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Review

Roles of long-non-coding RNAs in cancer therapy through the PI3K/Akt signalling pathway

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Summary. The vital need for Akt in maintaining basic cellular function has highlighted its importance in carcinogenesis. Unfortunately, Akt inhibitor development outcome has remained poor, as most of them have failed to show significant clinical benefit to cancer patients during the clinical trials. Recently, a new class of non-coding RNAs, known as long non-coding RNAs (lncRNAs), which show high tissue specificity, have demonstrated great influence in cancer progression and/or cancer inhibition. As both Akt signalling pathways and lncRNAs play such innate roles in carcinogenesis, identifying the specific roles that these lncRNAs play within this pathway may represent a novel research avenue for developing Akt inhibitors with better therapeutic properties. In addition, understanding the diverse mechanism by which lncRNAs regulate gene expression can assist in deciphering the fundamentals of carcinogenesis. The focus of interest should be on the lncRNAs, which affect Akt and finding the link between lncRNAs and Akt pathways associated with carcinogenesis. LncRNAs within the Akt pathways could affect multiple pathways in a particular cancer type, which ultimately creates an intricate web of connections between the pathways. In summary, lncRNAs have tremendous potential in cancer diagnosis, assessing cancer patient prognosis and in developing new therapeutic options for patients with resistance to current cancer therapies. Thus, understanding how lncRNAs influence the Akt pathway is essential for the development of novel and effective cancer therapies.

Key words: Akt, LncRNAs, Cancer, Resistance, CeRNA, PI3K/Akt

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Brief overview of Akt in cancer

A little over forty years ago, the protein serine-threonine kinase Akt, also known as protein kinase B (PKB) was discovered (Staal et al., 1977). Within a short span of 20 years, three Akt/PKB isoforms conserved in mammalian genomes (Manning and Toker, 2017) were identified: Akt1/PKBα, Akt2/PKBβ (Staal, 1987; Cheng et al., 1992) and Akt3/PKBγ (Ketchum and Slayman, 1996). Akt was found to play an essential role in various cellular processes (Hemmings and Restuccia, 2012) and its activation was often implicated in various cancer types (Davies, 2011; Kumar et al., 2013; Li et al., 2017a-f). Akt is located at the central node of the renowned signalling pathway – phosphoinositide 3-kinase (PI3K)/Akt signalling pathway, comprising of other components, which play important roles in cancer (Nitulescu et al., 2016). These components situate either upstream or downstream to Akt and can be broadly categorised as either tumour suppressors or oncoproteins. For example, tumour suppressor PTEN (phosphatase and tensin homolog) is located upstream of Akt (Fig. 1) while tumour suppressor FOXO3 (forkhead box O3) is located downstream of Akt (Fig. 1). Furthermore, activation of this pathway is frequently associated with therapy resistance in cancer (Brown and

Toker, 2015). Thus, the Akt pathway is deemed an alluring therapeutic target for cancer treatment (Davies, 2011). In this aspect, researchers have made multiple attempts to target this pathway.

To date, three major classes of Akt-inhibiting drugs have been developed. These include ATP-competitive inhibitors, allosteric inhibitors and irreversible inhibitors (Nitulescu et al., 2016). Unfortunately, only a limited number of compounds have made it to clinical trials and none of these has been approved for oncologic use (Nitulescu et al., 2016). Thus far, development of Akt inhibitors is primarily focusing on major components within the Akt pathways such as Akt, mTOR, PDK1 and PI3K (Carnero, 2010). Nevertheless, there is only a limited number of drugs emerging through this process. The reason for this is that, the drug discovery process has been hampered by the intra-structural similarity between the Akt isoforms, as well as the inter-structural between the other cAMP-dependent protein kinase C (AGC kinase) family (Nitulescu et al., 2016). Furthermore, while other forms of Akt inhibitors displayed promising activities within the *in vitro* and *in vivo* models, none of them showed clinical significance in cancer therapy (Nitulescu et al., 2016). Moreover, these Akt inhibitors displayed limited clinical activity as single therapies (Orlowski, 2013). Therefore, there is an urgent need to look into developing Akt inhibitors through a different perspective to achieve better therapeutic outcomes. In the following sections, we highlight one of the roles of long non-coding RNAs (lncRNAs) as potential Akt inhibitor for the management of cancer.

Looking beyond the coding region - non-coding RNAs (ncRNAs)

Of the 10-15% of the genomic region that is constantly under selection, the protein-coding region only accounts for a maximum of 2% of it (Weinhold et al., 2014; Li et al., 2015; Khurana et al., 2016). The majority of cancer studies focus only on this protein-coding region of a genome (Leucci, 2018). The remaining region is termed the non-coding region with a majority of the region still transcribed into RNA (Heery

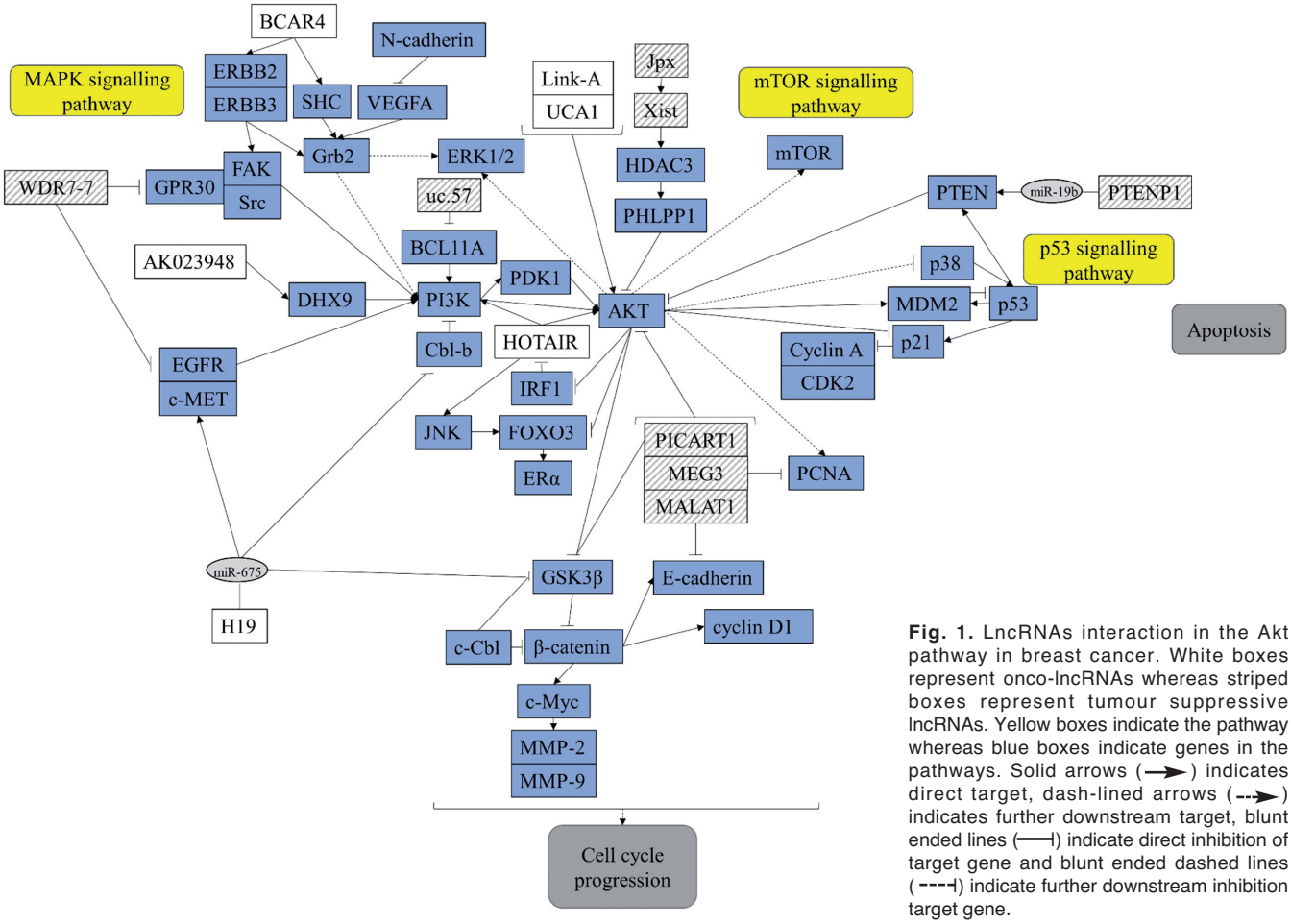

Fig. 1. LncRNAs interaction in the Akt pathway in breast cancer. White boxes represent onco-lncRNAs whereas striped boxes represent tumour suppressive lncRNAs. Yellow boxes indicate the pathway whereas blue boxes indicate genes in the pathways. Solid arrows (⟶) indicates direct target, dash-lined arrows (⇢) indicates further downstream target, blunt ended lines (⟙) indicate direct inhibition of target gene and blunt ended dashed lines (⇠) indicate further downstream inhibition target gene.

et al., 2017). Thus, the term non-coding RNAs (ncRNAs) was coined (Li et al., 2013). ncRNAs play impending roles in cancer by either having oncogenic or tumour suppressive activities (Irimie et al., 2018). They are classified according to sizes: <200 nucleotides long (small ncRNAs) and >200 nucleotides long (long ncRNAs; lncRNA) (Kapranov et al., 2007). Small ncRNAs are broadly made out of tRNAs, rRNAs, miRNAs, siRNAs, snoRNAs, snRNAs and piRNAs (Esteller, 2011). Among them, miRNAs are the most studied transcripts with many preclinical studies done to develop better diagnostic, prognostic and therapeutic options for cancer therapy (Prensner and Chinnaiyan, 2011; Lee et al., 2016; Vosgha et al., 2018).

LncRNAs have been classified by Kung and colleagues (Kung et al., 2013) as stand-alone lncRNAs or large intergenic noncoding RNAs – lincRNAs; natural antisense transcripts; pseudogenes; long intronic ncRNAs; and, divergent transcripts, promoter-associated transcripts and enhancer RNAs. These lncRNAs are expressed in a tissue-specific manner and have a very restricted expression pattern (Jiang et al., 2016). They can regulate or be regulated by diverse gene sets which influence a wide range of cellular functions ranging from pluripotency to cell survival (Guttman et al., 2009; Huarte, 2015), all of which are central to the process of carcinogenesis. The first association between lncRNA and cancer was made with the identification of prostate cancer associated 3 (PCA3) (Bussemakers et al., 1999) and could be used as a prostate cancer diagnostic marker (Hessels et al., 2003). Because lncRNAs have only recently been discovered, have tissue-specific expression and can target or be targeted by a combined gene set, lncRNAs present a massive range for possibilities in terms of diagnostics and treatment options in cancer.

It is clear that both Akt signalling pathway and lncRNAs play innate roles in carcinogenesis. Identifying the specific functions of these lncRNAs within the PI3K/Akt signalling pathway may represent a novel research avenue for developing Akt inhibitors with better therapeutic properties. In addition, understanding the diverse mechanisms by which lncRNAs regulate gene expressions can assist in deciphering the fundamentals of carcinogenesis. In the following section, the mechanisms by which lncRNAs affect the PI3K/Akt signalling pathway and the association of lncRNAs with anticancer drug resistance is explored (Fig. 2).

LncRNAs in Pi3K/Akt signalling pathway and cancer

Emerging reports have indicated the association of lncRNA with cancer. Within 2017 itself, there were over 1,600 articles related to lncRNAs and cancer published, indicating that lncRNAs play a significant role in the pathogenesis of cancer. Of these, over 140 papers published directly related to the Akt protein. LncRNAs have been broadly categorised as either onco-lncRNAs or tumour suppressive lncRNAs with the top three most frequently reported lncRNAs being HOTAIR (HOX transcript antisense RNA), UCA1 (urothelial cancer associated 1) and MALAT1 (metastasis-associated lung adenocarcinoma transcription 1) as shown in Table 1.

Interestingly, some of these lncRNAs seemed to alternate roles as either tumour suppressors or onco-lncRNAs in different cancer types as seen in Table 1. These include the lncRNA H19, XIST (X-inactive specific transcript) and MALAT1. This is not surprising as lncRNAs expression is tissue-specific (Jiang et al., 2016). For example, lncRNA H19 functioned as an onco-lncRNA in gastric cancer (Liu et al., 2016a,b),

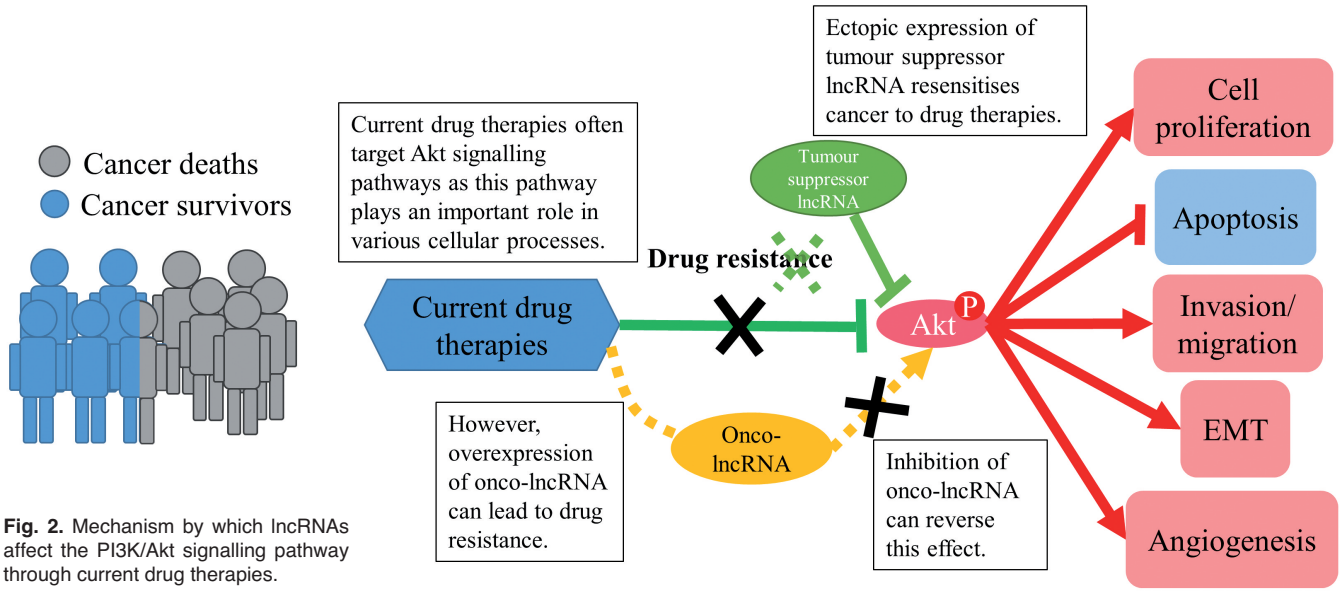

Fig. 2. Mechanism by which lncRNAs affect the PI3K/Akt signalling pathway through current drug therapies.

Table 1. AKT associated lncRNAs as oncogenes or tumour suppressor genes in different cancer types.

Tumour suppressor/ oncogene	lncRNAs	Types of cancer (references)
Onco-lncRNAs	AB073614	Colorectal carcinoma (Wang et al., 2017h), ovarian carcinoma (Cheng et al., 2015b)
	AFAP1-AS1	Gastric carcinoma (Guo et al., 2017), breast carcinoma (Yang et al., 2016a)
	AK023391	Gastric carcinoma (Huang et al., 2017)
	AK023948	Breast carcinoma (Koirala et al., 2017)
	ANRIL	Medulloblastoma (Zhang et al., 2017d), cervical carcinoma (Zhang et al., 2017c)
	ATB	Prostate carcinoma (Xu et al., 2016), bladder carcinoma (Zhai and Xu, 2018)
	BC087858	Non-small cell lung carcinoma (Pan et al., 2016)
	BCAR4	Breast carcinoma (Godinho et al., 2010, 2012)
	BDLNR	Cervical carcinoma (Yu et al., 2018)
	CCAT2	Endometrial carcinoma (Xie et al., 2017)
	CRNDE	Hepatocellular carcinoma (Chen et al., 2016), colorectal carcinoma (Ellis et al., 2014)
	DANCR	Osteosarcoma (Jiang et al., 2017)
	ecCEBPA	Gastric carcinoma, pancreatic carcinoma, lung adenocarcinomas (Nasrollahzadeh-Khakiani et al., 2017)
	FAL1	Non-small cell lung carcinoma (Pan et al., 2017)
	Ftx	Hepatocellular carcinoma (Liu et al., 2016b)
	HOTAIR	Osteosarcoma (Li et al., 2017d), gastric carcinoma (Cheng et al., 2018; Yan et al., 2016b), breast carcinoma (Chen et al., 2015b; Yang et al., 2016b; Yu et al., 2017b), chronic myeloid leukaemia (Wang et al., 2017c), diffuse large B cell lymphoma (Yan et al., 2016b), glioma (Ke et al., 2015), hepatocellular carcinoma (Yang et al., 2014)
	HOXA11-AS	Non-small cell lung carcinoma (Zhang et al., 2016), neuroblastoma (Yarmishyn et al., 2014)
	HULC	Bladder cancer (Wang et al., 2017e), osteosarcoma (Kong and Wang, 2018), chronic myeloid leukaemia (Lu et al., 2017), glioma (Zhu et al., 2016b)
	LEF1-AS1	Glioblastoma (Wang et al., 2017d)
	Linc00152	Non-small cell lung carcinoma (Zhang et al., 2017g), colorectal carcinoma (Yue et al., 2016), gastric carcinoma (Zhou et al., 2015)
	Linc00963/MetaLnc9	Prostate carcinoma (Wang et al., 2014), non-small cell lung carcinoma (Yu et al., 2017a)
	Linc01296	Prostate carcinoma (Wu et al., 2017a)
	LincRNA-p21	Hepatocellular carcinoma and glioma (Shen et al., 2017)
	Link-A	Breast carcinoma (Lin et al., 2017)
	lncRNA H19	Gastric carcinoma (Liu et al., 2016a), gallbladder carcinoma (Wang et al., 2016), hepatocellular carcinoma (Lv et al., 2014; Matouk et al., 2014), breast carcinoma (Vennin et al., 2015)
	lncRNA-PAGBC	Gallbladder carcinoma (Wu et al., 2017b)
	MALAT1	Ovarian carcinoma (Jin et al., 2017), cholangiocarcinoma (Wang et al., 2017b), hepatocellular carcinoma (Li et al., 2017c), Ewing sarcoma (Sun et al., 2017b), osteosarcoma (Dong et al., 2015b), breast carcinoma (Meseure et al., 2016)
	MIR31HG	Non-small cell lung carcinoma (Wang et al., 2017a)
	MIR4697HG	Ovarian carcinoma (Zhang et al., 2017f)
	NEAT1	Colorectal carcinoma (Peng et al., 2017)
	PANDAR	Clear cell renal cell carcinoma (Xu et al., 2017b)
	PIK3CA	Cervical carcinoma (Ma et al., 2000)
	PLIN2	Chronic myelogenous leukaemia (Sun et al., 2017a)
	PlncRNA-1	Colorectal carcinoma (Song et al., 2017)
	ROR	Non-small cell lung carcinoma (Shi et al., 2017b)
	SBDSP1	Colorectal carcinoma (Shi et al., 2017a)
	SNHG1	Colorectal carcinoma (Sun et al., 2017d)
	TFPI2AS1	Non-small-cell lung carcinoma (Gao et al., 2017)
	UCA1	Cholangiocarcinoma (Xu et al., 2017c), gastric cancer (Li et al., 2017b; Nasrollahzadeh-Khakiani et al., 2017; Wang et al., 2017i), prostate carcinoma (Fotouhi Ghiam et al., 2017), breast carcinoma (Chen et al., 2015c; Wu and Luo, 2016), non-small-cell lung carcinoma (Cheng et al., 2015a), bladder carcinoma (Wu et al., 2013; Yang et al., 2012), pancreatic, lung adenocarcinomas (Nasrollahzadeh-Khakiani et al., 2017)
	XIST	Hepatocellular carcinoma (Mo et al., 2017)
Tumour suppressor gene	CASC2	Pancreatic cancer (Yu et al., 2017b), cervical carcinoma (Feng et al., 2017), glioma (Liao et al., 2017)
	FER1L4	Endometrial carcinoma (Qiao and Li, 2016)
	Gas5	Colorectal carcinoma (Australian Institute of and Welfare, 2018; Yuan et al., 2017), gastric carcinoma (Li et al., 2017f,g), cervical carcinoma (Wen et al., 2017), prostate carcinoma (Xue et al., 2016), non-small-cell lung carcinoma (Dong et al., 2015a)
	IRAIN	Acute myeloid leukaemia (Sun et al., 2014), Breast carcinoma (Huang et al., 2016)
	lncRNA H19	Thyroid carcinoma (Wang et al., 2017f)
	lncRNA-442	Colorectal carcinoma (Shao et al., 2018)
	LOC572558	Bladder carcinoma (Zhu et al., 2016a)
	MALAT1	Breast carcinoma (Xu et al., 2015)
	MEG3	Pancreatic neuroendocrine tumours (Zhang and Feng, 2017), glioma (Zhang et al., 2017e), cervical cancer (Wang et al., 2017g), breast carcinoma (Zhang et al., 2017b), pancreatic carcinoma (Gu et al., 2017), lung carcinoma (Zhou et al., 2017)
	NBAT-1	Ovarian carcinoma (Yan et al., 2017)
	NONHSAT062994	Colorectal carcinoma (He et al., 2017)
	PICART1	Breast carcinoma, colorectal carcinoma (Cao et al., 2017)
	PTENP1	Breast carcinoma (Chen et al., 2017a; Li et al., 2017e), hepatocellular carcinoma (Chen et al., 2015a)
	RP11-708H21.4	Colorectal carcinoma (Sun et al., 2017c)
	SARCC	Renal cell carcinoma (Zhai et al., 2017)
	TUBA4B	Ovarian carcinoma (Zhu et al., 2017)
	TUG1	Non-small-cell lung carcinoma (Zhang et al., 2014)
	uc. 57	Breast carcinoma (Zhang et al., 2017a)
	uc002mbe.2	Hepatocellular carcinoma (Chen et al., 2017b)
	WDR7-7	Breast carcinoma (Tian et al., 2017)
	XIST	Breast carcinoma (Huang et al., 2016)

gallbladder cancer (Wang et al., 2016), hepatocellular carcinoma (Lv et al., 2014; Matouk et al., 2014) and breast cancer (Vennin et al., 2015) but played the role as a tumour suppressor gene in thyroid cancer (Wang et al., 2017a-i). Similarly, XIST was an onco-lncRNA in hepatocellular carcinoma (Mo et al., 2017) but acted as a tumour suppressor gene in breast cancer (Huang et al., 2016). On the other hand, MALAT1 was mainly reported as an onco-lncRNA with the various cancers associated such as ovarian cancer (Jin et al., 2017), cholangiocarcinoma (Wang et al., 2017b), hepatocellular carcinoma (Li et al., 2017b), Ewing sarcoma (Sun et al., 2017b), osteosarcoma (Dong et al., 2015b) and breast carcinoma (Meseure et al., 2016).

Interestingly, MALAT1 was reported to play dual roles in breast cancer itself (Xu et al., 2015; Meseure et al., 2016). Xu and colleagues (Xu et al., 2015) found that expression of MALAT1 was downregulated in breast cancer while Meseure and colleagues (Meseure et al., 2016) found that only approximately 3% of breast cancer patients had downregulation of MALAT1. Downregulation of MALAT1 correlated with axillary lymph node metastasis and shorter relapse-free survival (Xu et al., 2015) while overexpression had no significant clinical association between breast cancer patients (Meseure et al., 2016). However, overexpression of MALAT1 was significantly associated with hormone receptor-positive tumour, a probable indication that MALAT1 is an oestrogen receptor α-induced lncRNA (Meseure et al., 2016). However, knockdown of MALAT1 promoted migration and invasion *in vitro* and induced epithelial-to-mesenchymal transition (EMT) (Xu et al., 2015). This indicates that lncRNAs may play intricate roles in tumorigenesis and have differential expression patterns within the different sub-types of cancers as seen in breast carcinoma.

Mechanisms by which lncRNA affect the PI3K/Akt network

In this review, we focused on understanding how lncRNAs affect the top three most frequent studied cancers, breast cancer (Fig. 1), colorectal cancer (Fig. 3) and gastric cancer (Fig. 4). In the literature, two broadly categorised mechanisms by which lncRNAs influence cancer progression through the PI3K/Akt signalling can be seen. These include directly targeting the different nodes within PI3K/Akt pathway, or indirect targeting of the PI3K/Akt pathway such as working through miRNAs.

Directly targeting the nodes within PI3K/Akt pathway

Many reports have indicated that lncRNAs can directly target the nodes within the PI3K/Akt pathway. Oncogenic lncRNAs directly facilitate the sustained expression of phosphorylated Akt to drive cancer (Figs. 1-3). These lncRNAs include LINK-A (long intergenic non-coding RNA for kinase activation) (Lin et al., 2017), UCA1 (urothelial cancer associated 1) (Chen et al.,

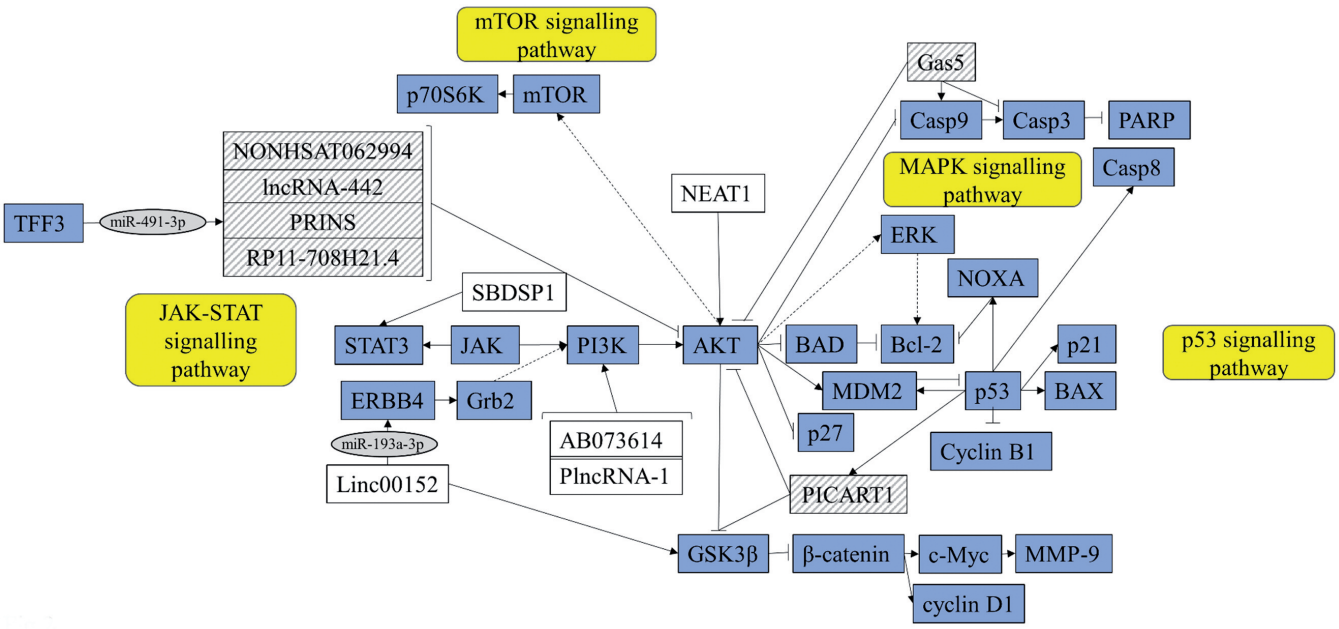

Fig. 3. LncRNAs interaction in the Akt pathway in colorectal cancer. White boxes represent onco-lncRNAs whereas striped boxes represent tumour suppressive lncRNAs. Yellow boxes indicate the pathway whereas blue boxes indicate genes in the pathways. Solid arrows (⟶) indicates direct target, dash-lined arrows (⇢) indicates further downstream target, blunt ended lines (⟞) indicate direct inhibition of target gene and blunt ended dashed lines (⇠) indicate further downstream inhibition target gene.

2015a-c; Wu and Luo, 2016; Li et al., 2017a-g; Nasrollahzadeh-Khakiani et al., 2017; Wang et al., 2017a-i), SBDSP1 (Shi et al., 2017a,b), NEAT1(nuclear enriched abundant transcript 1) (Peng et al., 2017), AB073614 (Huang et al., 2017), PlncRNA-1 (prostate cancer-up-regulated long noncoding RNA 1) (Song et al., 2017), AK023391 (Huang et al., 2017) and AFAP1-AS1(actin filament associated protein 1 antisense RNA1) (Yang et al., 2016a; Guo et al., 2017). Similarly, tumour suppressor lncRNAs such as MEG3 (maternally expressed gene 3), NONHSAT062994 (He et al., 2017), lncRNA-442 (Shao et al., 2018) and Gas5 (Growth arrest-specific 5) (Australian Institute of and Welfare, 2018) can directly weaken the phosphorylation of Akt (Figs. 1, 3, 4).

Multiple lncRNAs could affect the expression of PI3K through interacting with its subunit. For example, inhibition of MALAT1 reduced the expression level of p85 in osteosarcoma (Dong et al., 2015b). Similarly, the onco-lncRNA lncRNA AK023948 enhanced the interaction between p110 and p85 (subunits of PI3K) in breast cancer by targeting only the p85β subunit in p85 (Koirala et al., 2017). Other lncRNAs target a more upstream target such as the onco-lncRNA BCAR4 (Breast Cancer Anti-Estrogen Resistance 4) which upregulates Erb-B2 Receptor Tyrosine Kinase (ERBB) 2, ERBB3 and SHC (Godinho et al., 2010, 2012) all leading to an up-regulation of PI3K production (Fig. 1) and thus activation of Akt in breast cancer.

LncRNA could act in a more indirect way by influencing the binding of certain genes onto the subunits of PI3K and thus cause a downstream effect towards the Akt signalling pathway. For example, lncRNA BDLNR (baicalein down-regulated long noncoding RNA) promotes biding of YBX1 (Y-Box Binding Protein 1) to PIK3CA (p110α) promoter in cervical cancer, thereby augmenting the expression of PIK3CA (Yu et al., 2018). AK023948 could also facilitate the interaction between DXH9 (a target further up the PI3K/Akt pathway) and p85 (Koirala et al., 2017) which further affect the downstream production of phosphorylated Akt (Fig. 1). This increment ultimately led to an increased level of phosphorylated Akt.

In certain scenarios, lncRNAs can function as a positive feedback loop. For example, HOTAIR is known to facilitate Akt production. Coincidentally, IRF1 (interferon regulatory factor 1), which inhibits HOTAIR, is inhibited by Akt (Yang et al., 2016a,b). Therefore, with HOTAIR increasing the expression of Akt, the expression of IRF1 is inhibited and thereby allowing HOTAIR to be up-regulated (Fig. 1). Similarly, PICART1 (P53-Inducible Cancer-Associated RNA

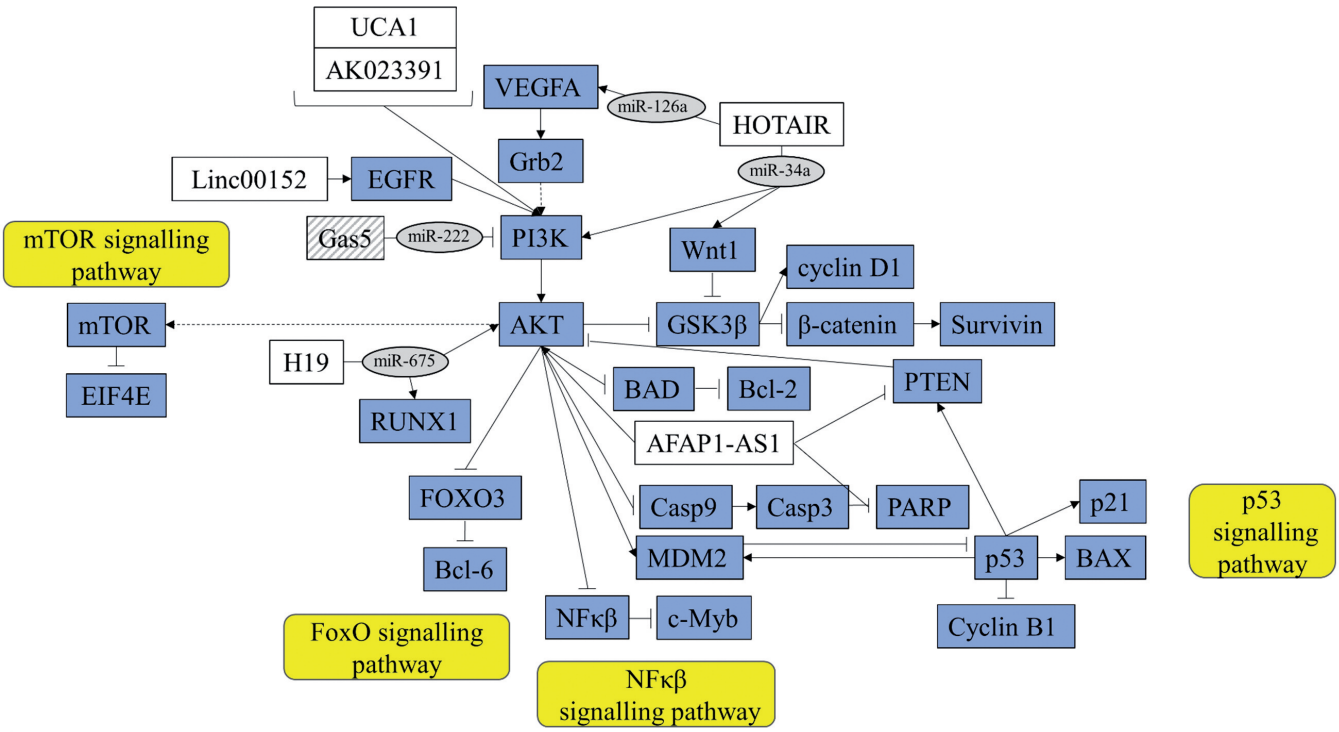

Fig. 4. LncRNAs interaction in the Akt pathway in gastric cancer. White boxes represent onco-lncRNAs whereas stripped boxes represent tumour suppressive lncRNAs. Yellow boxes indicate the pathway whereas blue boxes indicate genes in the pathways. Solid arrows (⟶) indicates direct target, dash-lined arrows (⇢) indicates further downstream target, blunt ended lines (⟙) indicate direct inhibition of target gene and blunt ended dashed lines (⇣) indicate further downstream inhibition target gene.

Transcript 1) facilitates the expression of p53 by inhibition of Akt (Figs. 1, 3) which subsequently promotes the sustained production of PICART1 (Cao et al., 2017). Interestingly, PICART1 also inhibits the expression of glycogen synthase kinase-3 beta (GSK3β), a gene that has both oncogenic and tumour suppressive potential as clearly summarised by McCubrey and colleagues (McCubrey et al., 2014). For example, when GSK-3 is supressed by the phosphorylation of Akt, GSK-3 functions as a tumour suppressor. On the other hand, GSK-3 functions as an oncogene when it stabilises beta-catenin production (McCubrey et al., 2014). In breast cancer and colorectal cancer, PICART1 clearly functioned as a tumour suppressor gene via inhibition of the Akt/GSK3β/β-catenin pathway (Cao et al., 2017).

Indirect targeting

Some lncRNAs even target other lncRNAs. For example Jpx, which positively regulates Xist, a tumour suppressor gene in breast cancer (Huang et al., 2016) then upregulates HDAC3 (histone deacetylase 3). Subsequently, HDAC3 upregulates PHLPP1 (PH Domain and Leucine Rich Repeat Protein Phosphatase 1) which, dephosphorylates Akt (Fig. 1). In other cases, lncRNAs are also able to exhibit their function by acting as a competing endogenous RNA (ceRNA) (Table 2) to sponge the effects of miRNAs toward the genes within PI3K/Akt signalling pathway

LncRNAs as a competing endogenous RNA (ceRNA)

From Table 2, it is notable that lncRNAs are reported as ceRNAs for different miRNAs in different cancer types. Of these, GAS5 functioned as an endogenous sponge for miR-222 in gastric cancer (Li et al., 2017f) and miR-103 in prostate cancer (Xue et al., 2016). Similarly, HULC acted as a ceRNA with miR-200a in chronic myeloid leukaemia (Lu et al., 2017) and miR-122 in osteosarcoma (Kong and Wang, 2018). In gastric cancer, the lncRNA HOTAIR promoted the expression of PIK3R2, a subunit of PI3K through sponging of miR-126 (Fig. 4) and thus activating PI3K/Akt signalling pathway (Yan et al., 2016a). Likewise, in the case of Linc00152 (Long intergenic non-coding RNA 00152), increment of Akt production was driven through sponging the effect of miR-193a-3p which targets ERBB4 (Yue et al., 2016), an upstream target of PI3K/Akt signalling pathway (Fig. 3).

Even more interestingly, a single lncRNA can

Table 2. Examples of lncRNAs as competing endogenous RNA (ceRNA).

lncRNAs	Cancer type	miRNA target	Reference
ANRIL	Medulloblastoma	miR-323	Zhang et al., 2017d
ATB	Bladder carcinoma	miR-126	Zhai and Xu, 2018
CASC2	Cervical carcinoma	miR-21	Feng et al., 2017
	Glioma	miR-181a	Liao et al., 2017
CCAT2	Endometrial carcinoma	miR-126b	Xie et al., 2017
Cdr1as	Hepatocellular carcinoma	miR-7	Xu et al., 2017a
CRNDE	Hepatocellular carcinoma	miR-384	Chen et al., 2016
DANCR	Osteosarcoma	miR-33a-5p	Jiang et al., 2017
Ftx	Hepatocellular carcinoma	miR-545	Liu et al., 2016b
GAS5	Cervical carcinoma	miR-21	Wen et al., 2017
	Gastric carcinoma	miR-222	Li et al., 2017a,b
	Prostate carcinoma	miR-103	Xue et al., 2016
HOTAIR	Gastric carcinoma	miR-34a	Cheng et al., 2018
		miR-126a	Yan et al., 2016a
	Glioma	miR-326	Ke et al., 2015
HULC	Chronic myeloid leukaemia	miR-200a	Lu et al., 2017
	Osteosarcoma	miR-122	Kong and Wang, 2018
Linc00152	Colorectal carcinoma	miR-193a-3p	Yue et al., 2016
lncRNA-PAGBC	Gallbladder carcinoma	miR-133b, miR-511	Wu et al., 2017b
lncRNA H19	Hepatocellular carcinoma	miR-675	Lv et al., 2014; Matouk et al., 2014
	Breast carcinoma	miR-675	Vennin et al., 2015
	Gastric carcinoma	miR-675	Liu et al., 2016a
	Gallbladder carcinoma	miR-194-5p	Wang et al., 2016
MALAT1	Hepatocellular carcinoma	miR-146-5p	Li et al., 2017c
MEG3	Glioma	miR-93	Zhang et al., 2017e
	Pancreatic neuroendocrine tumour	miR-183	Zhang and Feng, 2017
PRINS	Colorectal carcinoma	miR-491	Hanisch et al., 2017
PTENP1	Breast carcinoma	miR-19b	Li et al., 2017e
	Hepatocellular carcinoma	miR-17, miR-19b, miR-20a	Chen et al., 2015a
XIST	Hepatocellular carcinoma	miR-139-5p	Mo et al., 2017

function as a ceRNA for multiple different miRNAs. For example, HOTAIR sponges both miR-126a (Yan et al., 2016a) and miR-34a (Cheng et al., 2018) which target various points within the PI3K/Akt signalling pathway (VEGFA and GSK3β respectively) to enhance the phosphorylation of Akt in gastric cancer (Fig. 4). LncRNA H19 sponged miR-675 to activate Akt and RUNX1 (Runt Related Transcription Factor 1) in gastric cancer (Vennin et al., 2015). Correspondingly, onco-lncRNA PAGBC (prognosis-associated gallbladder cancer lncRNA) activates the Akt/mTOR pathway by competitively binding to different tumour suppressor miRNAs (miR-133b and mir-511) resulting in an increased expression of SOX4 (SRY-Box 4) and PIK3R3 in gallbladder cancer (Wu et al., 2017b). However, tumour suppressor PTENP1 (Phosphatase and Tensin Homolog Pseudogene 1) dampened miR-17, miR-19b and miR-20a to enhance the expression of PTEN to modulate hepatocellular carcinoma cell behaviour (Chen et al., 2015a). These findings suggest that lncRNAs could regulate the gene network through diverse means, thus further strengthening the idea of lncRNAs as future targeted therapeutic option.

There is a potential to incorporate miRNA therapy in addition to existing single gene therapy due to miRNA's capabilities in regulating an assortment of pathways and targets (Lee et al., 2016). The same concept could apply to lncRNAs as they can regulate more than just one pathway, thereby having a greater effect on the overall gene network. For example, ANRIL displays its capability in regulating both Wnt signalling pathway and Akt signalling pathway by regulating BRI3 expression through sponging the activity of miR-323 (Zhang et al., 2017d). However, GAS5 retards the expression of miR-103 thereby reducing the expression of both p-Akt and pmTOR (mTOR signalling pathway) in prostate cancer (Xue et al., 2016). The same lncRNA also hampered both the Akt signalling pathway and mTOR-signalling pathway in gastric cancer through regulating miR-222, which targets PTEN (Li et al., 2017f). This further emphasises the need to understand the roles lncRNAs play in this intricate web of gene network, which plays a pivotal role in orchestrating tumorigenesis.

LncRNAs association with anticancer drug resistance

Despite major improvements in cancer therapy, cancer remains the second leading cause of death globally (McGuire, 2016). One of the reasons for the high cancer mortality is drug resistance, either occurring intrinsically or acquired, restricts the effectiveness of current available anticancer drugs (Holohan et al., 2013). Drug resistance results in a transient therapeutic effect and is often seen in patients with relapse (Zheng, 2017). Once relapse occurs, the clinical outcomes are often bleak (Holohan et al., 2013; Miller et al., 2015; Tiefenbacher and Pirker, 2017).

Anticancer drugs often function by way of inactivating cancer driving pathways such as PI3K/Akt signalling pathways or activating cancer suppressive pathways such as p53 signalling pathways. These anti-cancer drug therapies can function through targeting lncRNAs. Tian and colleagues (2017) found that the phytoestrogen calycosin enhanced the expression of WDR7-7-GPR30 signalling pathway to inhibit breast cancer. However, when lncRNA WDR7 -7 is inhibited, breast cancer cells proliferated (Tian et al., 2017). Furthermore, numerous findings have shown that current anti-cancer drug resistance is caused by deregulated expression of lncRNAs. For example, overexpression of HOTAIR was observed in patients with cisplastin-resistant gastric cancer (Yan et al., 2016a; Cheng et al., 2018). When HOTAIR was knocked out, gastric cancer was resensitised to cisplatin treatment (Cheng et al., 2018). Additionally, lncRNA Linc00152 promoted tumour progression and conferred resistance to oxliplatin induced apoptosis through activating Akt pathway (Yue et al., 2016).

Table 3 reveals the effects of lncRNA on the progression of cancer through the PI3K/Akt signalling pathway when treated with common anticancer therapies. These include chemotherapy (Xiong et al., 2015; Wu and Luo, 2016; Yan et al., 2016a,b; Yue et al., 2016; Feng et al., 2017; Sun et al., 2017a-d; Wen et al., 2017; Cheng et al., 2018), hormonal therapy (Godinho et al., 2010; Chen et al., 2015a-c; Wu and Luo, 2016; Tian et al., 2017; Zhang et al., 2017a,b) and tyrosine kinase inhibitor (Godinho et al., 2012; Cheng et al., 2015a,b; Dong et al., 2015a,b; Pan et al., 2016; Lu et al., 2017; Wang et al., 2017a-i; Zhai et al., 2017). This pivotal information further enhances our knowledge on what drives cancer resistance as well as how lncRNAs tweaking can re-sensitise these cancers toward specific cancer therapy. This can ultimately help improve patient treatment outcome and enhance personalised treatment.

Chemoresistance

Chemoresistance is a major cause for cancer relapse and metastasis, making it a huge challenge to improve clinical outcomes for cancer patients (Zheng, 2017). Interestingly, current available chemotherapeutic agents often target the Akt pathway. The chemotherapeutic drug cisplatin induces phosphorylation of BAD (Bcl-2-associated death promoter), a downstream tumour suppressor target inhibited by Akt (Hayakawa et al., 2000). Similarly, doxorubicin, another chemotherapeutic drug, which inhibits the PI3K/Akt signalling pathway, could treat patients with gastric cancer (You et al., 2017). However, these cancers can build resistance via reactivation of the Akt signalling pathway (Li et al., 2017a-g; Miao et al., 2017).

LncRNAs such as HOTAIR (Yan et al., 2016a,b; Cheng et al., 2018), lncRNA ROR (lncRNA reprogramming) (Wen et al., 2017) and Linc00152 (Xiong et al., 2015; Yue et al., 2016) function as onco-lncRNAs and induce chemoresistance through

enforcement of key gene regulator expressions or through suppressing the expression of tumour suppressor miRNAs. For example, HOTAIR induced cisplatin resistance in gastric cancer by acting as an endogenous sponge for miR-34a (Cheng et al., 2018) and miR-126 (Yan et al., 2016a,b) to reactivate the PI3K/Akt signalling pathway, whereas knockdown of HOTAIR on the other hand, inhibited cisplatin resistance (Cheng et al., 2018). In colorectal cancer, Linc00152 modulated the expression of miR-193a-3p and restricted the PI3K/Akt signalling pathway to drive chemoresistance towards oxliplatin. When Linc00152 was knockdown, there was a decrease in the phosphorylation of Akt and oxaliplatin (Yue et al., 2016). ROR on the other hand, induced cisplatin resistance by driving the PI3K/Akt/mTOR signalling pathway through enhanced expression of PI3K, Akt, mTOR and Bcl-2 (B-cell lymphoma 2) and mitigation Bax (Bcl-2-associated X protein) in non-small-lung cancer. Not surprisingly, knockdown of ROR significantly increased the sensitivity of non-small-cell lung cancer to cisplatin (Wen et al., 2017).

Furthermore, LncRNAS such as RP11-708H21.4 (Sun et al., 2017c), CASC2 (Feng et al., 2017; Liao et al., 2017) and GAS5 (Wen et al., 2017) are weakly expressed in chemoresistent cancer (Table 3) and when overexpressed, can re-sensitise cancer cells to chemotherapy. RP11-708H21.4 blocked Akt/mTOR pathway and enhanced the sensitivity of colorectal cancer towards 5-fluorouracil drug (Sun et al., 2017c). CASC2 increased sensitivity of glioma cells in temozolomide resistant glioma cells towards the drug through upregulation of PTEN and phosphorylation of pAkt via inhibition of miR-181a (Liao et al., 2017).

Hormonal therapy resistance

Hormonal therapy could treat cancers that express hormone receptors and grow with hormones such as breast cancer and prostate cancer (Henson et al., 2018). Hormone therapy utilises inhibitors or competitive compounds (such as calycosin, genistein and tamoxifen) to block off hormone receptors within the cancer cells and activates cell death (Al-Mahmood et al., 2018). Sadly, resistance to hormonal therapy is common and most patients eventually face disease progression (Wilson and Chia, 2013). While thorough understanding of hormonal therapy resistance is lacking, significant findings have linked the vital importance of PI3K/Akt signalling pathway towards cancer therapy resistance

Table 3. Examples of lncRNAs involvement with current cancer treatment.

Cancer therapy	LncRNAs	Mode of action of LncRNA	Cancer type	Reference
Chemotherapy				
Cisplatin	HOTAIR	Confers resistance to cisplatin	Gastric carcinoma	Cheng et al., 2018; Yan et al., 2016a
	ROR	Knockout sensitises cells to cisplatin	Non-small-cell lung carcinoma	Wen et al., 2017
	CASC2	Overexpression sensitises cervical cancer to cisplatin	Cervical carcinoma	Feng et al., 2017
	GAS5			Wen et al., 2017
Oxliplatin	Linc00152	Confers resistance to oxaliplatin	Colorectal carcinoma	Xiong et al., 2015; Yue et al., 2016
5-fluorouracil	RP11-708H21.4	Enhances sensitivity to 5-flourouracil		Sun et al., 2017c
Temozolomide	CASC2	Sensitises glioma to temozolomide	Glioma	Wu and Luo, 2016
Hormonal therapy				
Calycosin	WDR7-7	Enhances cell proliferation	Breast carcinoma	Tian et al., 2017
	HOTAIR	Calycosin and genistein inhibited HOTAIR		Chen et al., 2015b
Genistein	HOTAIR			Chen et al., 2015b
Tamoxifen	BCAR4	Confers resistance to tamoxifen		Godinho et al., 2010
	uc. 57	Overexpression reduces resistance to tamoxifen		Zhang et al., 2017a
	UCA1	Overexpression reduces tamoxifen induced apoptosis		Wu and Luo, 2016
Tyrosine kinase inhibitor				
Gefitinib	BC087858	Confers resistance to gefitinib	Non-small cell lung carcinoma	Pan et al., 2016
	MIR31HG	Knockdown sensitises cells to gefitnib		Wang et al., 2017a
	GAS5	Overexpression may sensitises cells to gefitinib		Dong et al., 2015a
	UCA1	Knockdown sensitises cells to gefitnib		Cheng et al., 2015a
Imatinib	HULC	Knockdown enhances imatinib-induced apoptosis	Chronic myeloid leukaemia	Lu et al., 2017
	HOTAIR	Knockdown sensitises cells to imatinib		Wang et al., 2017c
Lapatinib	BCAR4	Expression sensitises cells to lapatinib and antiestrogens	Breast carcinoma	Godinho et al., 2012
Sunitinib	SARCC	Sunitinib treatment increases expression of SARCC and decreases cells resistance to Sunitinib	Renal cell carcinoma	Zhai et al., 2017

(Araki and Miyoshi, 2018) and work on developing inhibitors targeting the PI3K/Akt signalling pathway have since begun.

Nonetheless, it is not until recently that studies have shown how hormonal therapy can induce cancer cell death by regulating a number of lncRNAs. For instance, calycosin does this by inhibiting onco-lncRNA HOTAIR and upregulating tumour suppressor lncRNA WDR7-7 (Table 3) resulting in the suppression of the PI3K/Akt signalling pathway (Chen et al., 2015b; Tian et al., 2017). In cancer patients with tamoxifen resistance, low expression of uc.57 (Zhang et al., 2017a) and upregulated expression of both BCAR4 (Godinho et al., 2010) and UCA1 (Wu and Luo, 2016) were observed (Table 3). Up-regulation of BCAR4 was correlated with overexpression of ERBB2, ERBB3, ERK (extracellular signal-regulated kinase) 1/2 and Akt (Godinho et al., 2010) within the Akt signalling pathway (Fig. 1). Similarly, increased expression of UCA1 was correlated with elevated phosphorylation of Akt and mTOR (Wu and Luo, 2016), resulting in a sustained activation of the PI3K/Akt signalling pathway. Interestingly, when uc.57 was exogenously expressed, BCL11A was mitigated. This inhibition then retarded the function of PI3K/Akt and MAPK signalling pathway thus reducing tamoxifen resistance in breast cancer (Zhang et al., 2017a-g).

Tyrosine kinase inhibitor resistance

Tyrosine kinases are a class of enzyme that mediate a diverse biological process through modulating growth factor receptors such as VEGFR (vascular endothelial growth factor receptors) and EGFR (epidermal growth factor receptor). They mediate signalling cascades through the activation of numerous signalling pathways such as the Akt signalling pathway (Eso and Marusawa, 2018). When these enzymes are constitutively activated, cancer progression, angiogenesis and metastasis follow (Arora and Scholar, 2005; Eso and Marusawa, 2018). Tyrosine kinase inhibitors (TKIs) prevent cancer growth by specifically targeting and blocking the activation of these tyrosine kinases. Some of these include gefitinib, imatinib, lapatinib and sunitinib (Table 3). They are highly specific towards cancer cells and thus have minimal toxicity in comparison to tradition cancer therapy (Arora and Scholar, 2005). Furthermore, they are often used in combination with chemotherapy because their toxicity profiles do not overlap with chemotherapy cytotoxicity (Arora and Scholar, 2005). Reports have indicated that TKIs can induce cancer death through manipulating the expression of lncRNAs, as in the case of sunitinib in renal cancer carcinoma. Treatment of sunitinib increases lncRNA SARCC which

Table 4. Potential cancer biomarkers from lncRNAs.

lncRNA	Cancer	Remarks	Reference
ANRIL	Cervical carcinoma	Increased ANRIL expression is associated with advanced FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) stage, lymph node metastasis and poorer overall survival	Zhang et al., 2017c
ATB	Bladder carcinoma	Overexpression of onco-lncRNA-ATB enhances cell viability, migration and invasion	Zhai and Xu, 2018
	Prostate carcinoma	Stimulates epithelial-mesenchymal transition (EMT) and serves as an independent prognostic factor for biochemical recurrence free survival of prostate carcinoma	Xu et al., 2016
Ftx	Hepatoceullar carcinoma	Elevation of Ftx and miR-545 is associated with poor prognostic features, reduced 5-year overall survival rate and disease-free survival rate	Liu et al., 2016b
GAS5	Non-small cell lung carcinoma	Weakened expression of GAS5 is associated with larger tumour size, poor tumour differentiation and advanced pathological stages	Dong et al., 2015a
HOXD-AS1	Neuroblastoma	Gene signatures consisting of four HOXD-AS1 targets could successfully predict neuroblastoma replase up to 80% accuracy	Yarmishyn et al., 2014
Link-A	Breast carcinoma	LINK-A overexpression is detected in patients with breast carcinoma that has developed resistance towards AKT inhibitors and is often associated with poor outcomes in patients with breast carcinoma	Lin et al., 2017
MIR31HG	Non-small cell lung carcinoma	High expression of MIR31HG may contribute to gefitinib resistance and can therefore be a novel candidate biomarker for future therapeutic strategies involved in EGFR-TKIs	Wang et al., 2017a
NEAT1	Colorectal carcinoma	Overexpression of NEAT1 leads to adverse survival in patients with colorectal carcinoma whereas knock down of NEAT1 inhibited growth and facilitated apoptosis, proving its potential as a promising biomarker and target for novel treatment	Peng et al., 2017
PANDAR	Clear cell renal cell carcinoma	PANDAR expression is elevated in tumour tissues and positively correlated with advanced TNM stage. PANDAR serves as an independent predictor of overall survival	Xu et al., 2017b
PlncRNA-1	Colorectal carcinoma	Increased PlncRNA-1 expression is associated with the depth of invasion, lymph node metastasis, TNM stage and poorer patients' survival	Song et al., 2017
RP11-708H21.4		Low expression of RP11-708H121.4 is closely related with aggressive clinicopathological features and unfavourable prognosis in patients with colorectal carcinoma	Sun et al., 2017c
TUBA4B	Ovarian carcinoma	Weakened expression of TUBA4B is associated with pathological grade, FIGO stage and lymph node metastasis in patients with ovarian carcinoma	Zhu et al., 2017

binds and destabilises the androgen receptor protein (Zhai et al., 2017). Reduction in androgen receptor protein then leads to heightened expression of miR-143-3p which then inhibits downstream signals such as Akt, MMP (matrix metalloproteinase) 13, KRAS (Kirsten rat sarcoma oncogene 2) and Erk (Zhai et al., 2017).

Regrettably, patients can develop resistance to tyrosine kinase inhibitors, which impedes the overall benefits of these drugs. For example, non-small cell lung carcinoma are showing acquired resistance towards gefitinib (Cheng et al., 2015a,b; Dong et al., 2015a,b; Pan et al., 2016; Wang et al., 2017a-i). Reports indicate that these patients tend to have overexpressed lncRNA BC087858 (Pan et al., 2016), MIR31HG (Wang et al., 2017a-i), UCA1 (Cheng et al., 2015a,b) and/or reduced expression of GAS5 (Dong et al., 2015a,b) (Table 3), all of which results in sustained activation of Akt signalling pathway. Knockdown of BC087858 restored gefitinib sensitivity and inhibited the activation of PI3K/Akt, MEK/ERK signalling pathway and epithelial-mesenchymal transition via upregulation of ZEB1 (Zinc Finger E-Box Binding Homeobox 1) and Snail (Zinc finger protein SNAI1) (Pan et al., 2016). Attenuation of UCA1 in contrast, restrained the activation of Akt/mTOR signalling pathway and epithelial-mesenchymal transition and restored genitinib sensitivity in acquired resistant cells (Cheng et al., 2015a).

Imatinib targets the BCR-ABL (breakpoint cluster region - Abelson murine leukaemia viral oncogene homolog 1) gene fusion in chronic myeloid leukaemia (Lu et al., 2017; Wang et al., 2017c). Resistance to imatinib was observed in patients with activated PI3K/Akt signalling pathway due to enforced expression of HULC (Lu et al., 2017) and HOTAIR (Wang et al., 2017c). Suppression of HULC dulled the expression of c-Myc, Bcl-2, phosphorylated PI3K and Akt, all involved in the PI3K/Akt signalling pathway to reinstate imatinib sensitivity and drive apoptosis whilst inhibiting cell proliferation in chronic myeloid leukaemia (Lu et al., 2017). In breast cancer, the TKI lapatinib is used to target ERBB2 and its downstream mediators such as Akt, FAK (focal adhesion kinase), SHC, STAT (signal transducer and activator of transcription) 5 and STAT 6 (Godinho et al., 2012). Godinho and colleagues found that a group of patients with breast cancer that showed elevated expressions of BCAR4 but not ERBB2, would benefit better using a combination therapy of tamoxifen hormonal therapy and laptinib (Godinho et al., 2012).

lncRNAs as diagnostic and prognostic biomarkers in cancer

As detailed previously, lncRNAs can strongly influence the progression of cancer through the Akt pathway. This can be in terms of direct targeting the molecular targets within the PI3K/Akt signalling pathway, functioning as a competing endogenous RNA (ceRNA) and sponging the effects of various miRNAs. Furthermore, association of lnRNAs expression towards anticancer drug sensitivity is a strong indicator of their potential use as diagnostic and prognostic biomarker in cancer. The biomarker potential of lncRNAs has been evidenced by a distinct difference when it comes to either functioning as an onco-lncRNA or tumour suppressor lncRNA (Table 1). Furthermore, the tumour-specific expression characteristics of lncRNAs (Jiang et al., 2016) further strengthens the use of lncRNAs as biomarkers for their superior specificity.

For example, LINK-A overexpression is often detected in patients with breast cancer that has developed resistance towards AKT inhibitors, often associated with poor outcomes in patients with breast cancer (Lin et al., 2017). Similarly, increased expression of ANRIL was commonly associated with poor overall survival in patients with cervical cancer (Zhang et al., 2017c). Table 4 shows a list of lncRNAs that have proven their biomarker potentials in predicting cancer occurrences, treatment options and progression.

Conclusion

The studies of lncRNAs have exploded within a short span of time. The association of lncRNAs in cancer and the tremendous breakthrough made in understanding the mechanisms by which cancer evades current cancer therapy is undeniable. With the capabilities of lncRNAs to affect current cancer treatment therapy, many of these lncRNAs could potentially function as prognostic indicators of outcome of patients with cancer and predictors of drug responsiveness in cancer. What is more, lncRNAs are expressed differently in different subtypes of carcinoma, which enables quicker determination of treatment options, thus improving clinical outcomes. LncRNAs represent a superior candidate biomarker, as their expression is restricted in specific cancer types and/or pathological stages of cancer.

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