


## REVIEW ARTICLE

# The BRAF activated non-coding RNA: A pivotal long non-coding RNA in human malignancies

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**Abstract**

Long non-coding RNAs (lncRNAs) participate in the complex network of cancer and play an important role in tumorigenesis and progression. BRAF activated non-coding RNA (BANCR), a 4-exon transcript of 693-bp, was first discovered as an oncogenic long non-coding RNA in BRAF<sup>V600E</sup> melanomas cells in 2012 and was related to melanoma cell migration. Besides melanoma, increasing evidence has explored the potential role of BANCR in the development and progression of multiple other human malignancies, such as retinoblastoma, lung cancer, gastric cancer etc. since its discovery. The expression pattern of BANCR varies in different types of cancers, either as a tumour suppressor or as an accelerator. Functional BANCR may serve as a promising biomarker for cancer diagnosis as well as prognosis evaluation. BANCR-targeted intervention may also become a valuable novel therapeutic tool against human malignancies. This review summarized the advanced research progresses concerning the expression and role of BANCR in different human malignancies.

## 1 | INTRODUCTION

Cancer is a group of malignancy diseases with uncontrolled cell growth, migration and invasion. With hundreds of types, cancer is the leading cause of cancer related death worldwide. In 2015, an estimated 90.5 million people were diagnosed with cancer which has incidence of 14.1 million new cases per year, 15.7% of all human death are caused by cancer.<sup>1</sup> Present therapeutic methods for advanced stage cancers still have some limitations and early stage cancers tend to have a poor diagnosis due to the lack of efficient biomarkers. Therefore, identification of these potential efficient biomarkers may help in the early stage diagnosis of cancers.

Long non-coding RNAs (long ncRNAs, lncRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), small nucleolar RNAs (snoRNA), small nuclear RNA (snRNA) and microRNAs (miRNAs) all belong to the non-coding RNAs family. Due to the fact that non-coding RNAs do not encode any proteins, they were considered to possess no biological

function and once were neglected for a long time. Recently, more and more researches (studies) reveal that non-coding RNAs can be transcribed and exert essentially biological roles at RNA levels. The difference between lncRNAs and other members of non-coding RNAs family is that lncRNAs are transcripts >200 nucleotides, while the others are not. Though emerging and not well-characterized as microRNAs, lncRNAs play a vital role in the regulation of diverse biological processes, such as proliferation, apoptosis, invasion, differentiation, and etc. Increasing evidence demonstrates that lncRNAs are also abnormally expressed in varieties of cancers, such as melanoma, has roles in tumorigenesis and progression. lncRNAs are emerging as new biomarkers in many human malignancies.<sup>2</sup> Some studies have focused on analysing molecular mechanisms and networks, aiming to expose their role in the development of cancer. However, the exact underlying biological roles of lncRNAs in cancers remain largely unknown.

Potential medical applications of lncRNAs have gained extensive attention in recent years. Among lncRNAs, BRAF-activated non-coding RNA (BANCR) is a 4-exon transcript of 693-bp in a 60 kb gene desert region on chromosome 9. It was first identified in 2012 year

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**TABLE 1** Functional characterization of BANCR in various tumours

Tumour type	Expression	Role	Related molecules	Phenotypes affected	Ref.
Melanoma	Up-regulation	Tumour accelerator	Ras-1, ERK, JNK, miR-204, Notch2	Proliferation, migration, invasion, apoptosis	[3,6,7]
Retinoblastoma				Proliferation, migration, invasion	[8]
Osteosarcoma				Proliferation, migration, invasion	[19]
Endometrial cancer			MEK/ERK1/2, MMP1, MMP2	Proliferation, migration, invasion	[20]
Oesophageal cancer				Proliferation, migration, invasion	[24]
Gastric cancer			microRNA-9, NF- $\kappa$ B1	Proliferation, apoptosis, metastasis	[28-31]
Hepatocellular carcinoma			Vimentin, E-cadherin protein, ERK, JNK	Proliferation, apoptosis, migration, invasion	[36,37]
Colorectal cancer	Up-regulation	Tumour accelerator	ERK, Vimentin, E-cadherin protein	Proliferation, migration, and EMT	[41-43]
	Down-regulation	Tumour suppresser	p21 protein	Proliferation	[40]
Papillary thyroid carcinoma	Up-regulation	Tumour accelerator	cyclin D1, TSHR	Proliferation, apoptosis and autophagy	[45,46]
	Down-regulation	Tumour suppresser	ERK1/2, p38 MAPK	Proliferation apoptosis, migration and invasion	[47]
Bladder cancer	Down-regulation	Tumour suppresser		Proliferation, apoptosis and migration	[48]
Lung cancer			HDAC3, p38 MAPK, JNK, E-cadherin, N-cadherin, Vimentin	Proliferation, apoptosis, migration, invasion and EMT	[51,52,54]

Note: BANCR, BRAF-activated non-coding RNA; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal Kinase; MAPK, mitogen-activated protein kinase; MMP1, matrix metalloproteinase 1; MMP2, matrix metalloproteinase 2; F- $\kappa$ B1, Nuclear factor kappa B1; EMT, epithelial to mesenchymal transition; TSHR, thyroid stimulating hormone receptor; HDAC3, Histone deacetylase.

by Flockhart RJ et al. as a tumour accelerator via RNA-seq screening in BRAF<sup>V600E</sup> melanocyte cells.<sup>3</sup> However, its expression and clinical significance in other human malignancies remains unknown. This review will elucidate the advanced research progresses on the different expression pattern of BANCR, as well as its specific biological role it exhibited in different human cancers (Table 1). BANCR may serve as a novel biomarker for cancer diagnosis and disease prognosis evaluation. BANCR-targeting inventions may be explored as a promising therapeutic option in cancer treatments.

## 2 | BANCR IN HUMAN MALIGNANCIES

### 2.1 | Melanoma

Melanoma is a type of malignant cancer that originates from the melanocytes, which may occur in the skin, eye, mouth, intestines etc. Being the most aggressive skin cancer with rapid progression,<sup>4</sup> melanoma is the primary cause of skin cancer mortality in the United States.<sup>5</sup> The prognosis of melanoma is good if the disease is detected early and intervened timely. However, melanomas are sometimes inclined to be neglected when they appear as a small dot in the early stage, though all the melanomas are malignant. In-depth understanding of the complex process of melanomagenesis, both

epigenetic and genetic, may facilitate prevention, diagnosis and early intervention for melanomas.

LncRNAs can alter gene regulation and lead to epigenetic changes. BANCR, as one of the important lncRNAs, was found to be a potential melanoma biomarker. BANCR was overexpressed in BRAF<sup>V600E</sup> melanocyte cells and crucial for melanoma cell migration.<sup>3</sup> BANCR was also highly expressed in human melanoma tissues and cells when compared to naïve controls (melanocytic nevus or human melanocytes),<sup>6,7</sup> and the expression level of BANCR increased with clinical tumour stages.<sup>6</sup> Higher expression of BANCR was also found to be associated with a lower survival rate in melanoma patients. BANCR promoted melanoma cells proliferation, migration, invasion and inhibited apoptosis. These effects can be augmented by BANCR overexpression and inhibited by BANCR knockdown.<sup>6,7</sup> Tumourigenicity assay in nude mice further demonstrated that BANCR knockdown inhibited tumour growth in vivo.<sup>6,7</sup> Raf-ERK1/2,<sup>6</sup> JNK signalling pathways,<sup>6</sup> and BANCR/miR-204/Notch2 signalling were demonstrated to regulate the tumour progression of melanoma.

These results indicate that BANCR participates in the cell proliferation of melanoma both in vitro and in vivo. Raf-ERK1/2, JNK, miR-204, Notch2-targeted interpretations may provide novel options in malignant melanoma treatments.

## 2.2 | Retinoblastoma (Rb)

Long non-coding RNA BANCR regulates growth as well as metastasis and is associated with poor prognosis in retinoblastoma.<sup>8</sup> Rb is an uncommon childhood malignant tumour of the retina. Nearly 300 new cases of Rb are diagnosed in America and 5000-8000 cases are newly diagnosed worldwide, every year.<sup>9</sup> Untreated Rb is fatal within 2 years mainly because of intracranial spread as well as disease dissemination.<sup>10</sup> Nowadays, therapy rate for Rb is high in the developed world due to early diagnosis, along with aggressive multimodal therapy. The available effective treatment includes photocoagulation,<sup>11,12</sup> systemic chemotherapy,<sup>13</sup> external beam radiotherapy,<sup>14,15</sup> and enucleation, etc.<sup>3,16</sup> Further discovery of the biomarkers of Rb progression may contribute to the establishment of both novel molecular prognostic factors and therapeutic strategies.

Su et al reported that BANCR is overexpressed in 60 retinoblastoma tissues and cell lines by using RT-PCR, which is related to tumour size, optic nerve invasion, as well as choroidal invasion.<sup>8</sup> Besides, multivariate analysis revealed that increased expression of BANCR was a poor independent prognostic factor for Rb cases. Knocking down the expression of BANCR notably inhibited the proliferation and migration of Rb cell in vitro.<sup>8</sup> To sum up, BANCR plays an important role in the aggressiveness and prognosis of Rb and may act as a novel target for Rb treatment as well as prognostic prediction.

## 2.3 | Osteosarcoma (OS)

Osteosarcoma is the most usual primary malignant bone tumour that occurs mainly in young adults.<sup>17</sup> In spite of recent progressions in multimodal treatments such as tumour excision and adjuvant chemotherapy, survival expectancy is still limited.<sup>18</sup> The accurate mechanisms of the formation and progression of OS are ambiguous, and further identifying the biomarker of OS progression is essential for improving the diagnosis as well as treatment of OS. Peng et al reported that the overexpression of BANCR was observed in OS clinical specimens and cell lines, which was linked with tumour size, metastasis, and advanced TNM staging.<sup>19</sup> Elevated BANCR expression in OS is a poor independent prognostic factor. Downregulated BANCR inhibited OS cell proliferation, invasion and induced cell apoptosis in vitro.<sup>19</sup> These findings illustrate that BANCR may perform as a tumour promoter in OS and could be beneficial as a therapeutic target for OS.

## 2.4 | Endometrial cancer (EC)

Endometrial cancer is a cancer of the uterine endometrium of the women uterus or womb, and is prevalent in females. EC falls into two categories (Type 1 and Type 2) based on clinical and endocrine features, with Type 1 being the most common one that occurs before and around the time of menopause. Awareness of the EC pathogenesis is not fully clear. The expression level of BANCR, MMP2 and MMP1 were detected to be significantly higher in the

tissues from type 1 EC patients than from normal endometrium tissues by qRT-PCR. And highly expressed BANCR was revealed to be correlated with pathological grade, Federation International of Gynecology and Obstetrics (FIGO) stage, myometrial invasion, lymph node metastasis and enhanced expression of matrix metalloproteinases 1 (MMP1) and matrix metalloproteinases 2 (MMP2).<sup>20</sup> Knockdown of BANCR with si-BANCR dramatically suppressed cell proliferation, migration, and invasion of EC cell lines (HEC-1A cells and Ishikawa cells). It was further elucidated that BANCR induced cell proliferation, migration and invasion via activating ERK/MAPK/MMPs signalling pathway in EC cell lines, suggesting that BANCR plays roles in the EC progression, and BANCR may be explored as a promising biomarker for prognostic evaluation, as well as a potential therapeutic target for type 1 EC. In addition, the expression of BANCR in type 2 EC is still not clear, so more in vitro and in vivo studies based on human EC as well as animal EC model are needed.<sup>20</sup>

## 2.5 | Oesophageal cancer

Oesophageal cancer is the ninth and sixth most common cause of cancer-related death among females and male, respectively, worldwide.<sup>21</sup> Even though, pathogenesis of oesophageal cancer is not fully illustrated, various factors such as tobacco, alcohol, reflux esophagitis, dietary habits, nutrition, as well as environmental factors may contribute to the initiation of oesophageal cancer.<sup>22</sup> Presently, there are still no ideal biomarkers that can be used as a screening tool for oesophageal cancer strategies.<sup>23</sup>

Liu et al revealed that BANCR levels in plasma were considerably higher in oesophageal squamous cell carcinoma (ESCC) patients compared with normal controls.<sup>24</sup> Moreover, increased expression of BANCR was correlated with advanced TNM stage, more lymph node metastasis, as well as the shorter survival of ESCC patients. The expression level of BANCR improved with the disease progression, which reverts to normal after the resection of the tumour. Increased BANCR expression was confirmed to be an independent prognostic factor in ESCC patients.<sup>24</sup> In conclusion, BANCR may be a promising tumour biomarker for early detection, and a potential therapeutic target for ESCC patients. Further studies on the biological function of BANCR in plasma and tissue are needed.

## 2.6 | Gastric cancer (GC)

Among the malignant cancers, GC is ranked as the most common cancer worldwide. Being a disease of high mortality, it is the second commonest cause of cancer-related death worldwide. Although, the treatment option for GC patients is still challenging, surgery and systemic chemotherapy are the mainstay treatments.<sup>25</sup>

Moreover, the exact molecular mechanism of GC is still obscured. Molecular biomarker plays a critical role in the diagnosis, prognosis and treatment of most cancers.<sup>26,27</sup> Hence, it is urgent to find new molecular markers in early diagnosis of GC and investigate therapeutic targets for improving patient outcomes.

Up-regulation of BANCR expression was detected in human GC tissues in comparison with matched normal tissues or cell lines.<sup>28</sup> A close relationship between BANCR up-regulation and tumour size, invasion depth, advanced TNM stage, regional lymph nodes metastasis, as well as distant metastasis was noted in GC patients.<sup>29-31</sup> In survival analysis, high expression of BANCR in GC patients was an independent unfavourable prognostic factor.<sup>29-31</sup> These findings show that BANCR might play an important role in GC development and tumorigenesis, which may be linked with poor prognosis. Zhang et al. revealed down-regulation of BANCR hindered GC cell growth and induced cell apoptosis. Furthermore, it also leads to a sharp decrease in NF- $\kappa$ B1 (P50/105) expression, as well as 3'UTR of NF- $\kappa$ B1 activity. NF- $\kappa$ B1 overexpression overturned the effect of BANCR on GC cell growth and apoptosis. MiRNA-9 (miR-9) targeted NF- $\kappa$ B1, and miR-9 inhibitor could also reverse the roles of BANCR on GC cell growth and apoptosis. Therefore, both NF- $\kappa$ B1 and miR-9 were involved in the effects of BANCR in GC cell growth and apoptosis.<sup>28</sup> In conclusion, BANCR has been found to be linked with tumour suppressor or oncogenic pathways of GC, and altered expression of BANCR was associated with the occurrence and development of GC. This finding provides evidence that BANCR may be considered as an early detection biomarker as well as a novel therapeutic target in GC. However, there is still lacking the clear analysis of specific downstream proteins in details, as well as its role in multidrug resistance, which is one of the major reasons for therapy failure in GC. Thus, the role of BANCR in the development and progression of GC still has many limitations, and further researches are needed.

## 2.7 | Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma is the most common primary malignancy of the liver, and is responsible for approximately 600 000 HCC-related deaths every year, worldwide.<sup>32</sup> Even though various diagnostic and treatment methods are available for HCC, still the prognosis is poor.<sup>33,34</sup> It is urgent to discover effective biomarkers for diagnosis as well as targets for therapy, which will play an important role for the diagnosis and treatment of HCC.<sup>35</sup>

Zhou et al found that the expression of BANCR was significantly increased in HCC tissues in comparison with adjacent noncancerous tissues.<sup>36</sup> The expression of BANCR was also remarkably up-regulated in HCC cell lines.<sup>36,37</sup> Further analysis showed that high expression of BANCR is associated with high tumour grade, venous infiltration, large tumour size and metastasis stage, as well as shorter overall survival. In HCC patients, it is identified that BANCR overexpression is an independent unfavourable prognostic factor.<sup>36</sup> Furthermore, downregulation of BANCR in HCC cells has inhibited cell proliferation, induced cell apoptosis, weakened invasion, and migration of HCC cells, resulted in downregulated vimentin, as well as upregulated the levels of E-cadherin protein.<sup>36</sup> It was also demonstrated that ERK and JNK signalling pathways were involved in the BANCR-associated malignancy of HCC cells whereas, p38 MAPK signalling pathway was not involved.

These findings implied that BANCR might donate to HCC initiation and progression and its beneficial effects as a novel prognostic marker and a therapeutic target for HCC.

## 2.8 | Colorectal cancer (CRC)

Colorectal cancer is the third most common tumour and has the third highest mortality rate, worldwide.<sup>38</sup> Surgery, radiation therapy, chemotherapy and targeted therapy are the main treatments options for CRC. In spite of the death rate has decreased for many years mainly due to the advancement of standard treatment methods,<sup>39</sup> the occurrence of relapses and the unfavourable prognosis still considerably influences the consequences of treating CRC. Consequently, it is vital to detect novel CRC-specific biomarkers in CRC.

Shi et al reported that the expression of BANCR in CRC tissues was down-regulated in comparison with normal tissues, and BANCR overexpression has inhibited CRC cell growth both in vitro and in vivo.<sup>40</sup> They also found that pcDNA-BANCR-mediated CRC cell proliferation was linked with G0/G1 cell-cycle arrest and induction of apoptosis via the regulation of p21 protein.<sup>40</sup> On the contrary, some researches reported that BANCR was overexpressed in CRC tissues, which was considerably related with lymph node metastasis, tumour stage, as well as poor prognosis.<sup>41-43</sup> EMT was induced by BANCR via a MEK/extracellular signal-regulated kinase-dependent mechanism.<sup>42</sup> Li et al found that fentanyl indicated anti-tumour like effects on CRC cells, including hindered cell migration and invasion. Fentanyl induced the upregulation of BANCR and the downregulation of Ets-1 in CRC cells. Further studies revealed that Ets-1 negatively regulated the expression of BANCR through the deacetylation of histones H3 within the promoter of BANCR.<sup>44</sup>

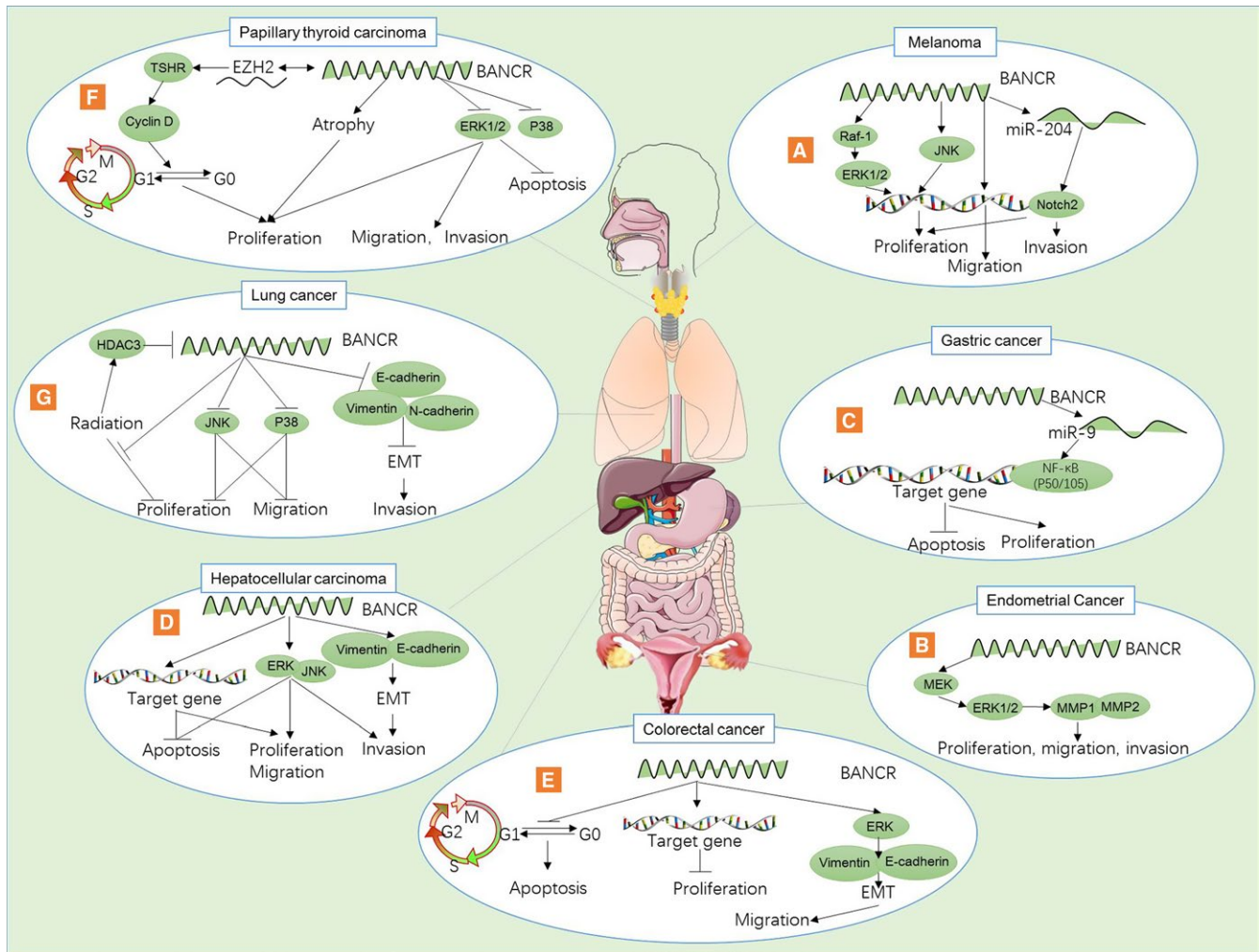
As a conclusion, these results showed the significance of BANCR in the molecular etiology of CRC and suggested the potential application of BANCR as an essential diagnostic marker and therapeutic target of CRC. The variation between the expression profile and function among different researches is probably due to the difference in the study size as well as diverse ethnic groups. Larger studies and extensive functional researches are required to confirm these findings.

## 2.9 | Papillary thyroid carcinoma (PTC)

Papillary thyroid carcinoma is the most common type of thyroid cancers. The prognosis of majority PTC is excellent if treated timely. An ideal biomarker for PTC may help in early detection and intervention, but it has not been identified yet. The role of BANCR in the pathogenesis of PTC remains largely unknown. Based on different studies, the role of BANCR varies either as an oncogene or tumour suppressor.<sup>45-47</sup> Wang et al. in 2014 and Zheng et al. in 2016 reported that BANCR was upregulated in the PTC tissues and PTC cells (IHH-4 cells) when compared with paired normal controls. BANCR overexpression leads to increased

cell proliferation via enhancing autophagy and inhibiting apoptosis of PTC cells, which was reversed by *BANCR knockdown*.<sup>45</sup> It was further demonstrated by *BANCR knockdown* technique that *BANCR* may contribute to PTC through cyclin D1 and thyroid stimulating hormone receptor (TSHR) regulation.<sup>46</sup> These two studies indicate that *BANCR* is an oncogenic lncRNA in PTC.<sup>45</sup> Whereas, Liao et al. in 2017 found that the expression of *BANCR* was lower in PTC tissues when compared to naïve controls, and decreased expressed *BANCR* was positively correlated with poor

prognosis (advanced PTC stage, tumour size and multifocal lesions). Overexpression of *BANCR* inhibited cell proliferation and promoted apoptosis of PTC cells (TPC-1 and K1 cells), resulting in the inhibition of metastasis of PTC evidenced by the xenograft mouse models. It was further confirmed that *BANCR* inhibited PTC tumorigenesis partially via the inhibition of the ERK/MAPK pathways. This study suggests that *BANCR* may be functioned as a tumour suppressor in PTC.<sup>47</sup> Different sample numbers, different PTC cell lines, different PTC differentiation status may



**FIGURE 1** The different regulatory mechanisms of *BANCR* in different human malignancy. (A). *BANCR* induced proliferation via the activation of the Ras-1/ERK and JNK pathway. *BANCR* also promoted migration and invasion in melanoma. *BANCR* promotes the proliferation and invasion of melanoma by functioning as a competing endogenous RNA to upregulate Notch2 expression by sponging miR-204. (B). *BANCR* promote cell proliferation, migration, and invasion by activating MEK/ERK1/2 signalling pathway that regulates MMP1 and MMP2 in endometrial cancer. (C). *BANCR* induced cell proliferation and inhibited apoptosis via the upregulation of MiroRNA-9 targeted NF-κB1 expression in gastric cancer. (D). *BANCR* inhibited cell apoptosis and induced cell proliferation, migration and invasion via activating the ERK and JNK pathways. *BANCR* also induced invasion by EMT (upregulated vimentin, and downregulated E-cadherin) in hepatocellular carcinoma. (E). *BANCR* inhibited cell proliferation by increasing p21 protein, and induced apoptosis by induction of G0/G1 arrest in colorectal cancer. *BANCR* promoted cell migration by EMT in colorectal cancer. (F). *BANCR* inhibited proliferation, migration, metastasis by inhibition of ERK1/2 and p38 pathways in papillary thyroid carcinoma. It also induced apoptosis in papillary thyroid carcinoma. *BANCR* increased papillary thyroid carcinoma cell proliferation by activating autophagy, as well as activating cell cycle via EZH2/TSHR/Cyclin D pathway. (G). *BANCR* inhibited proliferation, migration by inhibition of JNK and P38 pathways in lung cancer. *BANCR* inhibited invasion of lung cancer by inhibition of EMT. Radiation upregulated *BANCR*'s expression via the upregulation of HDAC3 and HDAC3 reversed the *BANCR*'s protective effect on radiation-induced cell death reversed radiation induced cell in lung cancer

account for the inconsistent results of BANCR expression patterns in PTC tumourigenesis. Further studies with larger samples are needed to solve the above puzzle.

## 2.10 | Bladder cancer (BC)

Bladder cancer is a common malignant cancer with frustrated survival rate worldwide. Lack of thorough understanding of underlying molecular mechanism partially accounts for the high fatality rate of BC. The expression level of BANCR RNA was found to be dramatically downregulated in human BC tissues, and decreased BANCR was revealed to be positively correlated with the TNM stage by clinicopathologic analysis.<sup>48</sup> The expression level of BANCR RNA was also downregulated in BC cell lines (SW780 and T24). Once BANCR was overexpressed with pcDNA-BANCR vector in BC cells, cell proliferation was inhibited, apoptosis was induced and migration was suppressed significantly.<sup>48</sup> These results indicate that BANCR participates in BC as a tumour suppressor, and it may serve as a potential biomarker and candidate therapeutic target for BC.

## 2.11 | Lung cancer (LC)

Lung cancer, including small cell lung cancers (SCLCs) and non-small cell lung cancers (NSCLCs), are one of the most aggressive malignant tumours, threatening to human health. NSCLCs are the predominant forms of LC and account for the majority of cancer-related deaths, worldwide,<sup>49</sup> with an estimated 5-years survival rate of 11%.<sup>50</sup> Metastasis is a crucial problem in NSCLC induced death, and understanding of the molecular mechanisms in metastasis may facilitate in identifying new therapeutic targets for anti-cancer therapy. Epithelial-mesenchymal transition (EMT), a biological process with epithelial cells lose their polarity and transit into a mesenchymal phenotype, is a vital step in cancer metastasis. BANCR expression was significantly downregulated in LC tissues (both SCLCs and NSCLCs) and LC cell lines.<sup>51,52</sup> Reduced BANCR was correlated with larger tumour size, advanced pathological stage, metastasis distance and shorter overall survival, revealing that decreased BANCR may serve as an independent biomarker for poor prognosis of NSCLC.<sup>51</sup> While overexpression of BANCR with pcDNA-BANCR transfection led to the significant inhibition of cell viability, migration, invasion and promotion of apoptosis.<sup>51,52</sup> Activation of p38 MAPK and JNK can promote LC tumour progression.<sup>53</sup> Overexpression of BANCR also led to the downregulation of p-p38 and p-JNK,<sup>52</sup> indicating that p38 MAPK and JNK were involved in the BANCR-related cell proliferation and migration of LC. To the opposite, BANCR knockdown with RNA interference significantly promoted cell proliferation, migration and invasion of LC.<sup>51,52</sup>

Enhanced BANCR was also revealed to inhibit EMT in NSCLC through the upregulation of E-cadherin, and downregulation of N-cadherin along with Vimentin expression.<sup>51</sup> Histone deacetylase (HDAC) inhibitor (trichostatin A) treatment or HDAC3 knockdown increased BANCR expression in NSCLC cell lines,<sup>51</sup> indicating that histone deacetylation is also involved in the negative regulation of BANCR.<sup>54</sup> BANCR was found to be elevated in mice receiving

radiation therapy, and HDAC3 overexpression significantly reversed the effect of radiation therapy on BANCR expression. These findings indicate that BANCR may serve as a potential biomarker for LC prognosis and a target for LC chemotherapy.

Further molecular investigations of LC are still needed, for example, the BANCR orientated EMT regulation in NSCLC, which may facilitate the understanding of LC oncogenesis and the discovery of lncRNA-targeted therapeutics.

## 3 | CONCLUSIONS

Emerging evidence reveals that lncRNAs plays an important role in the complex network of cancer and is also linked with tumourigenesis and progression. BANCR was first identified as an oncogenic lncRNAs in BRAF<sup>V600E</sup> melanomas cells. The clinical significance of BANCR, and its' molecular mechanisms in controlling cancer are unclear. Overview of BANCR in human malignancies may provide new insights into the mechanisms of cancer development. This review elucidates the advanced researches and progresses with the possible role of BANCR in different human malignancies (Table 1), as well as the underlying mechanism of BANCR involved (Figure 1). Studies show that the expression pattern and role of BANCR varies in different types of cancers, either as a tumour suppressor or tumour accelerator. The expression tendency of BANCR was inconsistent and the role of BANCR was even opposite in the same type of cancer (e.g. PTC, CRC) in different researches sometimes. Functional BANCR may serve as a promising biomarker for cancer diagnosing and prognosis evaluation, and BANCR-target interventions may also become a valuable novel therapeutic tool against human malignancies, though more-in-depth studies are needed which may explain the expression differences in BANCR in some human malignancies.

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The authors declare that they have no competing interests.

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## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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The topic was conceptualized by C.W.L. and D.D.Z. X.F.L., J.L.H., and T.X. contributed to the literature database search, and writing of the manuscript. C.W.L. and D.D.Z. contributed to vital revising. O.P.P. contributed to English Polishing. All authors read and approved the final manuscript.

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