintain cell survival after phenformin treatment. It is well established that phenformin enhances the activation of AMPK and the inactivation of mTORC1, and the inhibition of the AMPK pathway renders cancer cells more sensitive to phenformin-induced cell death. However, even if NBR2 promotes energy-induced AMPK activation through direct interaction, the interaction of NBR2 with AMPK is not influenced by phenformin, and phenformin induces AMPK activation independent of NBR2. On the other hand, NBR2 deficiency suppresses glucose uptake through the inhibition of phenformin-induced GLUT1 expression, which is
the glucose transporter with the most relevance to cancer biology, as it is overexpressed in many human cancers. It has been observed that GLUT1 deficiency sensitizes cancer cells to phenformin-induced cell death, whereas GLUT1 restoration in NBR2-deficient cells rescues the increased cell death after phenformin treatment. This finding identifies a new mechanism of NBR2 modulation of glucose metabolism in cancer cells, suggesting that NBR2 may predict the biguanide treatment response in cancer patients (71, 80). Furthermore, NBR2 impedes Beclin1-induced cytoprotective autophagy, thereby inhibiting cancer proliferation through ERK and JNK pathways.

FIGURE 3 | NBR2 functions as a tumor suppressor. NBR2 is responsible for the glucose metabolism in cancer dependent on the AMPK–mTOR pathway. Glucose starvation in TME induces the expression of NBR2 depending on the LKB1–AMPK pathway. As feedback, stress-induced NBR2 enhances the activity of AMPK kinase by directly interacting with its AMPKα subunit, thereby inhibiting the proliferation of cancer cells. Based on its regulation of the AMPK–mTOR pathway, curcumin-induced NBR2 enhances the antitumor effects of curcumin by suppressing cancer proliferation and clone formation. In addition, NBR2 attenuates EMT by blocking the NOTCH1 pathway and inhibiting miR-21 expression. Moreover, NBR2 impedes Beclin1-induced cytoprotective autophagy, thereby inhibiting cancer proliferation through ERK and JNK pathways.

mutations in the catenin beta 1 (CTNNB1) gene that encodes β-catenin. Within mammalian cells, the activation of Wnt–β-catenin pathway leads to β-catenin accumulation in the cytoplasm and its translocation into the nucleus to facilitate the transcriptional activation of the T-cell factor (TCF) family (81–83). TCF7 has been reported to be co-expressed with NBR2, and NBR2 deficiency leads to decreased TCF7 expression in hepatoblastoma cells, along with the down-regulation of the TCF7 protein that is involved in cell cycle progression, glucose entrapment, and epithelial-mesenchymal transition (EMT). The main regulatory mechanism of lncRNAs in the cytoplasm is to act as competing endogenous RNAs (ceRNAs) to sponge miRNAs. TCF7 has been defined as the target molecule of miR-22 and NBR2, which is localized in both the cytoplasm and nucleus, aggravates hepatoblastoma cell malignancy by sponging miR-22 under conditions of glucose starvation, thereby counteracting miR-22-induced TCF7 repression (Figure 4) (60). The above studies reveal the double-edged sword role of lncRNA NBR2 in regulating the glucose metabolism of different cancers, further emphasizing its importance in maintaining the energy balance.
NBR2 Suppresses EMT in Cancer

EMT is a process that is critical for wound healing, embryogenesis, and malignancy. During EMT, cell–extracellular matrix and cell–cell interactions are reprogrammed, which leads to the separation of epithelial cells from adjacent cells and the basement membrane, and new transcriptional events are induced to promote the mesenchymal fate. In cancer progression, EMT contributes to tumor initiation, metastasis, and therapeutic resistance, which is regulated by crucial TFs such as zinc-finger E-box-binding (ZEB) TFs and SNAIL. Both transcriptional reprogramming and non-transcriptional changes during EMT are induced by pathways responding to extracellular molecules (84, 85). Currently, lncRNAs are emerging as crucial regulators of EMT that can determine cancer progression (86). NBR2, an lncRNA that was initially identified as a cancer suppressor, is involved in the regulation of EMT in different cancers (Figure 3) (87–90).

In non-small cell lung cancer (NSCLC), the NBR2 level is low in tumor tissues and is correlated with tumor size and prognosis. NBR2 overexpression inhibits the proliferation, invasion, and migration of NSCLC cells. A mechanistic study has revealed that NBR2 inhibits EMT in NSCLC by suppressing the notch receptor 1 (NOTCH1) pathway (87). During the development of osteosarcoma, cancer patients with low NBR2 expression exhibit a shorter overall survival compared to those with high NBR2 expression. NBR2 inhibits the proliferation, invasion, and migration of osteosarcoma cells, but has no effect on cell apoptosis, thereby delaying tumor growth. NBR2 has also been identified to function as an EMT suppressor by regulating NOTCH1 at both transcriptional and post-transcriptional levels in osteosarcoma (89). Similarly, the NBR2 level is decreased in thyroid cancer (TC) tissues and cells, and it is associated with the histologic subtypes of TC. NBR2 overexpression significantly suppresses TC proliferation, clonogenicity, and invasion as well as tumor growth in vivo, whereas NBR2 knockdown has the opposite effects. Mechanistic studies have revealed that NBR2 inhibits GLUT1 expression and EMT, but promotes AMPK and acetyl-CoA carboxylase (ACC) activation in TC cells, thereby reducing the malignancy of TC and acting as a tumor suppressor (90, 91). In colorectal cancer, the low NBR2 level has been reported in tumor tissues, and decreased NBR2 expression is associated with the progression of clinical stages. The expression of miR-21, which is a cancer promoter, is
increased in colorectal cancer tissues and inversely correlated with the NBR2 level. Moreover, NBR2 overexpression inhibits miR-21 expression in colorectal cancer cells and attenuates colorectal cancer cell migration and invasion, whereas miR-21 has no influence on NBR2 expression (88). These findings revealing the role of NBR2 in EMT further confirm that NBR2 may be a potential target for cancer diagnosis and treatment.

**NBR2 Regulates the Autophagy of Cancer Cells**

Autophagy is a conserved catabolic process. It is initiated by the formation of autophagosomes, which encapsulate the cytoplasm and organelles, and then form autolysosomes by fusing with lysosomes, thereby leading to the degradation of the contents contained within the vesicles (92). Autophagy mediates the proliferation and apoptosis of liver cells in different contexts, and it has been confirmed that protective autophagy is the main cause of cancer survival in an adverse environment (93, 94). In addition to affecting the metabolism and EMT, NBR2 can also inhibit tumorigenesis by regulating autophagy. It has been demonstrated that in hepatocellular carcinoma (HCC) patients at advanced clinical stages, the overall survival of cases with low NBR2 expression is significantly worse compared to those with high NBR2 expression. As such, NBR2 acts as a negative regulator of HCC, as it inhibits cancer proliferation, invasion, and migration. Cell death is a complicated process, for which autophagy, as well as apoptosis, is essential. NBR2 regulates autophagy, but not apoptosis, of HCC cells. Basal autophagy suppresses tumor progression by maintaining cellular homeostasis. However, protective autophagy enhances the survival of cancer cells to facilitate tumor development in TME. Therefore, an inhibition of autophagy may be an ideal approach for cancer treatment. In HCC, NBR2 attenuates Beclin1-induced cytoprotective autophagy to inhibit cancer proliferation through the extracellular regulated protein kinase (ERK) and c-Jun N-terminal kinase (JNK) pathways, which provides novel insights on a treatment strategy for HCC (95, 96).

**CLINICAL APPLICATIONS OF NBR2 IN CANCER**

Similar to BRCA1, the potential application of NBR2 as a cancer biomarker was initially revealed in breast cancer, as the expression of NBR2 decreased in primary cancer cells derived from human breast cancer tissues (61). Subsequent studies further confirmed this finding and showed that low NBR2 expression correlates with poor clinical outcomes in breast and ovarian cancer patients (45, 97). Furthermore, a common breast cancer risk loci, rs9911630, is identified to be the most strongly expression-associated genotyped single nucleotide polymorphism (SNP) that affects the expression of BRCA1 and NBR2 in the Tunisian population, but whether this SNP is responsible for NBR2 expression in other populations is still not clear (98). Germline mutations in the coding region of the BRCA1 gene are responsible for familial breast and ovarian cancers (51–53). Different from BRCA1, there is no mutation in the NBR2 gene (46). However, it has been demonstrated that the deletion of the NBR2 gene may be closely related to the susceptibility of breast and ovarian cancers in different populations. For example, germline BRCA1 promoter deletions have been confirmed in familial breast cancer patients from the United Kingdom and Australia. The breakpoints for this deletion are in BRCA1 intron 2 and between NBR2 and BRCA1P1 exon 2, suggesting that this deletion takes place through a novel mechanism involving the recombination of BRCA1:BRCA1P1 (99). In a French breast–ovarian cancer family, a novel rare 161-kb deletion in the region extending from the NBR1 gene to the BRCA1 gene was identified. This deletion encompassed NBR1, BRCA1P1, NBR2, and BRCA1 genes, and it started from the Alu Y sequence of NBR1 intron 18 and ended at the Alu Sc sequence of BRCA1 intron 22. The hemizygosity of the four genes showed no specific phenotype (100). For sporadic breast cancer, a de novo complete BRCA1 gene deletion, which includes Rho family GTPase 2 (RND2), BRCA1P1, BRCA1, and NBR2 complete genes, has been reported in a Spanish woman with early bilateral breast cancer, supporting the large genomic rearrangement screening of BRCA genes in young breast cancer patients without a family history, as well as in hereditary breast and ovarian cancer families previously tested negative for other variations (101). In an Italian woman diagnosed with high-grade serous ovarian carcinoma, the deletion of a 137.8-kb region, encompassing the first six exons of the BRCA1 gene and the full length of NBR2, BRCA1P1, NBR1, and transmembrane protein 106A (TMEM106a) genes, was detected (102). In addition to breast and ovarian cancers, dysregulated NBR2 expression and function have also been observed in some other solid tumors (Table 1). Consistently, the NBR2 level was associated with the progression of these cancers (72, 80, 89, 90, 95, 97). For instance, the NBR2 level in advanced HCC patients is correlated with overall survival (95). These studies suggest that NBR2 is a potential biomarker for monitoring cancer development.

NBR2 is also a promising therapeutic target, as NBR2 is involved in regulating the proliferation, migration, and survival of different cancer cells (45, 87, 90, 95). Moreover, NBR2 affects cancer cell sensitivity to antitumor drugs, as NBR2 expression is related to drug resistance (104). As mentioned above, NBR2 deficiency renders cancer cells more sensitive to phenformin through the inhibition of GLUT1 expression, suggesting that the NBR2–GLUT1 axis may serve as an adaptive response for phenformin treatment (71, 80). In CRC, increased NBR2 expression enhances the antitumor effect of curcumin by activating the AMPK–mTOR pathway (72). Therefore, it is conceivable to expand the utilization of NBR2 in antitumor therapies.

**CHALLENGES AND FUTURE DIRECTIONS**

Despite considerable progress in the understanding of NBR2 function, significant obstacles remain to be overcome for better realizing the role of NBR2 in cancer. One challenge is the lack of a high-resolution map of NBR2’s interactions with its partners. LncRNA regulation is associated with its location in cells, and
TABLE 1 | Clinical applications of NBR2 in cancer.

| Cancer type       | Role of NBR2       | Outcome | Potential application | Refs        |
|-------------------|--------------------|---------|-----------------------|-------------|
| Glioma            | Oncogene           | Proliferation ↑ | Diagnosis /Therapy  | (103)       |
|                   | Viability ↑       |         |                       |             |
| Hepatoblastoma    | Oncogene           | Migration ↑  | Diagnosis /Therapy  | (60)        |
|                   | Invasion ↑        |         |                       |             |
|                   | Proliferation ↑   |         |                       |             |
|                   | Migration ↑       |         |                       |             |
| Hepatocellular carcinoma | Tumor suppressor | Invasion ↓ | Diagnosis /Therapy  | (95)        |
|                   | Proliferation ↓   |         |                       |             |
|                   | Migration ↓       |         |                       |             |
| Thyroid cancer    | Tumor suppressor   | Autophagy ↓ | Diagnosis /Therapy  | (90)        |
|                   | Proliferation ↓   |         |                       |             |
|                   | Migration ↓       |         |                       |             |
|                   | Invasion ↓        |         |                       |             |
|                   | Apoptosis ↑       |         |                       |             |
| Non-small-cell lung cancer | Tumor suppressor | Viability ↓  | Diagnosis /Therapy  | (87)        |
|                   | Migration ↓       |         |                       |             |
| Colorectal cancer | Tumor suppressor   | Invasion ↓ | Diagnosis /Therapy  | (88)        |
|                   | Migration ↓       |         |                       |             |
|                   | Proliferation ↓   |         |                       |             |
|                   | Curcumin sensitivity ↑ |       |                       |             |
| Ovarian cancer    | Tumor suppressor   | Prognosis | Diagnosis /Prognosis | (97)        |
| Osteosarcoma      | Tumor suppressor   |         |                       | (69)        |
|                   | Prognosis         |         |                       |             |
|                   | Prognosis         |         |                       |             |
| Breast & Renal cancer | Tumor suppressor | Curcumin sensitivity ↓ | Diagnosis /Therapy  | (45, 99–102) |
|                   | Proliferation ↓   |         |                       |             |
|                   | Curcumin sensitivity ↓ |       |                       |             |

Roles of NBR2 in different cancer types and its potential clinical applications: *"* represents "not identified".

NBR2 has been indicated to be localized in both the cytoplasm and nucleus, prompting the diversity of NBR2 regulatory mechanisms (19, 45). NBR2 in the cytoplasm can promote AMPK activity by interacting with AMPKα2, thereby regulating the proliferation, apoptosis, and autophagy of cancer cells (45). However, it is still unclear whether the NBR2-AMPK complex encompasses other molecules or whether the interaction of NBR2 with other proteins has the same effect. Therefore, the identification of molecules interacting with NBR2 will be helpful for defining the functions of NBR2. Moreover, NBR2 dysregulation can regulate the expression of cancer-associated genes, such as NOTCH1 and GLUT1, suggesting that NBR2 can affect the activation of gene transcription (71, 87). However, the precise mechanism of NBR2 in the regulation of gene expression at the transcriptional level still needs to be investigated.

The dual role of NBR2 in cancer biology is another challenge. NBR2 was initially identified as a tumor suppressor similar to BRCA1, and plenty of evidence has verified this perspective (45). However, an opposite role of NBR2 in cancer progression has also been revealed. It has been reported that the NBR2 level is significantly increased in hepatoblastoma tissues, where it aggravates hepatoblastoma cell malignancy under conditions of glucose starvation through the miR-22–TCF7 axis (60). Furthermore, NBR2 induces the resistance of cancer cells to phenformin treatment (71, 80). A recent study has also confirmed that NBR2 promotes the proliferation of glioma cells by inhibiting p15 expression (103). The adverse effects of NBR2 may result from the type, stage, or genetic context of these cancers, underlining that antitumor therapeutic strategies targeting NBR2 should be applied modestly.

Lastly, based on its mutation and dysregulated expression, the BRCA1 gene is one of the most important genes for the susceptibility of breast and ovarian cancers, and its clinical application in cancer diagnosis has been reported (50, 105). The potential application of the NBR2 gene, which shares a bi-directional promoter with the BRCA1 gene, has also been revealed in cancer diagnosis (95). The deletion of the NBR2 gene has been reported to be associated with the susceptibility of breast and ovarian cancers in different populations. However, these deletions, which usually contain BRCA1, NBR2, BRCA1P1, and NBR1 genes, are not restricted to the NBR2 gene, and further studies are needed to confirm whether a specific deletion of the NBR2 gene determines cancer susceptibility.

CONCLUSIONS

NBR2 has emerged as a crucial regulator of cancer biology, and a promising diagnostic and therapeutic target. Further
investigations underlying the NBR2 regulatory mechanisms in cancer are required for the materialization of its clinical application. Finally, these studies will improve our understanding of the roles of lncRNA in cancer through the investigation of NBR2.

**AUTHOR CONTRIBUTIONS**

TW, FY, and XT conceived the presented ideas and researched the background of the study. TW, ZL, and HS prepared the figures and tables. TW, LY, and XT wrote the manuscript. All authors contributed to the article and approved the submitted version.

**FUNDING**

This work was supported by the National Natural Science Foundation of China (Grant No. 81802855), the Natural Science Foundation of Jiangsu Province (Grant No. BK20180123), the Jiangsu Postdoctoral Research Foundation (Grant No. 2018K253C), and the China Postdoctoral Science Foundation (Grant No. 2018ZM64225).

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