Review

LncRNAs and the Angiogenic Switch in Cancer: Clinical Significance and Therapeutic Opportunities

Peace Mabeta 1,2,*, Rodney Hull 2 and Zodwa Dlamini 2,*

Abstract: Angiogenesis is one of the hallmarks of cancer, and the establishment of new blood vessels is vital to allow for a tumour to grow beyond 1–2 mm in size. The angiogenic switch is the term given to the point where the number or activity of the pro-angiogenic factors exceeds that of the anti-angiogenic factors, resulting in the angiogenic process proceeding, giving rise to new blood vessels accompanied by increased tumour growth, metastasis, and potential drug resistance. Long noncoding ribonucleic acids (lncRNAs) have been found to play a role in the angiogenic switch by regulating gene expression, transcription, translation, and post translation modification. In this regard they play both anti-angiogenic and pro-angiogenic roles. The expression levels of the pro-angiogenic lncRNAs have been found to correlate with patient survival. These lncRNAs are also potential drug targets for the development of therapies that will inhibit or modify tumour angiogenesis. Here we review the roles of lncRNAs in regulating the angiogenic switch. We cover specific examples of both pro and anti-angiogenic lncRNAs and discuss their potential use as both prognostic biomarkers and targets for the development of future therapies.

Keywords: vascular endothelial growth factor; metastasis-associated lung adeno-carcinoma transcript 1; HOX antisense intergenic RNA; maternally expressed gene3; MANTIS; myocardial infarction associated transcript

1. Introduction

Over the years the focus of cancer treatment has largely been on eliminating neoplastic cells. However, research has shown that most tumours need to establish a vascular supply through processes such as angiogenesis in order to grow beyond a critical size of 1–2 mm [1,2]. Angiogenesis is a complex multi-step process through which blood vessels are formed from a pre-existing microvasculature. The tumour vasculature can promote cancer progression, promote drug loss due to extravasation (leakage from a blood vessel) at the tumour site as well as drug resistance [2,3]. Angiogenesis involves a dynamic balance between pro- and anti-angiogenic factors which when disturbed can promote the development of various diseases [3]. The angiogenic switch, which represents the transition from the avascular tumour to the angiogenic phenotype, is driven by this shift in the balance between pro- and anti-angiogenic factors. Importantly, recent findings show that some of the factors that promote an angiogenic switch are regulated by noncoding ribonucleic acids [4–6]. Historically, deoxy-ribonucleic acid (DNA) that does not code for proteins was considered to possess no physiological relevance and was termed “junk DNA”. The human genome project has revealed that the amount of noncoding DNA exceeds that of coding DNA, with only about 2% of the genome coding for protein [7]. Further analysis of data from genomic platforms revealed that long non-coding RNA (LncRNA) accounted for approximately 68% of the human transcriptome [8]. LncRNAs are a major class of non-coding RNAs, are more than 200 base pairs (bps) in length and are tissue and cell specific.
However, even within cells the transcripts tend to be compartment specific. Although IncRNAs are largely noncoding, there is a growing appreciation for their contribution to physiological function, and this also extends to the vasculature [4,5]. Recent investigations have shown that they play a role in orchestrating angiogenesis through gene regulation, both at the transcriptional and post-transcriptional levels, although much remains to be done to elucidate their mechanisms of action [6–10]. Research has further revealed the importance of IncRNAs in the maintenance of vascular homeostasis. IncRNAs, which regulate the process of blood vessel formation include myocardial infarction associated transcript (MIAT), which functions as a miR-150-5p sponge to regulate vascular endothelial growth factor (VEGF) expression [6,8–10]. Its inhibition results in decreased endothelial cell (EC) proliferation. In addition, MIAT silencing leads to reduced EC migration and tube formation [6,8]. Metastasis-associated lung adeno-carcinoma transcript 1 (MALAT1), which is required for the regulation of cell cycle proteins, is also an important regulator of physiological angiogenesis [7–9]. MALAT1 plays a crucial role in the adaptation of the vasculature to hypoxia. It is not thus surprising that angiogenesis is dysregulated in MALAT1 null mice [8,9]. GATA Binding Protein 6 antisense (GATA6-AS) is expressed by ECs and through its interaction with Lysyl oxidase-like (LOXL)2 promotes angiogenesis. It is also upregulated during hypoxia [10]. Spliced transcript—endothelial-enriched IncRNA (STEEL) regulates physiological angiogenesis by transcriptionally reducing the expression of endothelial nitric oxide synthase (eNOS) and other EC function modulators such as Kruppel-like Factor 2 (KLF2) [10]. Another IncRNA, MANTIS, also known as IncRNA n342419, regulates vascularisation mainly in response to changes in blood flow patterns [8,9]. The silencing of MALAT1 through siRNA reduces angiogenesis both in vitro and in vivo [7–9]. In contrast, non-coding repressor of NFAT (NRON) is a negative regulator of angiogenesis [10]. When dysregulated, IncRNAs promote pathophysiological states. Moreover, aberrant expression of IncRNAs in endothelial cells is observed in various diseases, including cancer [5,7].

2. Expression Patterns of IncRNAs in Endothelial Cells

Deep sequencing results have shown that approximately 56% of the total RNA in endothelial cells (ECs) is noncoding and mainly constituted by IncRNAs [7]. Generally, IncRNAs are expressed at low levels in the normal physiological setting [6,7]. However, they are upregulated in most neoplasms, although in a few instances they have been shown to be downregulated [5,6,10]. Among the first IncRNAs to be identified in ECs was nitric oxide synthase 3 antisense (NOS3AS), also known as autophagy 9-like 2 (APG9L2) [10]. The expression of NOS3AS correlates with low levels of the enzyme endothelial nitric oxide synthase (eNOS) [10]. LncRNA subtypes in endothelial cells include natural antisense transcripts (NATs), which constitutes about 7% of the total noncoding RNA identified in human umbilical vein endothelial cells (HUVECs) [11]. In ECs, the IncRNA NAT for tyrosine kinase with immunoglobulin-like and epidermal growth factor (EGF)-like domains 1 (TIE1) binds to TIE1 mRNA and decreases its transcript levels (Figure 1) [11,12]. This in turn results in compromised cell–cell junctions between ECs [11]. It is noteworthy that TIE is exclusively expressed in ECs and is upregulated in the tumour vasculature. LNC00323-003 and MIR503HG, which are both expressed by venous and arterial endothelial cells, are not compartment-restricted and occur in the cytoplasm as well as the nucleus [12]. The expression of these two IncRNAs in ECs is altered when there is oxygen deprivation. Additionally, LNC00323 promotes angiogenesis in vitro in hypoxic conditions. The reported findings may underscore the importance of these oxygen sensitive IncRNAs in tumour angiogenesis as this process is largely triggered by hypoxia. One of the highly expressed IncRNAs in ECs, MALAT1, functions to protect ECs from the effects of oxygen deprivation and nutrient deprivation by stimulating moderate autophagy [13]. MALAT1 is active during the initiation stage of autophagy and during autolysosomal fusion [13,14]. Autophagy is a process of cellular degradation in response to various stresses such as nutrient deprivation and it plays an important role in the maintenance of homeostasis. The
The process of autophagy occurs in stages, which include initiation, phagophore nucleation, autophagosomal structure formation, and autolysosomal fusion that leads to the degradation of unwanted cellular components. In addition to MALAT1, angiogenic lncRNAs regulate EC autophagy at different stages. Maternally expressed gene (MEG3) and H19 regulate the initiation stage while highly upregulated in liver cancer (HULC) is involved in the elongation stage [14]. Autophagy enables stress tolerance in ECs, especially in the context of hypoxia or nutrient deprivation. The induction of autophagy also increases endothelial nitric oxide synthase expression and supports angiogenesis. Interestingly, when dysregulated, autophagy contributes to endothelial dysfunction and impaired angiogenesis [14,15]. In addition to increasing the stress tolerance of ECs, MALAT1 upregulates VEGF and angiopoietins (ANG) in the microvasculature and suppresses EC apoptosis [16]. Other important lncRNAs expressed in ECs are Linc00493 and MEG3 (Figure 1). Studies show that MEG3 is upregulated during senescence in late passage versus early passage ECs and contributes to the endothelial dysfunction associated with aging cells [17,18]. MEG3 promotes anti-angiogenesis through the suppression of miR-9 and VEGF [10,17,18]. LincRNA-ST8SIA3, also known as regulator of reprogramming (ROR), is a long, noncoding RNA located at 18q21.31 of chromatin that was detected in ECs and appears to promote angiogenesis [18]. In stem cells, ROR regulates self-renewal by modulating the functions of Oct4, Sox2, and Nanog. In endothelial cells, ROR regulates the proangiogenic VEGF. Importantly, VEGF is indispensable in the onset of the angiogenic switch [1,2]. Of note is that the silencing of ROR in vitro results in the downregulation of VEGF [16]. Several lncRNAs were reportedly expressed in ECs under conditions of hypoxia, including MEG8 and 9, as well as H19 [13,19]. Interestingly, the knockdown of H19 reduced the ability of ECs to form cords in an in-vitro assay of angiogenesis. MIR20HG and MIR22HG are also expressed by ECs subjected to hypoxic conditions [17]. Ubiquitin-conjugating enzyme E2C pseudogene 3 (UB32CP3) is a lncRNA that promotes epithelial to mesenchymal transition (EMT) and metastasis and has also been detected in ECs [4,19]. In models of co-cultured ECs and (hepatocellular carcinomas) HCC cells overexpressing UB32CP3, the ECs were stimulated to proliferate more rapidly [19]. Additionally, cell migration was increased markedly compared to controls that did not express UB32CP3 [19]. UB32CP3 has also been shown to induce an increase in microvessel density in vivo [3]. Hypoxia is the most important trigger of angiogenesis and understanding how these lncRNAs regulate EC behavior during hypoxic conditions, and how they affect angiogenesis in the tumour setting has clinical relevance.

**Figure 1.** Pro- and anti-angiogenic lncRNAs. Pro-angiogenic lncRNAs such as MIAT bind to miRNA and interfere with the ability of these molecules to perform their function. LncRNAs such as NAT interfere with miRNA translation. GATA6-AS, MANTIS, MALAT1 and SENCr affect gene expression by altering methylation of target DNA. LncRNAs such as STEEL regulate the activity of transcription factors. Anti-angiogenic lncRNAs function by inhibiting the activity of molecules that stimulate angiogenesis.
3. Functional Mechanisms of IncRNAs in Angiogenesis

Long noncoding RNAs were classically divided into four archetypes based on their mechanism of action, namely, signalling, decoy, guide, and scaffold IncRNAs (Figure 2) [10,19,20]. Signalling IncRNAs regulate transcription by acting as molecular signals [6]. Decoy IncRNAs, on the other hand, present alternate binding sites to catalytic and regulatory molecules, which include transcription factors and miRNAs [21,22]. This in turn limits the availability of these molecules and reduces their ability to modulate transcription. Guide IncRNAs support genomic positioning or localization, while scaffold IncRNAs provide a structural scaffold to enable the proper assembly of protein complexes such as ribonucleoproteins (RNP) [23–25]. Depending on the nature of the complex formed, it can induce transcriptional activation or suppression [25,26]. More recently, a fifth archetype, the enhancer IncRNA (eIncRNA) was described [6]. Enhancer IncRNAs stabilize and maintain chromatin loops [6,10].

![Figure 2. Mechanism of IncRNA action. Scaffold IncRNAs act as a framework for molecules such as proteins to bind to and be brought into close contact with each other, allowing them to perform their functions more easily. The red frame indicates the target sequence on the DNA strand. Guide IncRNAs recruit molecules such as proteins to a particular site on a nucleic acid molecule. Decoy IncRNAs act as decoy binding sites for molecules such as miRNAs or transcription factors. As such they are also known as sponge IncRNAs. Enhancer IncRNAs act to enhance the function of transcription factor-like molecule. Signalling IncRNAs act as signals to promote or repress the activity of transcription factors.](image)

The various IncRNA archetypes play important roles in the tumour vasculature by modulating gene expression at various levels. At the epigenetic level, IncRNAs recruit several epigenetic factors and regulate chromatin remodelling and gene splicing [27,28]. Plasmacytoma variant translocation 1 (PVT1) and LINC00313 are examples of angiogenesis regulating IncRNAs which exert their action at the epigenetic level [28]. Both PVT1 and LINC00313 combine with PRC2 and inhibit the transcription of ANGPTL4 and cell migration-regulating genes. ANGPTL4 regulates glucose metabolism in ECs and preserves the integrity of these cells [29]. Not surprising given its role in the regulation of EC function,
ANGPTL4 also regulates angiogenesis [29]. Another long noncoding RNA in this category is H-19, which regulates angiogenesis in the tumour microvasculature and is upregulated in multiple cancers [28]. At the transcriptional level, lncRNAs regulate transcription through interactions with transcription factors and target gene promoters [28]. One such lncRNA is HOX antisense intergenic RNA (HOTAIR), which promotes angiogenesis when upregulated, this activates the transcription of vascular endothelial growth factor by targeting the VEGF promoter [30–32]. Additionally, CPS1-IT1 interacts with BRG1 and inhibits the expression of Cyr61 as well as its downstream targets. These downstream targets, namely, VEGF and matrix metalloproteinase 9 (MMP9), regulate tumour angiogenesis [31,33]. Moreover, MMP-9 plays a key role in the remodelling of the extracellular matrix at the onset of neovessel formation. LINC00312 binds to YBX1 and promotes the expression of VEGF while Linc00665 promotes the transcription of ANGPTL4, ANGPTL3 and VEGF through binding to YB-1 [32–36]. Like ANGPTL4, ANGPTL3 regulates EC lipid metabolism and promotes angiogenesis [29]. By modulating proteins that are required in the early stages of tumour vessel formation, these lncRNAs play a key role in the angiogenic switch.

At the post-transcriptional level, lncRNAs sequester miRNAs, interact with splicing factors and with RNA-binding proteins (RBPs) [37]. MALAT1 and Taurine upregulated gene 1 (TUG1), which are upregulated in various tumours including HCC, colorectal cancer (CRC), breast cancer, glioblastoma, and hepatocellular carcinoma promote angiogenesis by increasing VEGF expression through sponging miRNAs. Microvascular invasion in hepatocellular carcinoma (MVIH) are also overexpressed in HCC and they promote tumour angiogenesis (Figure 3) [38–40]. Other mechanistic actions are orchestrated through protein modification and enhancer peptides. Protein-modifying lncRNAs coordinate the activation and stability of some proteins [41,42]. TNK2 Antisense RNA 1 (TNK2-AS1), a protein-modifying lncRNA, promotes angiogenesis via STAT3/VEGF and is upregulated in cancer [43,44]. In contrast, neuroblastoma-associated transcript 1 (NBAT1), which interacts with Sox9 and reduces its protein stability, resulting in anti-angiogenesis [45], is downregulated in gastric cancer (Figure 3) [45,46]. Similarly, the encoding peptide LINC00908 has an anti-angiogenic effect. It encodes ASRPS, which limits STAT3 phosphorylation and thereby inhibits VEGF [47]. LINC00908 is downregulated in triple-negative breast cancer [47].

Figure 3. A depiction of the activity of lncRNAs regulating gene transcription in a hierarchical fashion. LncRNAs can control gene expression by regulating the process at different stages. At the level of transcription lncRNAs can recruit transcription factors to promoters or inhibit promoter binding. The Red boxes indicate the target sequence on DNA strands. At the post-transcriptional level, lncRNAs can regulate alternate splicing by associating with splicing factors or altering the degradation of mRNA by regulating the activity of miRNAs. Finally, at the post translational level lncRNAs can modify proteins, for example by reducing the stability of a protein.
4. Clinical Significance of Angiogenesis Regulating lncRNAs in Cancer

In many cancers the current staging has limitations in terms of determining prognosis. Biomarkers are critical in completing clinical staging and improving the prediction of lymph node metastasis as well as in determining cancer prognosis. Many lncRNAs are over-expressed in various cancer cell lines, as well as in preclinical cancer models and patients. The expression patterns of angiogenesis regulating lncRNAs that have been shown to correlate with disease progression and treatment outcome in cancer patients are listed in Table 1. These lncRNAs have been explored for possible clinical application as biomarkers and as targets for therapeutic intervention [48–51].

Table 1. Angiogenic lncRNAs with potential as cancer biomarkers.

| lncR         | Cancer                           | Expression | Mechanism of Action                                                                 | Potential Application                  | Reference |
|--------------|----------------------------------|------------|--------------------------------------------------------------------------------------|----------------------------------------|-----------|
| LINC00313    | Lung, thyroid                    | Upregulated | Inhibits the transcription of genes regulating cell motility                        | Prognosis                              | [52,53]   |
| CPS1-IT1     | Multiple                         | Upregulated | Inhibits VEGF, MMP-9 and Cyr61                                                       | Prognosis                              | [54,55]   |
| CRNDE        | hepatoblastoma, leukemia         | Upregulated | Modulates the PI3K/PKB/mTOR pathway                                                 | Prognosis, Identification of subtype (in Leukemia) | [56]      |
| HOTAIR       | Nasopharyngeal carcinoma         | Upregulated | targets the VEGF promoter and activates the transcription of VEGF; modulates Ang2 expression through the upregulation of GRP78 | Prognosis, recurrence                   | [57–60]   |
| HOTAIR       | Melanoma                         | downregulated |                                                                                       | prognosis                              | [59,61]   |
| PVT1         | gastric cancer                   | Upregulated | activates VEGF via STAT3                                                              | aggressiveness                         | [62–64]   |
| MALAT1       | Multiple                         | Upregulated | promotes the expression of VEGF, SLUG and Twist                                       | detection, risk of metastasis, prognosis | [65,66]   |
| TUG1         | Multiple                         | Upregulated | modulates HIF-1α expression, promotes VEGF expression                                 | prognosis                              | [67,68]   |
| LINC00346    | Glioma                           | Upregulated | induces ZNF655 degradation                                                            | prognosis                              | [69,70]   |
| FLANC        | CRC                              | Upregulated | induces VEGF expression via STAT3                                                    | prognosis                              | [71,72]   |
| LINC00908    | TNBC, HCC                        | downregulated | inhibits STAT3 phosphorylation, decreases VEGF expression                             | prognosis                              | [73,74]   |
| LINC00312    | lung cancer, nasopharyngeal carcinoma | Upregulated | induces VEGF expression                                                              | prognosis                              | [48,75]   |
| H19          | bladder cancer, gastric cancer   | Upregulated | increases VEGF expression                                                            | early recurrence, prognosis            | [76–79]   |
| HULC         | HCC                              | Upregulated | promotes SPHK1 expression                                                            | metastasis                             | [80–83]   |
| MVIH         | HCC                              | Upregulated | interacts with PGK1                                                                  | prognosis                              | [84,85]   |
| TNK2-AS1     | NSCLC                            | Upregulated |                                                                                       | prognosis                              | [86]      |
| UBE2CP3      | glioma, HCC                      | Upregulated | activates the ERK1/2/HIF-1α/VEGF pathway                                             | prognosis                              | [49,87]   |

HCC, hepatocellular carcinoma; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; TNBC, Triple-negative breast cancer; HULC, highly upregulated in liver cancer; HIF, Hypoxia-inducible factor; MMP-9, matrix metalloproteinase-9; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; mTOR, mammalian target of rapamycin; STAT, signal transducer and activator of transcription; GRF, glucose-regulated protein; SPHK1, sphingosine kinase 1; Ang2, angiopoietin2 VEGF; vascular endothelial growth factor; CYR61, Cysteine-rich angiogenic inducer 61; PGKI—Phosphoglycerate kinase; ERK1/2, Extracellular signal-regulated protein kinase 1/2.

4.1. Angiogenesis Regulating lncRNAs: Role as Cancer Biomarkers

Investigations have revealed significant correlations between patient outcome and the expression levels of some of the angiogenesis regulating lncRNAs such as UBE2CP3, LINC00312, and HOTAIR [57,84,87]. In breast cancer, UBE2CP3 is highly expressed, promotes tumour angiogenesis, and is also associated with poor prognosis [18,87]. In patients with HCC, UBE2CP3 expression levels correlated with vessel density. Furthermore, pa-
patients overexpressing UBE2CP3 had a median overall survival (OS) that was lower than that of HCC patients with tumours that did not express UBE2CP3 [49]. Interestingly, the expression of UBE2CP3 is restricted to the tumour and has not been detected in the para-tumour tissue [49]. On the other hand, meta-analysis revealed that TUG1, SPRY4-IT1, and HULC did not correlate with lymph node metastasis in various cancers [49,51]. However, a correlation could be established between the expression levels of these three IncRNAs and low overall survival in cancer patients [50].

MVIH was initially identified in hepatocellular carcinoma but was later also detected in other neoplasms such as breast cancer [84,85]. Its overexpression in HCC patients correlates with increased tumour vascularization and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85]. In a mouse model of HCC, the induced overexpression of MVIH stimulated angiogenesis and promoted tumour growth and metastasis [51,85].

HOX transcript anti-sense RNA (HOTAIR), the first antisense transcription lncRNA to be discovered, is overexpressed in cancer tissues compared to normal tissues. It is linked to the development of gastric cancer (GC), breast cancer, lung cancer, and liver cancer [51]. HOTAIR promotes the expression of VEGF and activates the PI3K/AKT/multidrug resistance protein 1 (MRP1) pathway through direct binding to miR-126. Data has shown that serum HOTAIR levels were higher in patients with oesophageal squamous carcinoma when compared to controls without cancer, and that HOTAIR levels correlate with tumour node metastasis (TNM) stage [93]. In gastric cancer, HOTAIR correlates with lymph node and distant metastasis, while in colorectal carcinomas it is associated with advanced stage and metastases [94]. H19, another angiogenesis-regulating lncRNA, is also associated with lymph node metastasis [51]. These lncRNAs could serve as prognostic biomarkers in both gastric and colorectal carcinomas. Moreover, HOTAIR is currently used as a prognostic marker for recurrence in patients who have undergone liver transplantation [95]. Additionally, several studies have shown that blood levels of HOTAIR are good predictors of disease outcome [96]. HOTAIR and PVT1 detected in the saliva of early pancreatic patients were identified as possible biomarkers [97–99]. Homebox A11 antisense (HOXA11as) was highly expressed in cancerous tissue, and its expression showed a significant correlation with clinicopathological features in serous ovarian cancer (SOC) [100]. Additionally, patients with an elevated expression of HOXA11as had a significantly shorter progression-free and overall survival rates. These observations provide a basis for the further studies and the development of these lncRNAs as biomarkers.

4.2. Therapeutic Targeting of lncRNAs in Cancer Angiogenesis

Several lncRNAs that regulate tumour angiogenesis were shown to be aberrantly expressed in many cancers, making them an attractive target for drug design. Moreover, many of these lncRNAs are not readily detectable in normal tissue, and some are both tissue and cancer subtype specific [51,101]. A few studies have investigated the potential use of these lncRNAs as targets for cancer therapy mainly in preclinical models [65,67,102]. The silencing of SPRY4-IT1, inhibits the migration of oesophageal squamous cell carcinoma cell in vitro, while NEAT1 suppression inhibits tumour cell growth through p53 [102]. In several independent studies, MALAT1 promoted angiogenesis in vitro and its silencing led to an increase in EC migration, while the inhibition of MALAT1 expression by GapmeR inhibited EC sprout formation [9,65,67]. HOTAIR expression levels were found to be high in cisplatin resistant ovarian cancer cells. The knockdown of HOTAIR in these cells led to the inhibition of tumor cell growth and invasiveness [103]. The silencing of HOTAIR by siRNAs inhibits tumour cell invasiveness in breast cancer and reduces tumour growth in pancreatic cancer [102]. Furthermore, the knockdown of HOTAIR has been shown to improve the sensitivity of tumour cells to cisplatin and doxorubicin. The silencing of CRNDE in colorectal cancer cells suppresses tumour cell growth and reduces resistance
to chemotherapy [104]. While these studies have yielded positive results, they are in their infancy and much remains to be done. Additionally, recent reports on the mechanism of some lncRNAs reveal anecdotal results. The LINC000961 gene was shown to yield two molecules with different and opposing effects on angiogenesis [105]. Similarly, another angiogenesis-regulating lncRNA that has been explored for drug targeting is LincRNA-p21 [27]. While some studies showed that it correlates with microvessel density and that its silencing reduces VEGF expression, it was also found to be downregulated in tumour tissue [27]. These findings underscore the importance of more in-depth investigations to elucidate the roles and mechanisms of these lncRNAs.

5. Conclusions

It is evident from emerging studies that lncRNAs regulate the fine balance between pro- and antiangiogenic factors, and that their deregulation may contribute to the transition from the dormant avascular tumour to an angiogenic malignant phenotype. Emerging studies have identified several lncRNAs as key regulators of molecules which drive the angiogenic switch, such as VEGF, MMP9, and TIE (Figure 4). While most angiogenesis regulating lncRNAs are upregulated in various cancers, a few of these transcripts which exhibit antiangiogenic activity are downregulated. Of note is that in a diverse array of cancers the expression patterns of these lncRNAs correlate with clinical outcome. The findings of these studies render such angiogenesis modulating transcripts as potential cancer biomarkers. Moreover, some of the lncRNAs are stable in body fluids and can be useful in non-invasive applications. However, future investigations should focus on the sensitivity and specificity of MALAT1 and H19 in cancer detection. Studies with larger samples sizes are required to determine the degree of diagnostic accuracy. Important promoters of tumour angiogenesis can serve as therapeutic targets, including MALAT1, TUG1, LNC00323-003, PVT1, and MIR503HG. Antisense oligonucleotides have been employed for the modulation of gene expression, and their approval for the treatment of patients opens avenues for further exploration in the clinical application of silencing or targeting proangiogenic lncRNAs such as TUG1 and PVT1. The targeting of MALAT1 with GapmeR has recently been shown to be effective in myeloma. There is a need to further elaborate possible drug delivery platforms that will enhance tumour tissue specific targeting to minimize the off-target effects commonly encountered with most anti-cancer treatments. Furthermore, the limitations of current studies on angiogenic lncRNAs is that they have focused on inhibiting vessel formation. On the other hand, it is well-known that tumour blood vessels are structurally and functionally abnormal, and hamper drug delivery. The remodelling of the tumour vasculature may be more advantageous, especially for combination approaches that target various components of the tumour microenvironment, and as such studies are needed to determine ways to optimize lncRNA targeting to normalize tumour vessels and enhance the delivery of chemo- and immunotherapy drugs. In future, technologies such as CRISPR and genome-wide chromatin interrogation will improve our understanding of the functions of angiogenesis regulating lncRNAs and aide in informing drug design approaches.
Figure 4. Summary of lncRNAs role in angiogenesis and the practical application of this knowledge. The angiogenic switch relies on the change in the balance between the levels or activity of pro and anti-angiogenic factors. Pro-angiogenic lncRNAs promote the activity of the pro-angiogenic factors while inhibiting the anti-angiogenic factors. The expression profile of these lncRNAs can be used as prognostic markers or as targets for the development of new therapies. Anti-angiogenic lncRNAs promote the activity of anti-angiogenic factors while inhibiting those of the pro angiogenic factors.

Author Contributions: Conceptualization, P.M. and Z.D.; P.M.; writing—original draft preparation, P.M. and R.H.; writing—review and editing, Z.D.; supervision, Z.D.; funding acquisition, Z.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the South African Medical Research Council (SAMRC) Grant Number 23108 and the National Research Foundation (NRF) Grant Number 138139.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Mabeta, P. Paradigms of vascularization in melanoma: Clinical significance and potential for therapeutic targeting. Biomed. Pharmacother. 2020, 127, 110135. [CrossRef] [PubMed]
2. Folkman, J. Role of angiogenesis in tumor growth and metastasis. Semin. Oncol. 2002, 29, 15–18. [CrossRef] [PubMed]
3. Mabeta, P.; Pepper, M.S. Manipulating the tumor microenvironment: Opportunities for therapeutic targeting. Front. Anti Cancer Drug Discov. 2017, 8, 46–71.
4. Boulberdaa, M.; Scott, E.; Ballantyne, M.; Garcia, R.; Descamps, B.; Angelini, G.D.; Brittan, M.; Hunter, A.; McBride, M.; McClure, J.; et al. A role for the long noncoding RNA SENCR in commitment and function of endothelial cells. Mol. Ther. 2016, 24, 978–990. [CrossRef] [PubMed]
5. Jia, P.; Cai, H.; Liu, X.; Chen, J.; Ma, J.; Wang, P.; Liu, Y.; Zheng, J.; Xue, Y. Long non-coding RNA H19 regulates glioma angiogenesis and the biological behavior of glioma-associated endothelial cells by inhibiting microRNA-29a. Cancer Lett. 2016, 381, 359–369. [CrossRef]
6. Josipovic, I.; Pfüger, B.; Fork, C.; Vasconez, A.E.; Oo, J.A.; Hitzel, J.; Seredinski, S.; Gamen, E.; zu Heringdorf, D.M.; Chen, W.; et al. Long noncoding RNA LISP1 is required for S1P signaling and endothelial cell function. J. Mol. Cell. Cardiol. 2018, 116, 57–68. [CrossRef] [PubMed]
7. Li, Z.; Li, J.; Tang, N. Long noncoding RNA MALAT1 is a potent autophagy inducer protecting brain microvascular endothelial cells against oxygen-glucose deprivation/reoxygenation-induced injury by sponging miR-26b and upregulating ULK2 exression. Neuroscience 2017, 354, 1–10. [CrossRef]
8. Song, Y.; Yang, L.; Guo, R.; Lu, N.; Shi, Y.; Wang, X. Long noncoding RNA MALAT1 promotes high glucose-induced human endothelial cells pyroptosis by affecting NLRP3 expression through competitively binding miR-22. Biochem. Biophys. Res. Commun. 2019, 509, 359–366. [CrossRef] [PubMed]

9. Puthanveetil, P.; Chen, S.; Feng, B.; Gautam, A.; Chakrabarti, S. Long non-coding RNA MALAT1 regulates hyperglycaemia induced inflammatory process in the endothelial cells. J. Cell. Mol. Med. 2015, 19, 1418–1425. [CrossRef] [PubMed]

10. Wang, J.; Zhang, X.; Chen, W.; Hu, X.; Li, J.; Liu, C. Regulatory roles of long noncoding RNAs implicated in cancer hallmarks. Int. J. Cancer 2020, 146, 906–916. [CrossRef] [PubMed]

11. Hu, C.; Bai, X.; Liu, C.; Hu, Z. Long noncoding RNA XIST participates hypoxia-induced angiogenesis in human brain microvascular endothelial cells through regulating MIR-485/SOX7 axis. Am. J. Transl. Res. 2019, 11, 6487–6497. [PubMed]

12. Niu, Y.; Bao, L.; Chen, Y.; Wang, C.; Luo, M.; Zhang, B.; Zhou, M.; Wang, J.E.; Fang, Y.V.; Kumar, A.; et al. HIF2-Induced Long Noncoding RNA Enhances Angiogenesis in Human Hepatocellular Carcinoma by Targeting miR-485. Front. Pharmacol. 2020, 11, 1551. [CrossRef] [PubMed]

13. Mohammad, H.M.; Abdelghany, A.A.; Al Ageeli, E.; Kattan, S.W.; Hassan, R.; Toraih, E.A.; Fawzy, M.S.; Mokhtar, N. Long Non-Coding RNAs Gene Variants as Molecular Markers for Diabetic Retinopathy Risk and Response to Anti-VEGF Therapy. Pharm. Pers. Med. 2021, 14, 997–1014. [CrossRef] [PubMed]

14. Islam Khan, Z.; Tam, S.Y.; Law, H.K. Autophagy-Modulating Long Non-coding RNAs (lncRNAs) and Their Molecular Events in Cancer. Front. Genet. 2019, 9, 750. [CrossRef] [PubMed]

15. Jiang, F. Autophagy in vascular endothelial cells. Clin. Exp. Pharmacol. Physiol. 2016, 43, 1021–1028. [CrossRef] [PubMed]

16. Bao, H.; Su, H. Long NonCoding RNAs Act as Novel Biomarkers for Hepatocellular Carcinoma: Progress and Prospects. BioMed Res. Int. 2017, 2017, 6049480. [CrossRef] [PubMed]

17. Qiu, L.; Tang, Q.; Li, G.; Chen, K. Long non-coding RNAs as biomarkers and therapeutic targets: Recent insights into hepatocellular carcinoma. Life Sci. 2017, 191, 273–282. [CrossRef] [PubMed]

18. Bolha, L.; Ravnik-Glavač, M.; Glavač, D. Long Noncoding RNAs as Biomarkers in Cancer. Dis. Markers 2017, 2017, 7243968. [CrossRef] [PubMed]

19. Cossu, A.M.; Mosca, L.; Zappavigna, S.; Misso, G.; Bocchetti, M.; De Micco, F.; Quagliuolo, L.; Porcelli, M.; Caraglia, M.; Boccellino, M. Long non-coding RNAs as important biomarkers in laryngeal cancer and other head and neck tumours. Int. J. Mol. Sci. 2019, 20, 3444. [CrossRef] [PubMed]

20. Shi, T.; Gao, G.; Cao, Y. Long Noncoding RNAs as Novel Biomarkers Have a Promising Future in Cancer Diagnostics. Dis. Markers 2016, 2016, 9085195. [CrossRef] [PubMed]

21. Fatima, R.; Akhade, V.S.; Pal, D.; Rao, S.M. Long noncoding RNAs in development and cancer: Potential biomarkers and therapeutic targets. Mol. Cell. Ther. 2015, 3, 5. [CrossRef] [PubMed]

22. Jiang, C.; Li, X.; Zhao, H.; Liu, H. Long non-coding RNAs: Potential new biomarkers for predicting tumor invasion and metastasis. Mol. Cancer 2016, 15, 62. [CrossRef] [PubMed]

23. Zhao, J.; Li, L.; Han, Z.-Y.; Wang, Z.-X.; Qin, L.-X. Long noncoding RNAs, emerging and versatile regulators of tumor-induced angiogenesis. Am. J. Cancer Res. 2019, 9, 1367–1381. [PubMed]

24. Garajová, I.; Ferracin, M.; Porcellini, E.; Palloni, A.; Abbati, F.; Biasco, G.; Brandi, G. Non-coding RNAs as predictive biomarkers to current treatment in metastatic colorectal cancer. Int. J. Mol. Sci. 2017, 13, 1547. [CrossRef] [PubMed]

25. Chandra Gupta, S.; Nandan Tripathi, Y. Potential of long non-coding RNAs in cancer patients: From biomarkers to therapeutic targets. Int. J. Cancer 2017, 140, 1955–1967. [CrossRef] [PubMed]

26. Garajová, I.; Ferracin, M.; Porcellini, E.; Palloni, A.; Abbati, F.; Biasco, G.; Brandi, G. Non-coding RNAs as predictive biomarkers to current treatment in metastatic colorectal cancer. Int. J. Mol. Sci. 2017, 18, 1547. [CrossRef] [PubMed]

27. Man, H.S.; Sukumar, A.N.; Lam, G.C.; Turgeon, P.J.; Yan, M.S.; Ku, K.H.; Dubinsky, M.K.; Ho, J.J.D.; Wang, J.J.; Das, S.; et al. Angiogenic patterning by STELL, an endothelial-enriched long noncoding RNA. Proc. Natl. Acad. Sci. USA 2018, 115, 2401–2406. [CrossRef] [PubMed]

28. Yu, B.; Wang, S. Angio-Incrs: Lncrnas that regulate angiogenesis and vascular disease. Theranostics 2018, 8, 3654–3675. [CrossRef] [PubMed]

29. Xu, Y.; Li, J.; Zhang, Y.; Huang, S.; Zuo, Q.; Yang, N.; Chen, Y.; Wu, D.; Sun, L. The long non-coding RNA PVT1 represses ANGPTL4 transcription through binding with EZH2 in trophoblast cell. J. Cell. Mol. Med. 2018, 22, 1272–1282. [CrossRef]

30. Niu, Y.; Bao, L.; Chen, Y.; Yang, C.; Luo, M.; Zhang, B.; Zhou, M.; Wang, J.E.; Fang, Y.V.; Kumar, A.; et al. HIF2-Induced Long Noncoding RNA RAB11B-AS1 Promotes Hypoxia-Mediated Angiogenesis and Breast Cancer Metastasis. Cancer Res. 2020, 80, 964–975. [CrossRef]

31. Zhang, Y.; Lu, C.; Cui, H. Long non-coding RNA SNHG22 facilitates hepatocellular carcinoma tumorigenesis and angiogenesis via DNA methylation of microRNA miR-16-5p. Bioengineered 2021, 12, 7446–7458. [CrossRef]

32. Kondo, A.; Nonaka, A.; Shimamura, T.; Yamamoto, S.; Yoshida, T.; Kodama, T.; Aburatani, H.; Osawa, T. Long Noncoding RNA JHDM1D-AS1 Promotes Tumor Growth by Regulating Angiogenesis in Response to Nutrient Starvation. Mol. Cell. Biol. 2017, 37, 3654–3675. [CrossRef] [PubMed]

33. Zhang, X.; Tang, X.; Hamblin, M.H.; Yin, K.-J. Long non-coding RNA MALAT1 regulates angiogenesis in hindlimb ischemia. Int. J. Mol. Sci. 2018, 19, 1723. [CrossRef] [PubMed]

34. Lin, J.; Cao, S.; Wang, Y.; Hu, Y.; Liu, H.; Li, J.; Wang, Q.; Zheng, L. Long non-coding RNA UBE2CP3 enhances HCC cell secretion of VEGFA and promotes angiogenesis by activating ERK1/2/HIF-1α/VEGFA signalling in hepatocellular carcinoma. J. Exp. Clin. Cancer Res. 2018, 37, 113. [CrossRef] [PubMed]
34. Cheng, Z.; Li, Z.; Ma, K.; Li, X.; Tian, N.; Duan, J.; Xiao, X.; Wang, Y. Long non-coding RNA XIST promotes glioma tumor-igenicity and angiogenesis by acting as a molecular sponge of miR-429. J. Cancer 2017, 8, 4106–4116. [CrossRef] [PubMed]
35. Yousefi, H.; Maheronnaghsh, M.; Molaei, F.; Mashouri, L.; Aref, A.R.; Momeny, M.; Alahari, S.K. Long noncoding RNAs and exosomal lncRNAs: Classification, and mechanisms in breast cancer metastasis and drug resistance. Oncogene 2020, 39, 953–974. [CrossRef] [PubMed]
36. Bartonicek, N.; Maag, J.L.; Dinger, M.E. Long noncoding RNAs in cancer: Mechanisms of action and technological advances. Mol. Cancer 2016, 15, 43. [CrossRef] [PubMed]
37. Su, M.; Xiao, Y.; Ma, J.; Cao, D.; Zhou, Y.; Wang, H.; Liao, Q.; Wang, W. Long non-coding RNAs in esophageal cancer: Molecular mechanisms, functions, and potential applications. J. Hematol. Oncol. 2018, 11, 118. [CrossRef] [PubMed]
38. Cheng, Y.; Dai, X.; Yang, T.; Zhang, N.; Liu, Z.; Jiang, Y. Low long noncoding RNA Growth Arrest-Specific Transcript 5 expression in the exosomes of lung cancer cells promotes tumor angiogenesis. J. Oncol. 2019, 2019, 2476175. [CrossRef] [PubMed]
39. Zhao, Z.; Sun, W.; Guo, Z.; Zhang, J.; Yu, H.; Liu, B. Mechanisms of lncRNA/microRNA interactions in angiogenesis. Life Sci. 2020, 116900. [CrossRef] [PubMed]
40. Wang, S.-W.; Liu, Z.; Shi, Z.-S. Non-coding RNA in acute ischemic stroke: Mechanisms, biomarkers and therapeutic targets. Cell Transplant. 2018, 27, 1763–1777. [CrossRef] [PubMed]
41. Zhang, Z.-C.; Tang, C.; Dong, Y.; Zhang, J.; Yuan, T.; Tao, S.-C.; Li, X.-L. Targeting the long noncoding RNA MALAT1 blocks the pro-angiogenic effects of osteosarcoma and suppresses tumour growth. Int. J. Biol. Sci. 2017, 13, 1398–1408. [CrossRef] [PubMed]
42. Wang, F.; Zu, Y.; Huang, W.; Chen, H.; Xie, H.; Yang, Y. LncRNA CALML3-AS1 promotes tumorigenesis of bladder cancer via regulating ZBTB2 by suppression of microRNA-4316. Biochem. Biophys. Res. Commun. 2018, 504, 171–176. [CrossRef] [PubMed]
43. Tan, H.W.; Xu, Y.M.; Qin, S.H.; Chen, G.F.; Lau, A.T. Epigenetic regulation of angiogenesis in lung cancer. J. Cell. Physiol. 2021, 236, 3194–3206. [CrossRef] [PubMed]
44. Kok, F.O.; Baker, A.H. The function of long non-coding RNAs in vascular biology and disease. Vasc. Pharmacol. 2019, 114, 23–30. [CrossRef]
45. Leefer, C.; Le Bourhis, H.; Adriaenssens, E. The long non-coding RNA H19: An active player with multiple facets to sustain the hallmarks of cancer. Cell. Mol. Life Sci. 2019, 76, 4673–4687. [CrossRef] [PubMed]
46. Wu, R.; Hu, W.; Chen, H.; Wang, Y.; Li, Q.; Xiao, C.; Fan, L.; Zhong, Z.; Chen, X.; Lv, K.; et al. A Novel Human Long Noncoding RNA SCDAL Promotes Angiogenesis through SNF5-Mediated GDF6 Expression. Adv. Sci. 2021, 8, 2004629. [CrossRef] [PubMed]
47. Zhang, W.; Yuan, W.; Song, J.; Wang, S.; Gu, X. LncRNA CPS1-IT1 suppresses EMT and metastasis of colorectal cancer by inhibiting hypoxia-induced autophagy through inactivation of HIF-1α. Biochimie 2018, 144, 21–27. [CrossRef]
48. Peng, Z.; Wang, J.; Shan, B.; Li, B.; Peng, W.; Dong, Y.; Shi, W.; Zhao, W.; He, D.; Duan, M.; et al. The long noncoding RNA LINC00312 induces lung adenocarcinoma migration and vasculoegenic mimicry through directly binding YBX1. Mol. Cancer 2018, 17, 167. [CrossRef] [PubMed]
49. Huang, J.; Zheng, Y.; Xiao, X.; Liu, C.; Lin, J.; Zheng, S.; Yang, B.; Ou, Q. A circulating long noncoding RNA panel serves as a diagnostic marker for hepatocellular carcinoma. Dis. Markers 2020, 2020, 5417598. [CrossRef] [PubMed]
50. Lei, D.; Chen, Y.; Zhou, Y.; Hu, G.; Luo, F. An angiogenesis-related long noncoding RNA signature correlates with prognosis in patients with hepatocellular carcinoma. Biochip. Res. 2021, 41, bsr2020442. [CrossRef]
51. Liu, C.-G.; Li, J.; Xu, Y.; Li, W.; Fang, S.-X.; Zhang, Q.; Xin, H.-W.; Ma, Z. Long non-coding RNAs and circular RNAs in tumor angiogenesis: From mechanisms to clinical significance. Mol. Ther. Oncolytics 2021, 22, 336–354. [CrossRef] [PubMed]
52. Li, M.; Qiu, M.; Xu, Y.; Mao, Q.; Wang, J.; Dong, G.; Xia, W.; Yin, R.; Xu, L. Differentially expressed protein-coding genes and long noncoding RNA in early-stage lung cancer. Tumor. Biol. 2015, 36, 9969–9978. [CrossRef] [PubMed]
53. Wu, W.J.; Yin, H.; Hu, J.J.; Wei, X.Z. Long noncoding RNA LINC00312 modulates papillary thyroid cancer tumorigenesis via sponging miR-4429. Neoplasma 2018, 65, 933–942. [CrossRef]
54. Zhou, X.; Rao, Y.; Sun, Q.; Liu, Y.; Chen, J.; Bu, W. Long noncoding RNA CPS1-IT1 suppresses melanoma cell metastasis through inhibiting Cyr61 via competitively binding to BRG1. J. Cell Physiol. 2019, 234, 22017–22027. [CrossRef]
55. Dong, R.; Liu, X.-Q.; Zhang, B.-B.; Liu, B.-H.; Zheng, S.; Dong, K.-R. Long non-coding RNA-CRNDE: A novel regulator of tumor growth and angiogenesis in hepatoblastoma. Oncotarget 2017, 8, 42087–42097. [CrossRef] [PubMed]
56. Zhu, L.; Liu, Y.; Chen, Q.; Yu, G.; Chen, J.; Chen, K.; Yang, N.; Zeng, T.; Yan, S.; Huang, A.; et al. Long-noncoding RNA colorectal neoplasia differentially expressed gene as a potential target to upregulate the expression of IRX5 by miR-136-5P to promote oncogenic properties in hepatocellular carcinoma. Cell Physiol. Biochem. 2018, 50, 2229–2248. [CrossRef] [PubMed]
57. Fu, W.-M.; Lu, Y.-F.; Hu, B.-G.; Liang, W.-C.; Zhu, X.; Yang, H.-D.; Li, G.; Zhang, J.-F. Long noncoding RNA HOTAIR mediated angiogenesis in nasopharyngeal carcinoma by direct and indirect signaling pathways. Oncotarget 2016, 7, 4712–4723. [CrossRef] [PubMed]
58. Ma, D.D.; Yuan, L.L.; Lin, L.Q. LncRNA HOTAIR contributes to the tumorigenesis of nasopharyngeal carcinoma via up-regulating FASN. Eur Rev Med Pharmacol Sci 2017, 21, 5143–5152.
59. Qu, X.; Alsager, S.; Zhuo, Y.; Shan, B. HOX transcript antisense RNA (HOTAIR) in cancer. Cancer Lett. 2019, 454, 90–97. [CrossRef] [PubMed]
60. Toy, H.I.; Okmen, D.; Kontou, P.I.; Georgakilas, A.G.; Pavloupolou, A. HOTAIR as a Prognostic Predictor for Diverse Human Cancers: A Meta- and Bioinformatics Analysis. Cancers 2019, 11, 778. [CrossRef]
61. Xiao, Y.; Xia, Y.; Wang, Y.; Xue, C. Pathogenic roles of long noncoding RNAs in melanoma: Implications in diagnosis and therapies. Genes Dis. 2021. [CrossRef]

62. Zhao, J.; Du, P.; Cui, P.; Qin, Y.; Wu, J.; Zhou, Z.; Zhang, W.; Qin, L.; Huang, G. LncRNA PVT1 promotes angiogenesis via activating the STAT3/VEGFA axis in gastric cancer. Oncogene 2018, 37, 4094–4109. [CrossRef] [PubMed]

63. Ilboudo, A.; Chouhan, J.; McNeil, B.K.; Osborne, J.R.; Ogunwobi, O.O. PVT1 exon 9: A potential biomarker of aggressive prostate cancer. Int. J. Environ. Res. Public Health 2016, 13, 12. [CrossRef]

64. Ding, J.; Li, D.; Gong, M.; Wang, J.; Huang, X.; Wu, T.; Wang, C. Expression and clinical significance of the long non-coding RNA PVT1 in human gastric cancer. Onco Targets Ther. 2014, 7, 1625. [CrossRef] [PubMed]

65. Sun, Z.; Ou, C.; Liu, J.; Chen, C.; Zhou, Q.; Yang, S.; Li, G.; Wang, G.; Song, J.; Li, Z.; et al. YAP1-induced MALAT1 promotes epithelial–mesenchymal transition and angiogenesis by sponging miR-126-5p in colorectal cancer. Oncogene 2019, 38, 2627–2644. [CrossRef] [PubMed]

66. Goyal, B.; Yadav, S.R.M.; Awasthee, N.; Gupta, S.; Kunnunakkara, A.B.; Gupta, S.C. Diagnostic, prognostic, and therapeutic significance of long non-coding RNA MALAT1 in cancer. Biochim. Biophys. Acta Bioenerg. 2020, 1866, 866–878. [CrossRef]

67. Zhang, B.; Li, C.; Sun, Z. Long non-coding RNA LINC00346, LINC00578, LINC00673, LINC00671, LINC00261, and SNHG9 are novel prognostic markers for pancreatic cancer. Am. J. Transl. Res. 2018, 10, 2648. [CrossRef]

68. Yu, X.; Hu, L.; Li, S.; Shen, J.; Wang, D.; Xu, R.; Yang, H. Long non-coding RNA Taurine upregulated gene 1 promotes osteo-sarcoma cell metastasis by mediating HIF-1α via miR-143-5p. Cell Death Dis. 2019, 10, 280. [CrossRef] [PubMed]

69. Cai, H.; Liu, X.; Zheng, J.; Xue, Y.; Ma, J.; Li, Z.; Bao, M.; Liu, Y. Long non-coding RNA Taurine upregulated gene 1 enhances tu-mor-induced angiogenesis through inhibiting microRNA-299 in human glioblastoma. Oncogene 2017, 36, 318–331. [CrossRef]

70. Yang, C.; Zheng, J.; Liu, X.; Xue, Y.; He, Q.; Dong, Y.; Wang, D.; Li, Z.; Liu, L.; Ma, J.; et al. Role of ANKHHD1/LINC00346/ZNF655 feedback loop in regulating the glioma angiogenesis via staufen1-mediated mRNA decay. Mol. Ther. Nucleic Acids 2020, 20, 866–878. [CrossRef] [PubMed]

71. Ariel, I.; Sughayer, M.; Fellig, Y.; Pizov, G.; Ayesh, S.; Podeh, D.; Libdeh, B.A.; Levy, C.; Birman, C.T.; Tykocinski, M.L.; et al. The positive feedback between IncRNA TNK2-AS1 and STAT3 enhances angiogenesis in non-small cell lung cancer. Biochim. Biophys. Res. Commun. 2018, 507, 185–192. [CrossRef]
87. Luo, Z.; Pan, J.; Ding, Y.; Zhang, Y.-S.; Zeng, Y. The function and clinical relevance of IncRNA UBE2CP3-001 in human gliomas. *Arch. Med Sci.* 2018, 14, 1308–1320. [CrossRef]

88. Umeda, S.; Kanda, M.; Kodera, Y. Recent advances in molecular biomarkers for patients with hepatocellular carcinoma. *Expert Rev. Mol. Diagn.* 2019, 19, 725–738. [CrossRef]

89. Yuan, S.X.; Yang, F.; Yang, Y.; Tao, Q.F.; Zhang, J.; Huang, G.; Yang, Y.; Wang, R.-Y.; Yang, S.; Huo, X.-S.; et al. Long noncoding RNA associated with microvascular invasion in hepatocellular carcinoma promotes angiogenesis and serves as a predictor for hepatocellular carcinoma patients’ poor recurrence-free survival after hepatectomy. *Hepatology* 2012, 56, 2231–2241. [CrossRef]

90. Nie, F.-Q.; Zhu, Q.; Xu, T.-P.; Zou, Y.-F.; Xie, M.; Sun, M.; Xia, R.; Lu, K.-H. Long non-coding RNA MVIH indicates a poor prognosis for non-small cell lung cancer and promotes cell proliferation and invasion. *Tumor Biol.* 2014, 35, 7587–7594. [CrossRef]

91. Lei, B.; Xu, S.-P.; Liang, X.-S.; Li, Y.-W.; Zhang, J.-F.; Zhang, G.-Q.; Pang, D. Long non-coding RNA MVIH is associated with poor prognosis and malignant biological behavior in breast cancer. *Tumor Biol.* 2016, 37, 5257–5264. [CrossRef]

92. Kumar, M.M.; Goyal, R. LncRNA as a Therapeutic Target for Angiogenesis. *Curr. Top. Med. Chem.* 2017, 17, 1750–1757. [CrossRef]

93. Wang, W.; He, X.; Zheng, Z.; Ma, X.; Hu, X.; Wu, D.; Wang, M. Serum HOTAIR as a novel diagnostic biomarker for esophageal squamous cell carcinoma. *Mol. Cancer* 2017, 16, 75. [CrossRef]

94. Botti, G.; De Chiara, A.; Di Bonito, M.; Cerrone, M.; Malzone, M.G.; Collina, F.; Cantile, M. Noncoding RNAs within the HOX gene network in tumor pathogenesis and progression. *J. Cell. Physiol.* 2019, 234, 395–413. [CrossRef] [PubMed]

95. Yang, Z.; Zhou, L.; Wu, L.-M.; Lai, M.-C.; Xie, H.-Y.; Zhang, F.; Zheng, S.-S. Overexpression of Long Non-coding RNA HOTAIR Predicts Tumor Recurrence in Hepatocellular Carcinoma Patients Following Liver Transplantation. *Ann. Surg. Oncol.* 2011, 18, 1243–1250. [CrossRef]

96. Li, N.; Wang, Y.; Liu, X.; Luo, P.; Jing, W.; Zhu, M.; Jiancheng, T. Identification of Circulating Long Noncoding RNA HOTAIR as a Novel Biomarker for Diagnosis and Monitoring of Non–Small Cell Lung Cancer. *Technol. Cancer Res. Treat.* 2017, 16, 1060–1066. [CrossRef]

97. Li, X.; Cao, Y.; Gong, X.; Li, H. Long noncoding RNAs in head and neck cancer. *Oncotarget* 2017, 8, 10726–10740. [CrossRef]

98. Xie, Z.; Chen, X.; Li, J.; Guo, Y.; Li, H.; Pan, X.; Jiang, J.; Liu, H.; Wu, B. Salivary HOTAIR and PVT1 as novel biomarkers for early pancreatic cancer. *Oncotarget* 2016, 7, 25408–25419. [CrossRef]

99. Zou, H.; Wu, L.-X.; Yang, Y.; Li, S.; Mei, Y.; Liu, Y.-B.; Zhang, L.; Cheng, Y.; Zhou, H.-H. IncRNAs PVT1 and HAR1A are prognosis biomarkers and indicate therapy outcome for diffuse glioma patients. *Oncotarget* 2017, 8, 78767–78780. [CrossRef]

100. Yim, G.W.; Kim, H.J.; Kim, L.K.; Kim, S.W.; Kim, S.; Nam, E.J.; Kim, Y.T. Long Non-coding RNA HOXA11 Antisense Promotes Cell Proliferation and Invasion and Predicts Patient Prognosis in Serous Ovarian Cancer. *Cancer Res. Treat.* 2017, 49, 656–668. [CrossRef]

101. Bhan, A.; Soleimani, M.; Mandal, S.S. Long Noncoding RNA and Cancer: A New Paradigm. *Cancer Res.* 2017, 77, 3965–3981. [CrossRef]

102. Wu, X.-L.; Lu, R.-Y.; Wang, L.-K.; Wang, Y.-Y.; Dai, Y.-J.; Wang, C.-Y.; Yang, Y.-J.; Guo, F.; Xue, J.; Yang, D.-D. Long noncoding RNA HOTAIR silencing inhibits invasion and proliferation of human colon cancer LoVo cells via regulating IGF2BP2. *J. Cell. Biochem.* 2019, 120, 1221–1231. [CrossRef]

103. Michalik, K.M.; You, X.; Manavski, Y.; Doddaballapur, A.; Zörnig, M.; Braun, T.; John, D.; Ponomareva, Y.; Chen, W.; Uchida, S.; et al. Long Noncoding RNA MALAT1 Regulates Endothelial Cell Function and Vessel Growth. *Circ. Res.* 2014, 114, 1389–1397. [CrossRef]

104. Han, P.; Li, J.-W.; Zhang, B.-M.; Lv, J.-C.; Li, Y.-M.; Gu, X.-Y.; Yu, Z.-W.; Jia, Y.-H.; Bai, X.-F.; Li, L.; et al. The IncRNA CRNDE promotes colorectal cancer cell proliferation and chemoresistance via miR-181a-5p-mediated regulation of Wnt/β-catenin signaling. *Mol. Cancer* 2017, 16, 9. [CrossRef]

105. Spencer, H.L.; Sanders, R.; Boulberdaa, M.; Meloni, M.; Cochrane, A.; Spiroski, A.-M.; Mountford, J.; Emanueli, C.; Caporali, A.; Brittan, M.; et al. The LINC00961 transcript and its encoded micropeptide, small regulatory polypeptide of amino acid response, regulate endothelial cell function. *Cardiovasc. Res.* 2020, 116, 1981–1994. [CrossRef]