Nogo-B receptor in relevant carcinoma: Current achievements, challenges and aims (Review)

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Abstract. The novel neurite outgrowth inhibitor B (Nogo-B) receptor (NgBR) is specific for Nogo-B, which is highly expressed in various human organs and cells, including the lung, liver, kidney, smooth muscle cells, blood vessel endothelial cells and inflammatory cells. Previous studies have indicated that NgBR directly interacts with Nogo-B and is able to independently influence lipid and cholesterol homeostasis, angiogenesis, N-glycosylation, the epithelial-mesenchymal transition, the chemotaxis of endothelial cells and cellular proliferation and apoptosis. These multiple functions and actions of this receptor provide an understanding of the important roles of NgBR in various conditions, including fatty liver, atherosclerosis, intracranial microaneurysms, retinitis pigmentosa and severe neurological impairment. Furthermore, NgBR has been demonstrated to exert protean, multifunctional and enigmatic effects in cancer. The present review summarizes the latest knowledge on the suppressing and activating effects of NgBR, emphasizing its function in cancer. Further basic and medical research on this receptor may provide novel insight into its clinical implications on the prognosis of relevant human cancer types.

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1. Introduction

Neurite outgrowth inhibitor B (Nogo-B) receptor (NgBR), a type I transmembrane protein with multiple functions and actions at the plasma membrane that is mainly expressed in the lung, breast, smooth muscle and blood vessels and is widely distributed in the liver, is able to interact with Nogo-B and vascular endothelial growth factor (VEGF) or function independently to exert multiple effects (1-4). This protein is a key member of the reticulon (RTN) protein family. The reticulon isoforms of mammalian RTN1, RTN2, RTN3 and RTN4c proteins have been identified, and these form the largest branch of the reticulon superfamily (4-6). NgBR contains a putative residue signalling sequence in the N terminus, an extracellular domain, a single transmembrane region and a cytoplasmic domain, which are composed of residues 1-46, 47-119, 120-139 and 140-293, respectively (7). As indicated in the database of the National Centre for Biotechnology Information, the gene encoding NgBR in humans, Nus1, dehydrodolichyl diphosphate synthase subunit, may be located at 6q22.1 (8). Previous studies have provided an increasing body of evidence suggesting that NgBR has different cellular localizations and controls specific membrane transport pathways in numerous human diseases, including fatty liver, intrauterine pulmonary hypertension, atherosclerosis, protozoan infections, retinitis pigmentosa, congenital disorders of glycosylation and relevant cancer types (3,9).

A previous circular dichromatogram analysis indicated that the full-length NgBR macromolecule has a high content of helical structures, and its structure comprises ~38% α-helices, 15% β-sheets and 47% random coils in the ectodomain and the cytoplasmic domains (5). The ectodomain of NgBR, a member of the intrinsically unstructured protein family, is

characterized as intrinsically unstructured without secondary and tertiary structures (5). The NgBR cytoplasmic domain has partially secondary structures without tight tertiary packing and serves as a scaffold that utilizes short motifs for the assembly of two binding partners, which are isoprenyl lipids and/or prenylated proteins (5,7).

Activation of the Nogo-B/NgBR signalling axis may modulate angiogenesis (10), lipid and cholesterol metabolism (11) and N-linked glycosylation (12) and enhance axonal branching (13) and cellular proliferation and apoptosis (10) under different physiological and pathological conditions by interacting with multiple downstream targets, including mammalian target of Niemann-Pick type C2 (11), *cis*-prenyltransferase (12) and endothelial nitric oxide synthase (eNOS (10). More importantly, targeting this signalling axis has been revealed to be promising for the treatment of cancer. It has been predominantly reported to have an oncogenic function and elevated expression in certain cancer types, including invasive ductal breast carcinoma (IDC) (14), hepatocellular carcinoma (HCC) (15), malignant melanoma (MM) (16) and non-small cell lung carcinomas (NSCLC) (17), which implies that targeting this signalling axis may have potential for retarding or ameliorating cancer progression.

In summary, NgBR serves a notable role in a number of human diseases, particularly cancer, which is a highly studied and complex subject (3). Once the first report of its effect on breast cancer was published in 2013 (14), numerous studies on the function of NgBR in the mechanism of cancer have been reported, and NgBR has gradually become a novel research hotspot globally (14-17). However, no systematic review of the latest research results for NgBR in the cancer research field has been published, to the best of our knowledge. The present review assesses and discusses novel advances achieved in previous studies on NgBR, with a particular emphasis on the expression and pathophysiological effects of NgBR on relevant human cancer types (17), including IDC (14), MM (16), HCC (15) and NSCLC (17). The present review additionally assessed the data implicating NgBR in the regulation of lipid metabolism (11), N-linked glycosylation (12) and the epithelial-mesenchymal transition (EMT) (18). These results identify NgBR as a novel and potential therapeutic target for mitigating the complex disease states in relevant human cancer types.

2. Expression of NgBR in cancer

Researchers have demonstrated that NgBR is recognized as a highly important receptor associated with a number of cancer types, including IDC (14), HCC (15), MM (16) and NSCLC (17). Furthermore, longitudinal studies have revealed that the dysregulation of NgBR over time is a risk factor for the early development of these cancer types (14-17). NgBR is able to promote the development of IDC (14) and HCC (15) but has an inhibitory effect on MM (16) and NSCLC (17). Therefore, there is some dispute regarding the expression and mechanism of NgBR in different types of malignancies.

Upregulated expression of NgBR in relevant cancer types. Levels of NgBR are increased in IDC. IDC, a severe public health problem globally, represents a frequent cause of cancer-associated morbidity and primarily occurs in women

aged 20 to 59 years, resulting in a huge socioeconomic burden (19).

The contribution of NgBR-derived factors to cancer-induced mammary gland disease is an emerging area of research. A study conducted by Wang *et al* (14) revealed that the NgBR levels are higher in IDC compared with in normal breast tissue and are strongly associated with estrogen receptor (ER)(+) and human epidermal growth factor receptor 2 (HER2)(-) breast carcinoma. Furthermore, these observations suggest a strong association between altered NgBR protein expression and survivin gene expression in IDC. Oestradiol is able to increase survivin expression and proliferation (14). Interestingly, the downregulation of NgBR is able to decrease the effect of oestradiol on survivin expression and cellular proliferation (14). An inverse correlation has been revealed between NgBR expression and the expression of Ki-67 antigen, which is a negative prognostic factor for the initiation, promotion and progression of breast carcinoma (20). Furthermore, the malignancy grade of IDC has a close association with the expression of NgBR but no notable association with the levels of HER2, ER or progesterone receptor, the size of the primary tumour or lymph node metastasis (20). Different associations amongst NgBR, ER(+/-) and HER2(+/-) were revealed by Pula *et al* (20) and Wang *et al* (14), and the contradictory results in NgBR expression are likely due to differences in the socioeconomic status, race/ethnicity, geography, age and sex of the patients whose breast tumour tissues were tested. Furthermore, the studies used different antibodies produced by Imgenex (Novus Biologicals, LLC, Littleton, CO, USA) (20) and Epitomics (Abcam, Cambridge, UK) (14), which may have resulted in opposing conclusions. Further clinical discoveries through cell biology experiments are required. The study conducted by Wang *et al* (14) suggested that tissue sections from human patients with early onset IDC indicate a pattern of NgBR overexpression.

Levels of NgBR are increased in HCC. HCC is the fifth most common carcinoma in humans and the second most common cause of cancer-associated mortality globally (21). The expression of NgBR in HCC tissues is notably higher compared with that in their corresponding adjacent liver tissues. Western blot analysis was used to examine the levels of tumour protein p53 and p21 proteins in Bel7402 and chemoresistant HCC cells (Bel/5FU) (15). The results indicated that the protein levels of p53 and downstream p21 are downregulated more in Bel/5FU compared with in Bel7402 cells. In addition, these researchers also examined the effects of NgBR knockdown on p53 protein expression (15). A previous study revealed a notable association between p53 ubiquitination and 5-FU chemoresistance in patients with HCC and chemoresistant HCC cells (Bel/5FU) (15,22). However, clinical pathological parameters including sex, hepatitis history, liver cirrhosis, maximal tumour size, tumour number, vascular invasion and Tumour Node Metastasis stage are not specifically associated with NgBR expression (15). However, clinical data analyses indicated that patients with high NgBR levels have notably lower survival rates compared with those with low NgBR levels (15).

Downregulated expression of NgBR in relevant cancer types. Levels of NgBR are decreased in MM. MM is a severe public

health problem globally. The spread of MM cells from a MM primary tumour to form metastases at distant sites is the most life-threatening complication and the main cause of mortality in patients with MM (23). Metastasis is a complex, multistep and multifactorial process involving interrelated interactions between tumour and normal cells. Single MM cells translocate to distant secondary sites, thus these cells must dissociate and migrate away from the primary tumour (24).

Due to the consistent neuroectodermal origin of MM and the involvement of the RTN protein family, NgBR may serve an essential role in the development and progression of MM. Current research on MM metastasis aims to develop a greater understanding of the interactions between the depth of invasion of primary MM tumour cells and the NgBR levels. A study conducted by Calik et al (16) indicated that NgBR may serve an important role in reducing the migration and invasiveness of melanoma cells. Conversely, it has been suggested that NgBR serves an oncosuppressive role in MM. Future investigations with larger patient cohorts and in vitro studies may help to characterize the function of NgBR in MM biology (16).

Levels of NgBR are decreased in NSCLC. The most common respiratory cancer is lung carcinoma, which has a prevalence of ~12% among patients with newly diagnosed cancer. Furthermore, an increased incidence rate has been observed (19). Current therapy for NSCLC aims to relieve pain and control symptoms rather than interfere with the pathophysiology (17,25). A decrease in the levels of NgBR and Nogo-B have been observed in various cells, including pneumocytes, bronchial epithelial cells of non-malignant lung tissue (NMLT) and NSCLC cancer cells (17). In patients with NSCLC, low NgBR mRNA expression levels result in progressive and generalized increases in the primary tumour size, lymph node involvement and advanced disease stages (15), resulting in exaggerated mortality rates due to an unfavourable prognosis (17). This indicates that NgBR may potentially serve a role in tumour growth and lymph node involvement in patients with NSCLC and NMLT; however, this hypothesis requires further investigation (17). However, a study by Wu et al (25) revealed that the levels of NgBR in NSCLC tissues were higher compared with those in corresponding tumour cell-positive lymph nodes.

The lung cancer tissues used in the study conducted by Wu et al (25) were obtained from patients with different socioeconomic statuses, races/ethnicities, geographies, ages and sexes, which may have resulted in contradictory results regarding NgBR expression. Furthermore, the antibodies used in these previous studies were purchased from Abcam (25) and Imgenex (Novus Biologicals, LLC) (17), respectively, and the use of these different antibodies may result in opposing conclusions. Therefore, these clinical discoveries obtained from cell biology experiments require further validation.

3. Potential mechanism of NgBR in malignant tumour types

Dysregulation of the NgBR mechanism is a well-recognized aspect of cancer biology, and numerous therapeutic strategies rely on targeting cancer by altering cellular metabolic pathways (15). Until now, the pathophysiology of NgBR in cancer has remained elusive, and research has mainly focused on its potential mechanisms in malignant tumour types (3).

Carcinogenic mechanism of NgBR
NgBR facilitates the phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) pathway. The PI3K/Akt pathway has been implicated in the carcinogenesis of certain tumour types, and the effects are attributed to the regulation of cell growth, survival, metabolism and apoptosis in physiological conditions and are involved in the development and survival of multiple solid tumour types, including IDC (26).

Wang et al (14) studied the pathogenesis of breast cancer, and the results suggested that the expression of NgBR is essential for oestradiol-stimulated IDC cell growth and survivin expression. Furthermore, the upregulation of NgBR is associated with ER(+)/HER2(-) breast carcinoma (14). Zhao et al (27) revealed that the inhibition of NgBR is able to attenuate the activation of the Akt signalling pathway and subsequently decrease cellular growth, migration, survival and proliferation. A follow-up study revealed that the overexpression of NgBR enhanced the phosphorylation of Akt in MDA-MB-231 cells (28). Pula et al (20) revealed that NgBR is substantially increased in IDC at the protein and mRNA levels and concluded that a low expression of NgBR in IDC is able to downregulate the PI3K/Akt/mechanistic target of rapamycin (mTOR) signalling pathway and subsequently reduce cancer cell proliferation, migration, adhesion, survival and invasiveness. These research results clearly demonstrate that NgBR may mediate the PI3K/Akt/mTOR signalling pathway and thereby serves a major role in the pathogenesis of IDC.

Mouse double minute 2 homolog (MDM2) is a *bona fide* ubiquitin ligase for p53 that results in altered transcription in p53 disorders, indicating that it serves a role in the stability of p53 (29). p53, a nuclear phosphorylated protein, inhibits the transformation of human cancer cells (30). One previous study has suggested that the phosphorylation and nuclear translocation of MDM2 and the ubiquitination and destruction of p53 are promoted by the phosphorylation of Akt (31). A gradual and orderly change in the PI3K/Akt/MDM2 pathway caused by NgBR activation is considered an important mechanism in the pathogenesis of HCC (15). Researchers have observed that increased levels of NgBR enhance the phosphorylation of Akt, and that phosphorylated Akt subsequently upregulates the expression of phosphorylated MDM2, and phosphorylated MDM2 in turn mediates p53 ubiquitination (15). These changes in the signalling pathway will mediate the emergence of chemoresistance in HCC and may induce cancer development and progression (15). These data clearly demonstrate that the high levels of NgBR in patients with HCC bind to phosphorylated Akt and recruit MDM2 to the nucleus, which is an essential step for the activation of PI3K/Akt/MDM2 signalling and tumourigenesis in HCC cells.

NgBR upregulates the EMT. EMT, a well-recognized physiological phenomenon in embryonic development that promotes the migration of neural crest cells out of the neuroectoderm (32), is a critical contributor to the progression of breast cancer as it not only reinforces that epithelial cells lose their differentiated characteristics but also enhances

their migratory and invasive abilities by the acquisition of mesenchymal features, as indicated by the overexpression of vimentin, a typical marker of mesenchymal cells (33). Importantly, the expression of epithelial and mesenchymal genes may be regulated by tumour growth factor-β (TGF-β) activation, which has been proven to be an upstream regulator of EMT (33). Furthermore, the Akt signalling pathway is able to facilitate all these signalling-mediated EMTs (34).

The breast cancer pathogenesis study conducted by Zhao *et al* (18) revealed that the TGF-β-induced expression of zinc finger E-box binding homeobox 1 and twist family bHLH transcription factor may be attenuated by inhibiting NgBR, which is necessary for the progression of EMT. This previous study additionally revealed that the inhibition of NgBR may attenuate the phosphorylation of Akt mediated by TGF-β. Furthermore, previous studies have suggested that the inhibition of Akt may block the TGF-β-mediated progression of EMT (18,34). It has been suggested that NgBR functions as a switch between the mesenchymal-to-epithelial transition and the EMT (18,35,36). In addition, overexpression of the Akt signalling pathway promotes the EMT, which has been well-described in the carcinogenesis of IDC (37). The study of lung cancer pathogenesis conducted by Wu *et al* (25) revealed that the overexpression of NgBR requires the activation and plasma membrane localization of Ras to increase the levels of Snail family transcriptional repressor 1 through activation of the mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway, which may downregulate the levels of E-cadherin to promote the EMT in NSCLC cells.

NgBR may promote the epidermal growth factor (EGF)/Ras/ ERK signalling pathway. The EGF/Ras/Raf/ERK signalling pathway is a MEK pathway that may be widely activated (38,39). This signalling pathway is involved in the dysregulation of cell differentiation, proliferation and apoptosis, and tumorigenesis likely involves multiple mutations in this pathway (40). Dysregulation of this signalling pathway may be overactivated by the abnormal expression of numerous cell factors, including NgBR, the mutational activation of EGF-like ligands, and the mutation and overexpression of Ras (28).

In the plasma membrane, the combination of guanosine triphosphate (GTP)-bound H-Ras and K-Ras is reinforced by galectin, which is a cytosolic protein with hydrophobic farnesyl-binding pockets (41). Caveolin-1 has a membrane-docking site in its lipid raft domains that binds to guanosine diphosphate (GDP)-loaded H-Ras (42). The hydrophobic cytoplasmic domain of NgBR has a docking site for binding to prenylated Ras, and this binding promotes the translocation of GDP/GTP-bound H-Ras and K-Ras to the plasmalemma, a step that has a pivotal role in oncogenic signalling by these GTPases (28).

A recent cancer pathogenesis study revealed that NgBR preferentially binds to farnesylated H-Ras, and its carboxyl terminus composed of hydrophobic residues is essential for integrating with farnesylated Ras to form a steady complex that mediates H-Ras signalling (28,43). Through a cell surface biotinylation assay, Zhao *et al* (28) revealed that the upregulation of NgBR enhances the amounts of membrane-associated K-Ras and H-Ras without changing their total levels. It has

been reported that NgBR only mediates the accumulation of Ras at the plasma membrane and does not enhance the levels of Ras (43). In addition, the downregulation of NgBR decreases the EGF-stimulated phosphorylation of ERK and Akt (43). These results are sufficient to suggest that the overexpression of NgBR is able to enhance the EGF-mediated activation of Ras and its downstream kinases, including Akt and ERK (28). That NgBR is essential for the accumulation of Ras in the tumour cell membrane indicates that NgBR serves a pivotal role in the oncogenic function of Ras in tumour growth. Furthermore, NgBR may influence the EGF-mediated activation of K-Ras and H-Ras, as K-Ras and H-Ras must be translocated to the cell membrane in order to be activated (44) and the upregulation of K-Ras and H-Ras is thought to mediate downstream kinases throughout the cell (45).

NgBR facilitates angiogenesis. Angiogenesis, an important step in cancer progression, involves the development of novel blood vessels necessary for tumour growth (46). Furthermore, a recent study of cancer cell invasion indicated that angiogenesis serves a key role in the proliferation and motility of cancer cells (47). In the early phase of the carcinogenic process, proliferating cancer cells mediate a proangiogenic microenvironment that increases the amount of supplied nutrients, energy and oxygen (48). VEGF, the primary angiogenic factor produced and secreted by cancer cells, is strongly involved in this progression (49). The VEGF/VEGF receptor (VEGFR) proangiogenic pathway, which is upregulated in human carcinoma, is the most extensively studied pathway (49). eNOS mediated by VEGFR has a notable function in carcinogenesis, including the inhibition of DNA repair systems, the epigenetic regulation of different oncogenic pathways and the inhibition of apoptosis (50). Furthermore, a recent study by Ricciuti *et al* (51) suggested that angiogenesis promotes the procession of cancer and is responsible for the invasion and metastasis induced by VEGF, eNOS, Akt and ERK.

NgBR is able to attenuate defects in angiogenesis by promoting eNOS and Akt phosphorylation. Furthermore, NgBR may facilitate tube formation to ameliorate angiogenesis disorders (52). NgBR is necessary for the development of cerebral blood vessels. Nogo-B and VEGF may interact with NgBR, resulting in the phosphorylation of Akt to reinforce angiogenesis (2). Interestingly, miR-26a may directly interact with NgBR to inhibit the VEGF-NgBR pathway and attenuate the phosphorylation of eNOS, which is able to substantially decrease tube formation, angiogenesis and cellular migration and proliferation (53). These results implicate NgBR as necessary for angiogenesis and the maintenance of migration.

The targeting of endothelial cell metabolism is an appealing strategy to impact tumour-driven angiogenesis, particularly given that proangiogenesis proteins, including NgBR, VEGF and eNOS, are thought to mediate endothelial cell migration, proliferation and tube formation; therefore, this NgBR/eNOS/ angiogenesis axis may be a potential therapeutic target in the switch from neoangiogenesis to carcinogenesis (53).

Anticarcinogenic mechanism of NgBR
NgBR attenuates the Liver X receptor α (LXRα) signalling pathway. Cholesterol, a precursor of bile acids and steroid hormones, is essential for various biological functions,

including increased tumour angiogenesis, reduced tumour apoptosis and increased tumour cell proliferation. Lipids, the main cell membrane component, serve a pivotal role in cell growth and division during their maintenance of cell integrity (54).

It is thought that lipids are implicated in the development of a number of carcinomas, including breast cancer, lung cancer and HCC. A low level of high density lipoprotein-cholesterol (HDL-C) was revealed to elevate the risk of breast cancer in 38,823 women in Norway, all between the ages of 17 to 54 years (55). A study on the pathogenesis of breast cancer conducted by Alikhani *et al* (56) suggested that primary mammary tumour growth and metastasis are substantially accelerated by dyslipidaemia and that cholesterol may upregulate the metastasis and growth of breast cancer. These results indicate that dyslipidaemia serves a key role in the metastasis, recurrence and growth of breast cancer and that hyperlipidaemia is able to increase the risk of breast cancer. In a study of the pathogenesis of liver cancer, Ooi *et al* (57) revealed that the levels of HDL-C are lower in metastatic liver cancer compared with in primary HCC. A study conducted by Rice *et al* (58) indicates the involvement of apolipoprotein E in the induction of lung cancer, which may be due to enhanced cholesterol transport into tumour cells. Altogether, these data suggest that decreasing the levels of lipids and cholesterol may suppress cancer development.

LXRα are primarily expressed in the liver and to a lesser extent in the kidney, small intestine, spleen and adrenal gland (59). A study conducted by Hu *et al* (11) suggests that NgBR integrates the liver X receptor response element with LXRα, and this interaction serves an important role in lipid synthesis. Furthermore, NgBR prevents the translocation of LXR from the cytoplasm to the nucleus and attenuates the induction of sterol-regulatory element-binding protein (SREBP-1c), the lipid regulatory gene of ATP-binding cassette subfamily A member 1 and fatty acid synthase (FASN), which reduces the lipid levels in vitro. These results suggest that NgBR is able to mediate LXRα activation to reduce the levels of lipids.

In summary, these results imply that the NgBR-LXRα axis may reduce the levels of free fatty acid (FFA) and triglyceride (TG) in the liver and plasma to suppress the occurrence and development of cancer types including HCC, breast cancer and lung cancer.

NgBR facilitates the adenosine monophosphate-activated protein kinase α (AMPKα) signalling pathway. AMPK signalling participates in numerous pathophysiologic processes, particularly lipid metabolism and tumourigenesis (60,61) During activation, AMPKα enhances the levels of ATP by regulating the metabolism of fats, proteins and sugars, thus inducing cells to evade death and engage in metastasis and the development of drug resistance (61,62). Furthermore, a previous study suggested that AMPKα is closely associated with the tumour suppressor gene p53 (63). This protein mediates the expression of cellular survival-associated signals, including Akt and mTOR. It has been demonstrated that AMPKα serves an important role in cancer prevention by inducing cell cycle arrest and blocking tumour growth (64). Jones *et al* (65) previously demonstrated that AMPKα may

directly promote the phosphorylation of p53 on serine 15. Furthermore, the activation of AMPKα may enhance the levels of p53 in addition to its phosphorylation and ultimately induce cell arrest at the G1/S phase (66). Compound C, a cell-permeable pyrazolopyrimidine compound, may function as a reversible and ATP-competitive inhibitor of AMPK (67). In addition, Hadad *et al* (68) demonstrated that the activation of AMPKα is notably downregulated in biopsies of breast cancer compared with normal tissue, which suggests that AMPKα has a cancer suppressive role. These results suggest that AMPKα has a carcinostatic action in tumourigenesis.

A previous study by Hu *et al* (10) revealed that NgBR may not only enhance the phosphorylation of AMPKα but also upregulate the expression of phosphorylated acetyl-coenzyme A carboxylase-1 (ACC-1), which is downstream of phosphorylated AMPKα. Ultimately, the activation of ACC-1 and AMPKα represses the expression of FASN, SREBP-1c and stearoyl coenzyme A desaturase-1 and enhances the levels of FFA and TG. Furthermore, the activation of AMPKα may rescue the translocation of LXRα mediated by a NgBR deficiency to ensure the maintenance of lipid metabolism (11,69). These results suggest that NgBR is able to mediate AMPKα in order to impact lipid homeostasis and LXRα. As mentioned previously, disorders of lipid homeostasis may serve a role in tumourigenesis. The AMPKα axis may reduce the levels of lipids and suppress the translocation of LXRα.

NgBR is able to promote N-glycosylation to attenuate endoplasmic reticulum stress and the unfolded protein response (UPR). NgBR is an extremely conserved subunit of *cis*-prenyltransferase, which is essential for the biosynthesis and phosphorylation of dolichol and ultimately contributes to the maintenance of protein N-glycosylation (9,70). Nevertheless, a NgBR deficiency may induce an N-glycosylation disorder to mediate endoplasmic reticulum stress and thus activation of the UPR (12). These results suggest that NgBR is able to modulate this N-glycosylation/endoplasmic reticulum stress/UPR signalling pathway.

One previous study suggested that a glycosylation disorder is a common occurrence in human cancer, and that these changes are characteristics of cancer types including breast cancer and NSCLC (71). Furthermore, glycosylation serves a key role in the EMT, cell-cell contact, cancer progression and cancer cell metastasis (72,73). These results indicate that the inhibitory mechanisms of NgBR on cancer cells may be mediated by the maintenance of N-glycosylation.

Recent studies have further investigated whether the UPR may be involved in intervening in the carcinogenic process and may be a novel therapeutic target for controlling neoplasia development or arresting the progression of the malignant phenotype (77-80). One previous lung cancer study noted that the upregulation of the UPR is able to induce the expression of glucose-regulated protein 78 kDa (GRP78) to suppress apoptosis and resistance to anticancer drugs in lung cancer (74). A previous study indicated that C/EBP homologous protein and GRP78 may mediate the development and progression of lung adenocarcinoma (75). Furthermore, the activation of GRP78 is upregulated in lung cancer cells, which are able to induce endoplasmic reticulum stress tolerance against the pharmacological action of anticancer drugs (76). Breast cancer cells may also
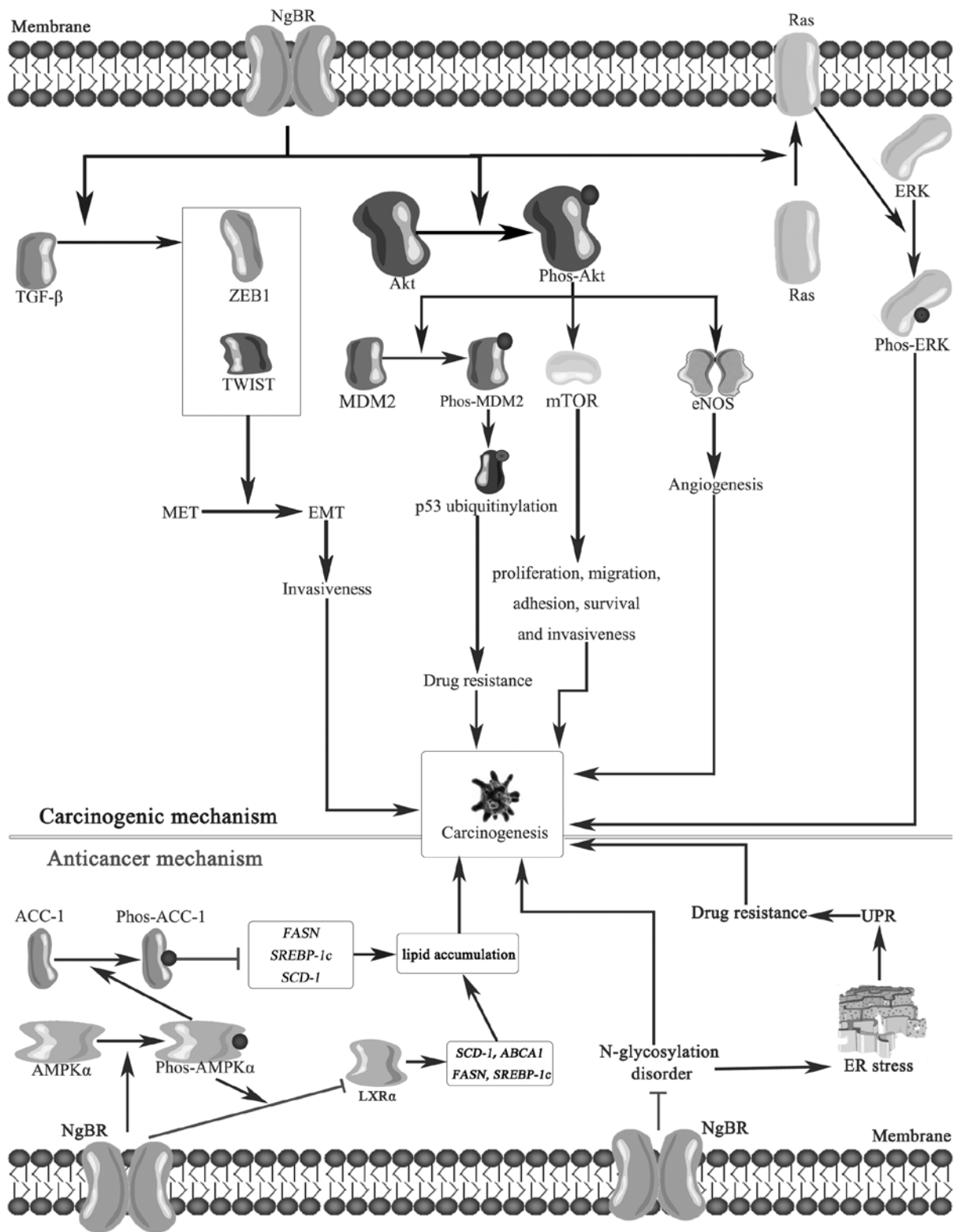
Figure 1. Potential mechanisms underlying the anticancer and carcinogenetic effects of NgBR. NgBR may promote the switch from the MET to the EMT via TGF-β, which upregulates the invasiveness of cancer cells. Furthermore, NgBR enhances the phosphorylation of Akt, and phos-Akt subsequently activates mTOR, which promotes cancer cell proliferation, migration, adhesion, survival and invasiveness. Furthermore, activated Akt enhances the phosphorylation of MDM2 to promote p53 ubiquitylation, which induces drug resistance, and increases eNOS to induce angiogenesis. The phosphorylation of ERK is stimulated by NgBR through the recruitment of Ras to the plasma membrane. Altogether, these potential mechanisms all induce carcinogenesis. However, NgBR may also mediate the phosphorylation of AMPKα and suppress the activation of LXRα to reduce the level of lipids, which have anticancer effects. Furthermore, NgBR may maintain normal N-glycosylation and inhibit ER stress and the UPR to induce a significant anticancer effect. NgBR, neurite outgrowth inhibitor B receptor receptor; MET, mesenchymal-to-epithelial transition; EMT, epithelial-to-mesenchymal transition; TGF-β, tumor growth factor β; ZEB1, zinc finger E-box binding homeobox 1; TWIST, twist family bHLH transcription factor 1; Akt, protein kinase B; phos, phosphorylated; MDM2, mouse double minute 2 homolog; mTOR, mechanistic target of rapamycin; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; ACC-1, acetyl-coenzyme A carboxylase-1; AMPKα, adenosine monophosphate-activated protein kinase α; LXRα, Liver X receptor α; SCD-1, stearoyl coenzyme A desaturase-1; ABCA1, ATP-binding cassette subfamily A member 1; FASN, fatty acid synthase; SREBP-1c, sterol-regulatory element-binding protein; ER, estrogen receptor; UPR, unfolded protein response.

reduce cell apoptosis and the effects of antioestrogen therapy by a mechanism similar to the UPR. Activation of the UPR is induced by tumour hypoxia and endoplasmic reticulum stress during breast cancer. Subsequently, the upregulated mRNA of X-box binding protein may bind to oestrogen receptors and induce agonistic activities, and these agonistic activities are able to promote the transcription of the mRNA encoding the B-cell lymphoma 2 protein, which serves a crucial role in anti-apoptosis and the effects of antioestrogen therapy (77). A previous study on MM suggested that the most important oncogenic factor is a B-Raf proto-oncogene, serine/threonine kinase (BRAF) gene mutation. This mutation upregulates the Ras-Raf-MEK signalling pathway, which may produce carcinogenic effects on the human body (78). A recent study indicated that BRAF mutations also induce the consistent and modest activation of the UPR with GRP78 upregulation, which is considered a tumour marker of MM metastasis and recurrence. This mechanism may be considered an essential factor in MM metastasis (79).

4. Conclusions and future perspectives

The present review summarizes the expression, characteristics and biological functions of NgBR in numerous cancer types, which are complicated and novel and had remained unclear until now. This information is presented in the schematic representation presented in Fig. 1. Numerous pathophysiologic studies have confirmed that NgBR serves an important role in carcinogenesis and that its activation promotes cell proliferation and migration and inhibits apoptosis via multiple physiopathological mechanisms, including the AMPKα (11,69), LXRα (11,69), Akt (20,43) and ERK (28,43) signalling pathways.

NgBR offers novel clinical opportunities, but it is necessary for researchers to obtain an improved understanding of the mechanisms underlying the protective biological characteristics achieved following the elimination of drug resistance, which will improve the design of systemic therapies for numerous cancer types. To better understand the chemoresistance mediated by NgBR, the characteristics of NgBR must be confirmed, including its size, shape, pathophysiological effect and structure-function associations (15,43).

Novel studies demonstrated that NgBR activation serves a key role in reprogramming the metabolism of drug-resistant cancer cells, including promoting p53 ubiquitylation (15) and the UPR (12). In addition, NgBR has been demonstrated to be effective in facilitating the EMT, which has been confirmed to be a root factor affecting cancer chemosensitivity (18). NgBR inhibition may be a more powerful and promising tool for reversing chemoresistance compared with NgBR activation.

Furthermore, the development of highly selective NgBR inhibitors, including miR-26a, will not only promote further study on the molecular function of NgBR but also provide a potential approach for cancer therapy (53). Interestingly, doxycycline is able to induce the expression of inducible short hairpin RNA interference targeting NgBR, which is currently being considered for use in cancer prevention and treatment (29). Doxycycline has been demonstrated to result in cell transformation and tumour growth arrest in breast cancer (80).

In contrast, certain molecular mechanisms underlying the anticancer properties of NgBR may be classified as part of the LXRα, AMPKα and N-glycosylation/endoplasmic reticulum stress/UPR pathways, which may aid maintenance of a normal cellular phenotype. The study of different tumour types and their treatments indicate that NgBR may be a tumour suppressor protein. Altogether, these results suggest that NgBR may serve a dual role in carcinogenesis. In the early stages, NgBR functions as an anticancer molecule, and its dysregulation may result in the initiation and development of cancer, whereas in the later stages, the activation of NgBR may help cancer cells escape from death and develop drug resistance (11,12).

Therefore, ongoing and future studies are expected to elaborate on the fundamental structure-function associations of NgBR that may be useful for the development of novel drugs that directly target NgBR by providing available projects for the laboratory validation of its molecular function. Therefore, the genesis of contraindications postulates that NgBR may induce the rejuvenation of suppressed vascularity and heighten an opposite effect conducive to tumour growth. Furthermore, further clinical research of NgBR is also required to increase its stability in plasma, the transfer of one of its components to dehydrodolichyl diphosphate synthase subunit, the dynamics of its metabolism, its disease specificity, its cell type-specific targeting in cancer development and responses to conventional therapy.

Availability of data and materials

Not applicable.

Author contributions

YKL conceptualized the study, performed the analysis, collected data and participated in writing the paper. YJX collected data, acquired funding and participated in writing the paper. DCW participated in the collection of data and in the writing the paper. SLL performed the analysis and editing and also participated in the data collection. ST and ZCM reviewed and edited the paper and jointly designed the structure of the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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