Review Article
BANCR: a cancer-related long non-coding RNA

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Abstract: Long non-coding RNAs (lncRNAs) are a group of non-protein-coding RNAs with more than 200 nucleotides in length. lncRNAs are involved in diverse biological processes, including development, cell proliferation and differentiation. Emerging evidences also suggest that lncRNAs may participate in cancer development by functioning as tumor suppressors and oncogenes. BRAF-activated non-coding RNA (BANCR) was first identified as an oncogene in melanoma. Later studies demonstrated that BANCR was frequently deregulated in human cancers, including lung cancer, gastric cancer, colorectal cancer, thyroid cancer and osteosarcoma. Nevertheless, the direction of deregulation was tissue-specific in which BANCR could as an oncogene or tumor-suppressor gene. In this review, we compile current evidences concerning the functional roles and molecular mechanisms of BANCR in tumor development.

Keywords: Long non-coding RNAs, BANCR, cancer, oncogene

Introduction

Long noncoding RNAs (lncRNAs) are long RNAs (longer than 200 nucleotides) with limited protein coding potential [1-4] and play critical roles in transcriptional and post-transcriptional regulation of gene expression [2, 5, 6]. Recent studies have shown that deregulation of lncRNAs is involved in the initiation and progression of various types of cancer and correlated with cancer prognosis, including metastasis, recurrence and response to therapy [7-11]. Deregulation of lncRNAs contributes to the progression of cancer through modulating several cellular processes crucial to oncogenesis, including cell proliferation, migration and apoptosis [12-16].

BRAF-activated non-coding RNA (BANCR) was first identified in 2012 by Flockhart et al. in a RNA sequencing screen with an aim to identify transcripts affected by oncogenic BRAF[V600E] in melanoma [17, 18]. They established that BANCR was a 693-bp lncRNA with its gene having four exons located on chromosome 9 [17, 19]. Increasing number of studies later showed that BANCR was deregulated in various types of human cancer [17, 20-22]. The expression and

function of BANCR, however, are tissue-specific. BANCR contributes to tumorigenesis through modulating various mechanisms, including altering cell proliferation and migration.

In this review, we examine current evidences regarding the deregulation and roles of BANCR as one of the most important regulatory RNAs in human cancers. In addition, we review the potential molecular functions and mechanisms associated with BANCR deregulation in cancer. Moreover, we discuss the potential clinical applications of BANCR and its future perspectives.

Lung cancer

Lung cancer has become the second most common cancer and one of the leading causes of cancer-related deaths in the United States [23, 24]. Lung cancer can be divided into two classes, namely small cell lung cancer and non-small cell lung cancer (NSCLC) [25-27]. Somatic mutations in BRAF have been found in ~3% of all NSCLC, in which ~50% is V600E [28]. The expression of BANCR was significantly lower in NSCLC tissues than normal tissues [19]. Lower BANCR expression was also associated with

advanced clinical and pathological stages, as well as shorter overall survival of NSCLC patients independent of other clinicopathological parameters. Functionally, overexpression of BANCR inhibited cell viability, invasion and metastasis while knockdown of BANCR increased cell migration and invasion. In particular, enforced expression of BANCR suppressed epithelial-mesenchymal transition (EMT) through regulating E-cadherin, N-cadherin and vimentin. Further investigations revealed that histone deacetylation of *BANCR* promoter could mediate its downregulation in NSCLC cells. BANCR expression was higher in lung cancer-bearing C57BL/6 mice exposed to radiation therapy than in the control mice [29]. Consistent with previous studies, lower levels of BANCR were associated with larger lung tumor size in these mice and increased tolerance to radiation *in vitro*. These findings suggested that radiation therapy might exert its anti-tumor role in lung cancer at least in part through upregulating BANCR.

Gastric cancer

Gastric cancer is the third leading cause of cancer-related death worldwide [30-33]. Most patients with gastric cancer present with advanced stage of disease at the time of diagnosis, resulting in poor prognosis [34-37]. Therefore, molecular biomarkers are urgently needed to promote early diagnosis and prognostication in gastric cancer patients. While *BRAF* mutation is extremely rare in gastric cancer [38], BANCR was significantly upregulated in gastric cancer tissues compared with adjacent normal tissues [39]. Moreover, high expression of BANCR as an independent unfavorable prognostic factor was associated with advanced clinical and tumor-node-metastasis (TNM) staging in gastric cancer patients. An independent study also showed that BANCR was abnormally overexpressed in gastric cancer tissues and cell lines [40], in which knockdown of BANCR reduced cancer cell proliferation and induced apoptosis, accompanied by the inhibition of NF-κB1 expression. Importantly, overexpression of NF-κB1 reversed the tumor-suppressing effects of BANCR knockdown in gastric cancer cells. NF-κB1 was a target of microRNA-9, whose inhibitor could also reverse the effects of BANCR knockdown in gastric cancer cells. These results suggested that BANCR is overexpressed and exerts oncogenic function in gastric cancer through the microRNA-9/

NF-κB1 cascade. Overexpression of BANCR is also an unfavorable prognostic marker in gastric cancer patients.

Colorectal cancer

Colorectal cancer is common worldwide, with most patients diagnosed at the late stage in China [41-45]. It is therefore urgent to identify novel molecular markers and therapeutic targets for early detection and treatment, respectively, to improve the clinical outcomes. *BRAF* mutations occur in ~10% of colorectal cancer with 3% in non-hypermutated tumors and 47% in and hypermutated tumors [46].

Two contrasting views on the role of BANCR in colorectal cancer exist in the literature. Guo *et al.* reported that BANCR expression was frequently upregulated in colorectal cancer as compared with the matched adjacent normal tissues and positively correlated with lymph node metastasis and tumor stage [47]. In addition, enforced expression of BANCR promoted the migration of colon cancer cells *in vitro*, while downregulation of BANCR exerted an opposite effect. Further investigation demonstrated that BANCR induced EMT in colorectal cancer whereas the MAP kinase-ERK kinase (MEK) inhibitor U0126 decreased migration and reversed EMT in BANCR-overexpressing colon cancer cells, indicating that BANCR-induced EMT was MEK/extracellular signal-regulated kinase (ERK)-dependent. However, another study reported contradictory evidence in which BANCR expression was found to be significantly lower in colorectal cancer tissues as compared with normal tissues [48]. In addition, ectopic expression of BANCR inhibited colon cancer cell proliferation *in vitro* and *in vivo*. p21 is a well-known cyclin-dependent kinase inhibitor that arrests the cell cycle to inhibit cell proliferation. In this regard, ectopic expression of BANCR upregulated p21 and induced G_0/G_1 cell-cycle arrest and apoptosis in colorectal cancer cells, suggesting that downregulation of BANCR might contribute to the proliferation of colorectal cancer cells, at least in part, through the regulation of p21. Consistent with the latter study, BANCR was found to be involved in the unexpected tumor-suppressing effect of fentanyl, which is an anesthetic analgesic drug widely used in cancer pain management. To this end, fentanyl downregulated the transcription factor Ets-1 to derepress BANCR expression via altering histone 3 acetylation in colon

cancer cells [49]. Furthermore, fentanyl-induced inhibition of cell proliferation, migration and invasion was reversed by Ets-1 overexpression and such rescuing effects of Ets-1 could be abrogated by BANCR co-overexpression. This study supports that BANCR could exert tumor-suppressing effects in colorectal cancer. The reason underlying these contradictory findings remain unclear but it is hopeful that larger sample size together with more information on $BRAF^{V600E}$ and microsatellite instability statuses of tumor tissues in future studies will minimize inconsistency arising from inter-individual or subtype-specific difference.

Melanoma

Melanoma is a leading cause of skin cancer deaths with a poor survival rate [50-53]. Methods for early melanoma detection and innovative therapies to control advanced melanomas are needed [54-56]. Activating mutations in the BRAF oncogene are present in >70% of melanomas, 90% of which produce the active mutant $BRAF^{V600E}$ protein [57]. Flockhart et al. identified 39 differentially regulated lncRNAs, including BANCR, in $BRAF^{V600E}$-positive melanomas cells [17, 18], in which BANCR was recurrently upregulated and associated with cell migration. BANCR knockdown reduced melanoma cell migration by downregulating several related genes, including the chemokine CXCL11, which is a mediator of cell migration. Consistently, Li et al. showed that BANCR was upregulated in human melanoma cell lines and tissues [20, 58]. In addition, increased BANCR expression was associated with higher tumor stages and lower survival rates. Knockdown of BANCR significantly reduced melanoma cell proliferation through inhibiting the mitogen-activated protein kinase (MAPK) pathway, in which the reduced phosphorylation of ERK1/2 and JNK caused by pharmacological inhibition could be rescued by BANCR overexpression. Moreover, combination of BANCR knockdown with ERK1/2 or JNK suppression resulted in synergistic inhibitory effects on melanoma cell proliferation in vitro. BANCR knockdown could also inhibit melanoma growth in vivo in BALB/c nude mice. In summary, BANCR is abnormally upregulated in human malignant melanoma and promotes cell proliferation and migration. The oncogenic effect of BANCR is dependent at least in part on CXCL11 and the MAPK pathway, suggesting the existence of a novel molecular circuitry that regulates malignant phenotypes in melanoma.

Thyroid cancer

Papillary thyroid carcinoma (PTC) accounts for approximately 80% of all thyroid cancers [59-61]. Most PTCs exhibit excellent prognoses due to early diagnosis and effective treatment, including surgery [62, 63]. Accumulating evidence has shown that epigenetic alteration plays a critical role in the development of thyroid cancer [60, 64]. $BRAF^{V600E}$ is the most common somatic mutation in PTC and could be detected in ~45% of tumor tissues [65]. Concordantly, BANCR expression was higher in PTC tissues and cell lines than in the normal controls [66]. Overexpression of BANCR induced cell proliferation, inhibited apoptosis and activated autophagy in PTC cells in vitro whereas BANCR knockdown exerted opposite effects. These results suggested that BANCR is oncogenic in PTC. Consistently, an independent study showed that the expression level of BANCR was significantly higher in PTC than in normal tissue [67]. In addition, BANCR knockdown dramatically inhibited thyroid-stimulating hormone receptor and suppressed PTC cell proliferation through inducing cell cycle arrest. BANCR silencing in PTC cells also reduced chromatin recruitment of enhancer of zeste homolog 2 (EZH2), an oncogenic histone methyltransferase whose overexpression inhibits a repertoire of tumor suppressors in different types of cancer. Therefore, BANCR is a potential therapeutic target in PTC.

Osteosarcoma

Osteosarcoma is the most common primary and aggressive bone malignancy in adolescents. It is characterized by poor prognosis because of its high local aggressiveness and metastasizing potentials as well as its resistance to chemotherapy. However, no useful biomarker for osteosarcoma detection and prognostication has been identified. BRAF was found to be mutated in approximately one-tenth of osteosarcoma patients [68]. The expression level of the BANCR was lower in osteosarcoma MG-63 cells as compared with normal osteoblasts SV-HFO. Overexpression of BANCR significantly reduced the level of β-catenin and suppressed MG-63 cell viability. Its expression was also induced by a phytochemical that

Table 1. Dysregulation and functions of BANCR in human cancers

Cancer type	Dysregulation	Phenotypes affected	Related genes	Role	References
Lung cancer	Downregulated	Viability, invasion metastasis, EMT		Tumor suppressor gene	[19, 29]
Gastric cancer	Upregulated	Growth, apoptosis	NF-kB1 miR-9	Oncogene	[39, 40]
Colorectal cancer	Upregulated Downregulated	Migration, EMT, cell cycle	MEK p21 Ets-1	Oncogene or tumor suppressor gene	[47-49]
Melanoma	Upregulated	Growth, migration	CXCL11 ERK1/2 JNK	Oncogene	[17, 18, 20, 58]
Thyroid cancer	Upregulated	Proliferation, apoptosis, autophagy	TSHR EZH2	Oncogene	[64, 67]
Osteosarcoma	Downregulated	Viability, Proliferation, apoptosis	JNK	Tumor suppressor gene	[67]
Retinoblastoma	Upregulated	Proliferation, migration, invasion		Oncogene	[22]
Hepatocellular carcinoma	Upregulated	Proliferation, apoptosis, migration, invasion, EMT		Oncogene	[79]

Figure 1. Proposed oncogenic mechanisms of BANCR.
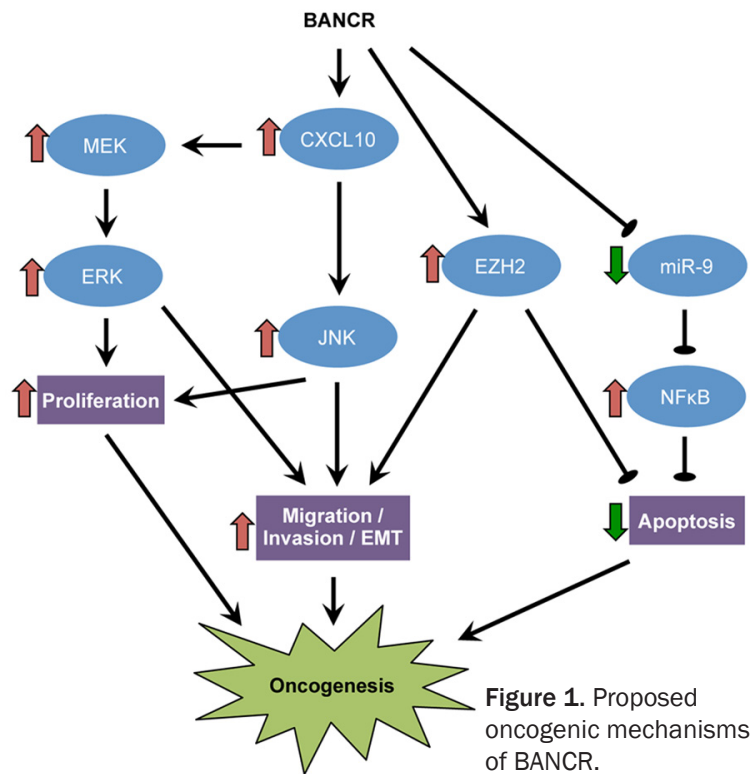
the advancement in its diagnosis and treatment [72-74]. The identification of novel molecular markers may also help develop new prognostic and therapeutic strategies. *BRAF* mutations are rare in retinoblastoma [75] but BANCR expression was higher in retinoblastoma tissues and cell lines than in normal retina samples [22]. In addition, BANCR expression was associated with tumor size, choroidal and optic nerve invasion as well as poor survival. Functionally, downregulation of BANCR inhibited proliferation, migration, and invasion of retinoblastoma cells *in vitro*. Taken together, BANCR plays a critical role in retinoblastoma progression and may serve as a promising candidate for prognostication and therapeutic targeting in retinoblastoma patients.

exerted potent anti-cancer effects in osteosarcoma cells [69]. These findings suggest that BANCR could function as a tumor suppressor in osteosarcoma, in which this lncRNA negatively regulates cell proliferation through targeting the oncogenic Wnt/β-catenin signaling.

Retinoblastoma

Retinoblastoma is the most common primary intraocular malignancy of childhood, seriously impairing patient's vision [70, 71]. Retinoblastoma has become largely curable thanks to

Hepatocellular carcinoma

The epidemiology of hepatocellular carcinoma (HCC) is undergoing a dynamic change in which its incidence in many Asian countries is declining because of infant hepatitis B virus immunization but on the rise in Western countries owing to increasing chronic hepatitis C virus infection [76]. The usual outcome of HCC is poor as only 10%-20% of tumors could be surgically removed. Moreover, there is no effective therapeutic agent for HCC except sorafinib which could extend the median survival of

advanced-stage patients for ~3 months [77]. It is therefore pivotal to better understand the molecular pathogenesis of HCC in order to identify novel therapeutic targets.

While *BRAF* mutation occurs in <1% of HCC [78], a recent study showed that BANCR expression was remarkably upregulated in HCC tissues and cell lines compared with adjacent noncancerous tissues and normal hepatocyte CL-48O cells, respectively. High BANCR expression was also associated with high tumor grade, large tumor size, venous infiltration, advanced TNM staging, and shorter overall survival. Multivariate analysis further revealed that BANCR was an independent unfavorable prognostic factor in HCC. Functional characterization in HCC cells showed that knockdown of BANCR impaired cell proliferation, promoted apoptosis and reduced cell invasion and migration. The latter might be attributed to EMT reversal, which was marked by upregulation of E-cadherin and downregulation of vimentin [79]. These findings suggested BANCR is not only an oncogenic lncRNA in HCC, but also a novel prognostic marker as well as a potential therapeutic target.

Conclusions and future perspectives

Emerging evidences have shown the crucial roles of BANCR in the initiation and progression of different cancers (**Table 1**), in which the expression and functions of BANCR are tissue-specific. BANCR is upregulated in gastric cancer, melanoma, thyroid cancer, retinoblastoma and HCC where it promotes multiple oncogenic signaling cascades (**Figure 1**). In contrast, BANCR is downregulated in lung cancer and osteosarcoma where suppression of EMT and inhibition of Wnt/β-catenin signaling mediate its tumor-suppressing action. In colorectal cancer, different studies yielded contradictory results. Although BANCR seems to be upregulated in cancers with high prevalence of *BRAF* mutations, such as melanoma and PTC, the relationship between *BRAF* mutations and BANCR dysregulation is less apparent in other cancer types. Moreover, the mechanism underlying the tissue-specific effect of BANCR remains elusive. To this end, many lncRNAs have been shown to function as a microRNA-sponge to mediate their biological actions [80-82]. Thus, it is highly possible that tissue-specific expression profiles of microRNAs [83] in different cancer types would dictate whether

BANCR functions as an oncogene or tumor-suppressor gene. Understanding the deregulated expression and functional roles of BANCR in cancers together with its association with clinic pathological parameters will help develop BANCR-based diagnostic or prognostic methods. In particularly, expression analysis of BANCR can be readily achieved by standardized quantitative techniques, including RT-PCR.

Future investigation should analyze BANCR levels in urine, blood, and mucus for non-invasive detection or monitoring of cancer. A systematic analysis of BANCR expression using existing datasets, including The Cancer Genome Atlas (TCGA), may also help to identify cancers with deregulated BANCR expression levels. Moreover, although some upstream regulatory pathways mediating BANCR deregulation in cancers have been reported, the exact molecular mechanisms remain largely unknown. Further experiments are also required to delineate the downstream mechanism of BANCR, including elucidation of the molecular identities of its binding partners.

Acknowledgements

Disclosure of conflict of interest

None.

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