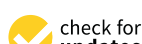
Review

Competing Endogenous RNAs in Cervical Carcinogenesis: A New Layer of Complexity

Fernanda Costa Brandão Berti [1], Sara Cristina Lobo-Alves [2], Camila de Freitas Oliveira-Toré [3], Amanda Salviano-Silva [1], Karen Brajão de Oliveira [4], Patrícia Savio de Araújo-Souza [1], Jong Kook Park [5], Gabriel Adelman Cipolla [1,†] and Danielle Malheiros [1,*,†]

[1] Postgraduate Program in Genetics, Department of Genetics, Federal University of Paraná, Curitiba 81531-990, Brazil; nandabrandao@hotmail.com (F.C.B.B.); amandasalviano@ufpr.br (A.S.-S.); psas@ufpr.br (P.S.d.A.-S.); gabriel.cipolla@ufpr.br (G.A.C.)
[2] Research Institute Pelé Pequeno Príncipe, Curitiba 80250-060, Brazil; saralobo5@yahoo.com.br
[3] Postgraduate Program in Internal Medicine, Department of Internal Medicine, Federal University of Paraná, Curitiba 81531-990, Brazil; camila_oliveira15@hotmail.com
[4] Postgraduate Program in Experimental Pathology, Department of Pathological Sciences, Londrina State University, Londrina 86057-970, Brazil; karen.brajao@uel.br
[5] Department of Biomedical Science and Research Institute for Bioscience & Biotechnology, Hallym University, Chuncheon 24252, Korea; jkpark@hallym.ac.kr
* Correspondence: dani_malheiros@ufpr.br; Tel.: +55-41-3361-1724
† Both authors contributed equally to this work.



Citation: Berti, F.C.B.; Lobo-Alves, S.C.; Oliveira-Toré, C.d.F.; Salviano-Silva, A.; de Oliveira, K.B.; de Araújo-Souza, P.S.; Park, J.K.; Cipolla, G.A.; Malheiros, D. Competing Endogenous RNAs in Cervical Carcinogenesis: A New Layer of Complexity. *Processes* **2021**, *9*, 991. https://doi.org/10.3390/pr9060991

Academic Editor: Carla Vitorino

Received: 12 May 2021
Accepted: 1 June 2021
Published: 3 June 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Abstract: MicroRNAs (miRNAs) regulate gene expression by binding to complementary sequences within target mRNAs. Apart from working 'solo', miRNAs may interact in important molecular networks such as competing endogenous RNA (ceRNA) axes. By competing for a limited pool of miRNAs, transcripts such as long noncoding RNAs (lncRNAs) and mRNAs can regulate each other, fine-tuning gene expression. Several ceRNA networks led by different lncRNAs—described here as lncRNA-mediated ceRNAs—seem to play essential roles in cervical cancer (CC). By conducting an extensive search, we summarized networks involved in CC, highlighting the major impacts of such dynamic molecular changes over multiple cellular processes. Through the sponging of distinct miRNAs, some lncRNAs as HOTAIR, MALAT1, NEAT1, OIP5-AS1, and XIST trigger crucial molecular changes, ultimately increasing cell proliferation, migration, invasion, and inhibiting apoptosis. Likewise, several lncRNAs seem to be a sponge for important tumor-suppressive miRNAs (as miR-140-5p, miR-143-3p, miR-148a-3p, and miR-206), impairing such molecules from exerting a negative post-transcriptional regulation over target mRNAs. Curiously, some of the involved mRNAs code for important proteins such as PTEN, ROCK1, and MAPK1, known to modulate cell growth, proliferation, apoptosis, and adhesion in CC. Overall, we highlight important lncRNA-mediated functional interactions occurring in cervical cells and their closely related impact on cervical carcinogenesis.

Keywords: long noncoding RNA; microRNA; mRNA; competing endogenous RNA; cervical cancer

1. Introduction

Cervical cancer (CC) is the fourth leading cause of death by cancer among women, with over 311,000 deaths in 2018 worldwide [1], even though it can be prevented by vaccination programs [2]. Generally, CC develops slowly, and there is a great opportunity to detect initial cervical alteration through cytology screening programs and HPV testing, which were showed to impact CC mortality [3]. Indeed, higher CC mortality rates are observed in poor countries [4] where screening programs are less effective [5]. Therefore, understanding the pathogenesis and exact molecular mechanisms underlying the emergence and progression of CC is crucial for defining promising biomarkers and an opportunity to develop better diagnostic and therapeutic interventions for CC.

Recently, emerging evidence has suggested promising applications of noncoding RNAs (ncRNAs)—including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs)—as novel candidate biomarkers and/or potential targets of treatment in multiple cancers. Different networks engaged by different ncRNAs influence numerous molecular targets, acting as key regulators of several biological programs in developmental and disease contexts, being particularly relevant in cancer [6].

For their important roles in cancer, both miRNAs and lncRNAs have been extensively described in the past few years as master regulators of cancer themselves. Most recently, considerable evidence has shown that besides regulating messenger RNA (mRNA) expression through independent mechanisms, these ncRNAs may 'work' together in complex networks of interactions, fine-tuning their expression [7]. Among different types of miRNA–lncRNA crosstalk, lncRNAs can act as ceRNAs, being a sponge for miRNAs and obstructing their interaction with target mRNAs, consequently favoring the expression of these coding RNAs [8,9]. In the ceRNA hypothesis, ceRNAs refer to all transcripts that have sequence similarity with protein-coding transcripts and act in competition for regulatory molecules, such as lncRNA, pseudogenes, and circular RNA (circRNAs) [8,10].

Different RNAs, expressed concurrently and with a similar set of miRNA recognition elements (MREs), are capable of indirectly regulating one another by competing for a shared, limited pool of miRNA molecules [8,9]. LncRNAs and mRNAs, for example, may compete for their common pair(s)—their 'matching' miRNA(s). Consequently, as miRNAs act as negative post-transcriptional regulators, any activity that decreases their interaction with their target mRNAs may positively contribute to gene expression regulation [7,11,12]. Therefore, the lncRNA–miRNA–mRNA crosstalk seems to crucially influence the overall activity and functional balance of gene networks in a cell [13]. Although still relatively scant, some studies investigating the lncRNA–miRNA crosstalk in CC have already demonstrated the importance of these networks in cervical tumorigenesis, defining specific ncRNAs involved in CC development as well as unveiling new promising biomarkers and potential therapeutic targets for CC. Thus, in the present review, we aim to summarize previously well-described functional interactions between pairs of lncRNA and miRNA (focusing on ceRNA networks) involved in cervical carcinogenesis and to present the current progress of research in this field. Understanding their role in the cervical microenvironment might be of great benefit to better comprehend the pathogenesis of CC and its progression. Additional goals are to discuss their use in CC screening as well as their application as therapeutic strategies for CC treatment.

2. Cross-Regulatory Mechanisms Involving lncRNAs and miRNAs

Several cross-regulatory mechanisms allow the lncRNA–miRNA crosstalk. LncRNAs may act as ceRNAs, being a sponge for miRNAs and obstructing miRNA action on the target mRNA, consequently favoring its expression [8]. In addition, lncRNAs may be precursors of miRNAs as part of their biogenesis—e.g., H19 lncRNA is the precursor of miR-675 [14]; miRNAs can decrease lncRNA stability through sequence-specific interaction, as occurs between MALAT1 and miR-9 [15]; lncRNAs may compete with miRNAs for shared target mRNAs—e.g., BACE1AS lncRNA, BACE1 mRNA, and miR-485-5p [16]. Such mechanisms highlight the wide range of molecular strategies involved in the lncRNA–miRNA crosstalk in eukaryotic cells. Figure 1 schematically presents such cross-regulatory mechanisms involving lncRNAs and miRNAs.

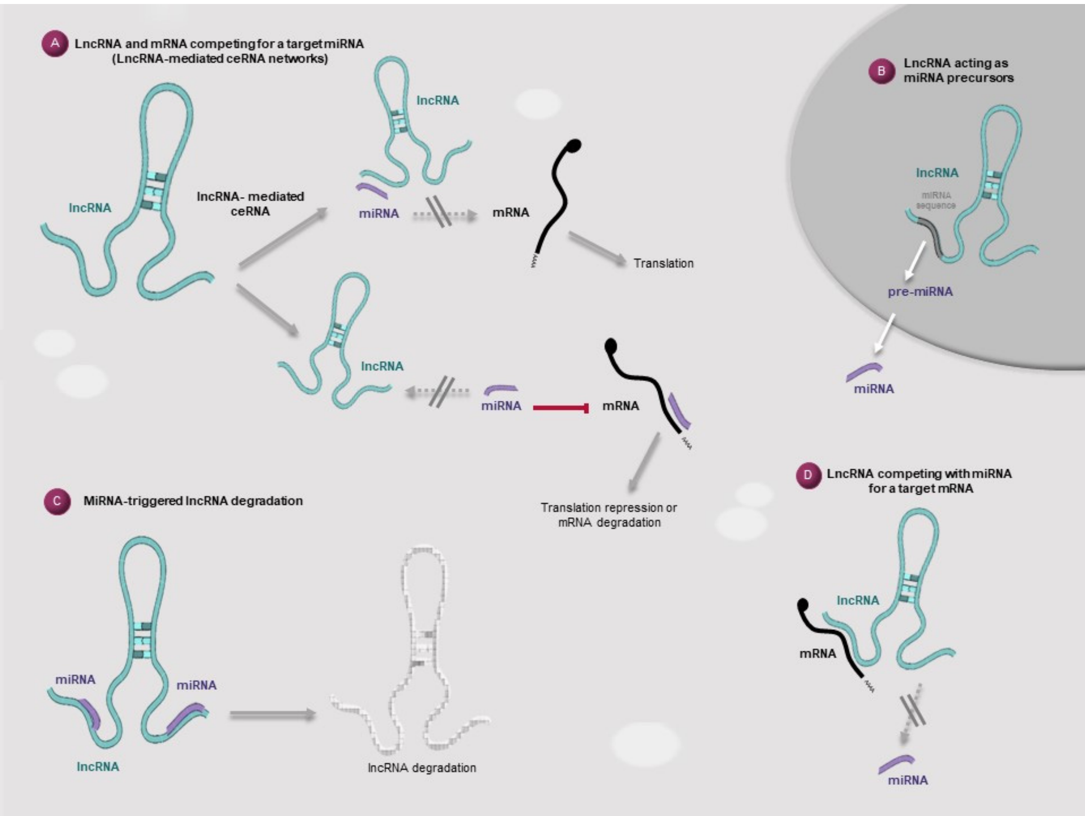


Figure 1. Cross-regulatory mechanisms involving lncRNAs and miRNAs. LncRNAs can act as ceRNAs, sponging miRNAs and obstructing their interaction with target mRNAs, consequently allowing for mRNA translation (upper **A**); alternatively, the respective miRNA may bind to a target mRNA, inducing mRNA degradation or translation repression (lower **A**). LncRNAs can be precursors of miRNAs as part of their biogenesis (**B**). MiRNAs can also decrease lncRNA stability through sequence-specific interaction, leading to lncRNA degradation (**C**). Finally, lncRNAs can compete with miRNAs for shared target mRNAs (**D**). (Image source: Mind the Graph).

3. The ceRNA Hypothesis: A miRNA-Mediated Interplay through Complex Networks of Interactions between Coding and Noncoding RNAs

Initially, miRNAs were shown to inhibit their target genes through binding to MREs of complementary coding RNA transcripts, leading to decreased expression of the respective proteins, either by mRNA degradation or translation inhibition [17]. Once mature, miRNAs guide the miRNA-programmed RNA-induced silencing complex (miR–RISC) to MREs, leading to mRNA destabilization or posttranslational repression, which results in inhibition of gene expression [18]. MREs are normally located in 3′ untranslated regions (3′UTRs) of various types of RNA transcripts, such as of mRNAs and ncRNAs [19].

Despite the important implications of miRNA-mediated regulation in homeostasis/disease, miRNA-mediated repression is surprisingly less impacting than most well-tolerated, intrinsic variations in gene expression [20,21]. Through computational analysis, several miRNA-binding sites that can titrate miRNAs and, thereby, regulate miRNA availability were identified, redefining the initial concept about miRNA targets [21]. In such a context, the hypothesis of different transcripts 'talking' to each other using MREs as letters of a new language—known as the ceRNA hypothesis—has emerged [8]. Therefore, several transcripts such as mRNAs, transcribed pseudogenes, and lncRNAs, expressed concurrently and with a similar set of MREs, are capable of indirectly regulating one another by competing for a shared, limited pool of miRNA molecules [8,10].

More recently, experimental evidence started to unveil several ceRNA axes in CC, especially lncRNA-mediated ceRNA networks, highlighting their importance in cervical carcinogenesis. As lncRNAs (i) constitute a large fraction of the transcriptome (with thousands of new

lncRNAs reported each year) [22], (ii) exert multiple functions [23], and (iii) tend to be longer than other ncRNAs [24] (which may reflect in an abundance of multiple MREs), such molecules may actively participate in cervical cell ceRNA interactome. Here, we especially present and discuss the recently identified lncRNA-mediated ceRNA axes in the cervical microenvironment. Figure 1A schematically exemplifies a lncRNA acting as a ceRNA.

4. LncRNA-Mediated ceRNA Axes in Cervical Tissue: Unveiling Important Networks in CC

Despite the importance of all the aforementioned cross-regulatory mechanisms, the final impact of different ceRNA networks in global gene expression in many different cellular contexts highlights the impact of such complex molecular networks of interactions on both normal physiology and tumorigenesis. In such a context, the perturbation of crucial interactions in ceRNA networks may potentially contribute to carcinogenesis by affecting the balance of the cellular regulatory system [25,26]. Several ceRNA networks involving different transcripts seem to play essential roles in CC. Up to date, only a few studies have focused on ceRNAs involving circRNAs [27,28]; none have evaluated networks involving pseudogenes, while a considerable number of original articles have already described several ceRNA networks led by different lncRNAs—described here as lncRNA-mediated ceRNAs.

Through an extensive literature search, we compiled different lncRNA-mediated ceRNA networks involved in CC. Despite all the potentially relevant studies initially identified, only those strongly evidencing the proposed molecular interactions and their final impact on cervical carcinogenesis were included and discussed in the present review. Table 1 summarizes the main characteristics of the included studies (and Table S1 presents information on the quality assessment of all potentially relevant papers). Additionally, in order to highlight the major impacts of such dynamic molecular changes over multiple cellular processes, we carefully focused on the different adopted strategies (in silico, in vitro, and in vivo approaches, as well as experiments performed using patients' samples), as presented through the following sections.

Table 1. Summary of studies investigating lncRNA-mediated ceRNA networks involved in cervical carcinogenesis.

Reference	Investigated Molecular Targets				Study Design (Strategies)				LncRNA-Mediated ceRNA Networks (Axes)
	lncRNA	miRNA	mRNA	Protein	In Silico	In Vitro	In Vivo	Patients	
A [29]	BBOX1-AS1	miR-361-3p	*HOXC6*	HOXC6	✓	✓	✓	✓	BBOX1-AS1/miR-361-3p/*HOXC6* axis *
A [30]	C5orf66-AS1	miR-637	*RING1*	RING1	✓	✓	✓	✓	C5orf66-AS1/miR-637/*RING1* axis
A [31]	CTS	miR-505	*ZEB2*	ZEB2	✓	✓	✓	✓	CTS/miR-505/*ZEB2* axis **
A [32]	DANCR	miR-335-5p	*ROCK1*	ROCK1	✓	✓	X	✓	DANCR/miR-335-5p/*ROCK1*
A [33]	DANCR	miR-665	*TGFBR1*	TGFBR1	✓	✓	✓	✓	DANCR/miR-665/*TGFBR1* axis
B [34]	DLG1-AS1	miR-107	*ZHX1*	-	✓	✓	X	✓	DLG1-AS1/miR-107/*ZHX1* axis
A [35]	GAS5	miR-196a	-	FOXO	✓	✓	✓	✓	GAS5/miR-196a/*FOXO1* axis
A [35]	GAS5	miR-205	-	PTEN	✓	✓	✓	✓	GAS5/miR-205/*PTEN* axis
B [36]	HCP5	miR-15a	*MACC1*	MACC1	✓	✓	X	✓	HCP5/miR-15a/*MACC1* axis
A [37]	HOTAIR	miR-23b	*MAPK1*	MAPK1	✓	✓	✓	✓	HOTAIR/miR-23b/*MAPK1* axis
B [38]	HOTAIR	miR-206	*MKL1*	MKL1	✓	✓	X	✓	HOTAIR/miR-206/*MKL1* axis ***
A [39]	HOTAIR	miR-148a	*HLA-G*	HLA-G	✓	✓	✓	✓	HOTAIR/miR-148a/*HLA-G* axis
A [40]	HOTAIR	miR-143-3p	*BCL2*	Bcl-2	✓	✓	✓	✓	HOTAIR/miR-143-3p/*BCL2* axis
A [41]	LINC00152	miR-216b-5p	*HOXA1*	HOXA1	✓	✓	X	✓	LINC00152/miR-216b-5p/*HOXA1* axis
A [42]	LINC00467	miR-107	*KIF23*	KIF23	X	✓	✓	✓	LINC00467/miR-107/*KIF23* axis
A [43]	LINC00483	miR-508-3p	*RGS17*	RGS17	✓	✓	✓	✓	LINC00483/miR-508-3p/*RGS17* axis
A [44]	LINC01128	miR-383-5p	*SFN*	Stratifin	✓	✓	X	✓	LINC01128/miR-383-5p/*SFN* axis
A [45]	LINC01535	miR-214	-	EZH2	✓	✓	✓	✓	LINC01535/miR-214/*EZH2* axis ***
B [46]	MALAT1	miR-202-3p	*POSTN*	Periostin	✓	✓	X	✓	MALAT1/miR-202-3p/*POSTN* axis
B [47]	MALAT1	miR-124	*GRB2*	Grb2	✓	✓	X	✓	MALAT1/miR-124/GRB2 axis
A [48]	NEAT1	miR-9-5p	*PTEN*	PTEN	✓	✓	X	✓	NEAT1/miR-9-5p/*PTEN* axis
A [48]	NEAT1	miR-9-5p	*POU2F1*	POU2F1	✓	✓	X	✓	NEAT1/miR-9-5p/*POU2F1* axis
A [49]	NEAT1	miR-101	*FOS*	-	✓	✓	X	✓	NEAT1/miR-101/*FOS* axis
B [50]	NEAT1	miR-133a	*SOX4*	SOX4	X	✓	✓	X	NEAT1/miR-133a/*SOX4* axis
B [51]	NOC2L-4.1	miR-630	*YAP1*	YAP1	✓	✓	✓	X	NOC2L-4.1/miR-630/*YAP1* axis
A [52]	NORAD	miR-590-3p	*SIP1*	SIP1	✓	✓	✓	✓	NORAD/miR-590-3p/*SIP1* axis

Table 1. *Cont.*

Reference	Investigated Molecular Targets				Study Design (Strategies)				LncRNA-Mediated ceRNA Networks (Axes)
	lncRNA	miRNA	mRNA	Protein	In Silico	In Vitro	In Vivo	Patients	
[B] [53]	OIP5-AS1	miR-143-3p	*SMAD3*	SMAD3	✓	✓	X	✓	OIP5-AS1/miR-143-3p/*SMAD3* axis
[A] [54]	OIP5-AS1	miR-143-3p	*ROCK1*	ROCK1	✓	✓	X	✓	OIP5-AS1/miR-143-3p/*ROCK1* axis
[A] [55]	POU3F3	miR-127-5p	*FOXD1*	FOXD1	✓	✓	✓	✓	POU3F3/miR-127-5p/*FOXD1* axis [1]
[A] [56]	PTENP1	miR-106b	*PTEN*	PTEN	✓	✓	X	✓	PTENP1/miR-106b/*PTEN* axis
[A] [57]	RP11-552-M11.4	miR-3941	*ATF1*	ATF1	✓	✓	✓	✓	RP11-552M11.4/miR-3941/*ATF1* axis
[A] [58]	RSU1P2	let-7a	*IGF1R*	IGF1R	✓	✓	✓	✓	RSU1P2/let-7a/*IGF1R* axis
[A] [58]	RSU1P2	let-7a	*NMYC*	N-Myc	✓	✓	✓	✓	RSU1P2/let-7a/*NMYC* axis
[A] [58]	RSU1P2	let-7a	*EPHA4*	EPHA4	✓	✓	✓	✓	RSU1P2/let-7a/*EPHA4* axis
[A] [59]	SBF2-AS1	miR-361-5p	*FOXM1*	FOXM1	✓	✓	✓	✓	SBF2-AS1/miR-361-5p/*FOXM1* axis
[A] [60]	SNHG4	miR-148a-3p	*MET*	c-Met	✓	✓	✓	✓	SNHG4/miR-148a-3p/*MET* axis
[B] [61]	SNHG12	miR-125b	*STAT3*	STAT3	✓	✓	X	X	SNHG12/miR-125b/*STAT3* axis
[A] [62]	SNHG14	miR-206	*YWHAZ*	YWHAZ	✓	✓	X	✓	SNHG14/miR-206/*YWHAZ* axis
[A] [63]	SNHG20	miR-140-5p	*ADAM10*	ADAM10	✓	✓	✓	✓	SNHG20/miR-140-5p/*ADAM10* axis
[A] [64]	SOX21-AS1	miR-7	*VDAC1*	VDAC1	✓	✓	X	✓	SOX21-AS1/miR-7/*VDAC1* axis
[A] [65]	STXBP5-AS1	miR-96-5p	*PTEN*	PTEN	✓	✓	X	✓	STXBP5-AS1/miR-96-5p/*PTEN* axis
[A] [66]	TCONS_00026907	miR-143-5p	*ELK1*	ELK1	X	✓	✓	✓	TCONS_00026907/miR-143-5p/*ELK1* axis
[A] [67]	TDRG1	miR-326	*MAPK1*	MAPK1	✓	✓	✓	✓	TDRG1/miR-326/*MAPK1* axis
[A] [68]	TP73-AS1	miR-329-3p	*SMAD2*	SMAD2	✓	✓	✓	✓	TP73-AS1/miR-329-3p/*SMAD2* axis
[A] [69]	TTN-AS1	miR-573	*E2F3*	E2F3	✓	✓	✓	✓	TTN-AS1/miR-573/*E2F3* axis
[A] [70]	TUSC8	miR-641	*PTEN*	PTEN	✓	✓	X	✓	TUSC8/miR-641/*PTEN* axis
[A] [71]	WT1-AS	miR-203a-5p	*FOXN2*	-	✓	✓	✓	✓	WT1-AS/miR-203a-5p/*FOXN2* axis
[A] [72]	XIST	miR-200a	*FUS*	FUS	✓	✓	X	✓	XIST/miR-200a/*FUS* axis
[A] [73]	XIST	miR-140-5p	*ORC1*	ORC1	✓	✓	✓	✓	XIST/miR-140-5p/*ORC1* axis
[A] [74]	ZNF667-AS1	miR-93-3p	*PEG3*	PEG3	✓	✓	✓	✓	ZNF667-AS1/miR-93-3p/*PEG3* axis

According to the score obtained in the quality assessment analysis, articles were classified into [A] high-quality assessment or [B] moderate-quality assessment (see Table S1). CeRNA = competing endogenous RNA; [ref] = reference; - = not applicable; X = not performed; ✓ = performed. * BBOX1-AS1 upregulates HOXC6 expression through miR-361-3p but also through ELAV-like RBP 1 (HuR). ** Apart from sponging miR-505 and regulating the expression of *ZEB2*, CTS was shown to activate the TGF-β/SMAD signaling pathway. *** ceRNA interaction, but with an additional mechanism described (as MKL1 exerting a positive loop over the *HOTAIR* gene and EZH2 exerting a negative loop over the *miR-214* gene). [1] The transcriptional expression of *POU3F3* is activated by transcription factor SP1. Here, miRNA nomenclature was reproduced exactly as mentioned by the author in the respective article (thus, not all follow miRBase's most recent IDs). For further information, consult the miRBase database. All the abovementioned miRNAs are hsa-miRNAs (*Homo sapiens* miRNAs). The lncRNA nomenclature applied here was reproduced exactly as mentioned by the author in the respective article and is better described in the list of abbreviations (except for some lncRNAs such as RP11-552-M11.4 and TCONS_0026907, which correspond to transcript codes).

4.1. In Silico Predictions and In Vitro Strategies Reveal Molecular Interactions between Different Components of the Proposed ceRNA Networks

Basically, in silico analysis explored the prediction of ceRNA interactions based on the identification of MREs within the transcripts of interest, representing an interesting 'start' in order to suggest potential downstream targets of distinct lncRNAs and miRNAs. Almost all studies performed in silico analysis, aiming to predict the potential miRNAs targeted (sponged) by distinct lncRNAs as well as potential target mRNAs of the previously predicted miRNA.

After predicting potential lncRNA–miRNA and miRNA–mRNA molecular interactions, in order to validate such results, in vitro approaches were performed. Essentially, the adopted techniques focused on observing two major aspects: (1) evaluating the patterns of expression of the different components of the investigated ceRNA axes (lncRNA/miRNA/mRNA) as well as positive/negative correlations between them, and (2) validating potential molecular interactions within such components.

Therefore, most studies firstly investigated the expression of the candidate lncRNA (and miRNA/mRNA) in different CC cell lineages compared to control lineage(s). Overall, for almost all ceRNA axes, the following pattern of expression was observed: the involved lncRNAs and mRNAs were significantly upregulated in CC cell lines in comparison to control cell lineage(s), while their 'matching' miRNA was significantly downregulated. For instance, HOTAIR expression was significantly upregulated in different CC cell lines in comparison to that in control lineages in different studies as well as the involved mRNAs [37–40]. Contrarily, the expression of the involved miRNAs was significantly downregulated [37–40]. Curiously, an opposed pattern was observed for nontumoral cells in comparison to normal cells.

As mentioned above, such pattern was reproducible in almost all the included studies except for the references investigating ceRNA axes led by tumor-suppressive lncRNAs such as GAS5 [35], PTENP1 [56], STXBP5-AS1 [65], TUSC8 [70], WT1-AS [71], and ZNF667-AS1 [74]. In those cases, an opposite pattern of expression was observed (with the lncRNA and mRNA being downregulated in CC, while the miRNA was upregulated). For instance, TUSC8 and *PTEN* were significantly downregulated in different CC cell lines in comparison to that in control lineages [56], while miR-641 was significantly upregulated in the respective studies [37–40]. Likewise, an opposed pattern was observed for nontumoral cells in comparison to normal cells.

Additionally, based on those results, several studies also highlighted important correlations between lncRNAs × miRNAs and/or miRNAs × mRNAs involved in distinct ceRNA axes, proposing potential direct interactions between some of these molecular targets. For all ceRNA axes, a significantly positive correlation was observed between the involved lncRNA and mRNA, while a negative correlation was observed between the lncRNA and the miRNA (or between the miRNA and the mRNA). As expected, such patterns of correlation were also observed between GAS5, PTENP1, STXBP5-AS1, TUSC8, WT1-AS, and ZNF667-AS1 and the particular molecular components involved in the respective axes.

Furthermore, the lncRNA–miRNA and/or miRNA–mRNA crosstalk was further validated. Here, we only reported on ceRNA axes validated by the luciferase reporter assay, considered the 'gold standard' technique in validating miRNA targets [75], which may be extended for validating lncRNA–miRNA targets. Details on the molecular interactions of different lncRNA-mediated ceRNA axes involved in CC are provided in Table S2. Essentially, all interactions previously predicted by in silico methodologies and suggested by the observed patterns of expression/correlations were ultimately validated.

4.2. In Vitro and In Vivo Experiments Demonstrate the Final Biological Impacts of the Respective Molecules/ceRNA Axes over Important Cellular Processes and Tumor Growth

Despite the remarkable diversity of neoplastic diseases, several biological capabilities acquired during the multistep development of human tumors—well known as 'the hallmarks of cancer'—seem to be present in all cancer types. Such capabilities include sustaining proliferative signaling, enabling replicative immortality, resisting cell death, and activating invasion and metastasis [76]. In such a context, the effects of the involved lncRNA (and miRNA/mRNA) over crucial cellular processes closely related to the aforementioned hallmarks (such as cell proliferation, cell cycle, apoptosis, migration/invasion, and metastasis) were investigated. Through in vitro gain- and/or loss-of-function strategies evaluating the effect of the lncRNA and/or miRNA (silenced and/or overexpressed), it was possible to observe the biological effects induced by these molecules and their respective ceRNA network.

Essentially, almost all described ceRNA axes led to an increase in cell proliferation and/or stimulated colony formation and/or cell cycle progression, as well as invasion and/or migration; contrarily, apoptosis was inhibited (see Table 2). For instance, HOTAIR led to an increase in cell proliferation [37,39,40], stimulated cell migration and invasion [37,38], and inhibited apoptosis [37,39,40]. Likewise, MALAT1-, NEAT1-, OIP5-AS1, and XIST-mediated ceRNA axes were reported by independent studies to affect distinct cellular processes [46–48,50,53,54,72,73]. Therefore, these ceRNA axes present oncogenic roles as they favor cervical carcinogenesis. On the other hand, a few lncRNA-mediated axes led by tumor-suppressive lncRNAs, such as GAS5 [35], PTENP1 [56], STXBP5-AS1 [65], TUSC8 [70], WT1-AS [71], and ZNF667-AS1 [74], present a tumor-suppressive role in CC. For instance, GAS5, STXBP5-AS1, WT1-AS, and ZNF667-AS1 overexpression suppressed cell growth and/or cell cycle progression and migration/invasion [35,65,71,74], while GAS5- and PTENP1-mediated ceRNA axes markedly increased apoptosis in CC cells [35,56]. It is actually important to highlight that such observed effects are mainly exerted through the lncRNA involved (and in a condition where they are 'overexpressed'). As they are downregulated in CC cells/tissue/patients' samples, the endogenous competitions through such axes are not likely to occur.

Table 2. Biological effects promoted by different lncRNA-mediated ceRNA networks (in vitro strategies).

LncRNA-Mediated ceRNA Networks (Axes) [Ref]	Cell Proliferation	Colony Formation	Cell Cycle Progression	Migration	Invasion	Apoptosis	Metastasis
BBOX1-AS1/miR-361-3p/*HOXC6* [29]	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↓ (HeLa/SiHa)	- *
C5orf66-AS1/miR-637/*RING1* [30]	↑ (C-4 I/SiHa)	↑ (C-4 I/SiHa)	↑ (C-4 I/SiHa)	-	-	↓ (C-4 I/SiHa)	-
CTS/miR-505/*ZEB2* axis [31]	-	-	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	- **
DANCR/miR-665/*TGFBR1* [33]	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↓ (C33A/HeLa)	-
DANCR/miR-335-5p/*ROCK1* [32]	↑ (CaSki/HeLa)	-	-	↑ (CaSki/HeLa)	↑ (CaSki/HeLa)	-	- *
DLG1-AS1/miR-107/*ZHX1* [34]	↑ (C4-1/HeLa)	-	-	-	-	-	-
GAS5/miR-196a/*FOXO1* [35] ***	↓ (ME180/SiHa)	↓ (ME180/SiHa)	-	-	↓ (ME180/SiHa)	↑ (ME180/SiHa)	-
GAS5/miR-205/*PTEN* [35] ***	↓ (ME180/SiHa)	↓ (ME180/SiHa)	-	-	↓ (ME180/SiHa)	↑ (ME180/SiHa)	-
HCP5/miR-15a/*MACC1* [36]	↑ (HeLa/SiHa)	-	-	-	-	-	-
HOTAIR/miR-23b/*MAPK1* [37]	↑ (HeLa)	-	-	↑ (HeLa)	↑ (HeLa)	↓ (HeLa)	- *
HOTAIR/miR-206/*MKL1* [38]	-	-	-	↑ (HeLa)	↑ (HeLa)	-	-
HOTAIR/miR-148a/*HLA-G* [39] [1]	↑ (CaSki/HeLa)	-	-	- *	- *	↓ (CaSki/HeLa)	-
HOTAIR/miR-143-3p/*BCL2* [40]	↑ (HeLa/SiHa)	-	-	-	-	↓ (HeLa/SiHa)	-
LINC00152/miR-216b-5p/*HOXA1* [41]	↑ (CaSki/C33A)	-	↑ (CaSki/C33A)	-	-	↓ (CaSki/C33A)	-
LINC00467/miR-107/*KIF23* [42]	↑ (HeLa/SiHa)	-	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	- **
LINC00483/miR-508-3p/*RGS17* [43] [2]	↑ (CaSki/HeLa)	-	-	↑ (CaSki/HeLa)	↑ (CaSki/HeLa)	↓ (CasKi/HeLa)	- **
LINC01128/miR-383-5p/*SFN* [44]	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↓ (HeLa/SiHa)	-
LINC01535/miR-214/*EZH2* [45]	↑ (HeLa/SiHa)	-	-	↑ (CasKi/HeLa/SiHa)	↑ (CasKi/HeLa/SiHa)	-	-
MALAT1/miR-202-3p/*POSTN* [46]	↑ (HeLa/SiHa)	-	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	-
MALAT1/miR-124/*GRB2* [47]	↑ (HeLa/SiHa)	-	-	-	↑ (HeLa/SiHa)	↓ (HeLa/SiHa)	-
NEAT1/miR-9-5p/*POU2F1* [48]	↑ (C33A/HeLa)	↑ (C33A/HeLa)	-	↑ (C33A/HeLa)	-	-	-
NEAT1/miR-9-5p/*PTEN* [48]	↑ (C33A/HeLa)	↑ (C33A/HeLa)	-	↑ (C33A/HeLa)	-	-	-
NEAT1/miR-101/*FOS* [49]	↑ (CaSki/HeLa)	↑ (CaSki/HeLa)	↑ (CaSki/HeLa)	↑ (CaSki/HeLa)	↑ (CaSki/HeLa)	↓ (CaSki/HeLa)	-
NEAT1/miR-133a/*SOX4* [50]	↑ (C33A/SiHa)	↑ (C33A/SiHa)	-	↑ (C33A/SiHa)	↑ (C33A/SiHa)	↓ (C33A/SiHa)	-
NOC2L-4.1/miR-630/*YAP1* [51]	↑ (HeLa/SW756)	↑ (HeLa/SW756)	-	↑ (HeLa/SW756)	-	-	-
NORAD/miR-590-3p/*SIP1* [52]	↑ (CaSki/SiHa)	↑ (CaSki/SiHa)	-	-	↑ (CaSki/SiHa)	-	-
OIP5-AS1/miR-143-3p/*SMAD3* [53]	↑ (HeLa/SiHa)	-	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	- *
OIP5-AS1/miR-143-3p/*ROCK1* [54]	↑ (C33A)	-	-	-	-	↓ (C33A)	-
POU3F3/miR-127-5p/*FOXD1* [55]	↑ (CaSki/HT-3)	↑ (CaSki/HT-3)	-	-	↑ (CaSki/HT-3)	-	-
PTENP1/miR-106b/*PTEN* [56] ***	↓ (CaSki/HeLa)	-	-	-	-	↑ (CaSki/HeLa)	- **
RP11-552M11.4/miR-3941/*ATF1* [57]	↑ (CaSki/HeLa)	↑ (CaSki/HeLa)	↑ (CaSki/HeLa)	↑ (CaSki/HeLa)	↑ (CaSki/HeLa)	↓ (CaSki/HeLa)	-
RSU1P2/let-7a/*IGF1R* [58]	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↓ (C33A/HeLa)	-
RSU1P2/let-7a/*NMYC* [58]	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↓ (C33A/HeLa)	-
RSU1P2/let-7a/*EPHA4* [58]	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↑ (C33A/HeLa)	↓ (C33A/HeLa)	-
SBF2-AS1/miR-361-5p/*FOXM1* [59]	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	-	↓ (HeLa/SiHa)	-

Table 2. *Cont.*

LncRNA-Mediated ceRNA Networks (Axes) [Ref]	Cell Proliferation	Colony Formation	Cell Cycle Progression	Migration	Invasion	Apoptosis	Metastasis
SNHG4/miR-148a-3p/*MET* [60]	↑ (HeLa/SiHa)	-	-	-	-	↓ (HeLa/SiHa)	-
SNHG12/miR-125b/*STAT3* [61]	↑ (HeLa/SiHa)	-	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	-
SNHG14/miR-206/*YWHAZ* [62]	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↓ (HeLa/SiHa)	- *
SNHG20/miR-140-5p/*ADAM10* [63]	↑ (HeLa/SW756)	↑ (HeLa/SW756)	-	-	↑ (HeLa/SW756)	-	-
SOX21-AS1/miR-7/*VDAC1* [64]	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↓ (HeLa/SiHa)	- *
STXBP5-AS1/miR-96-5p/*PTEN* [65] ***	↓ (HeLa/SiHa)	-	-	-	↓ (HeLa/SiHa)	-	- **
TCONS_00026907/miR-143-5p/*ELK1* [66]	↑ (HeLa/SiHa)	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↓ (HeLa/SiHa)	-
TDRG1/miR-326/*MAPK1* [67]	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	↓ (HeLa/SiHa)	- *
TP73-AS1/miR-329-3p/*SMAD2* [68]	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	-
TTN-AS1/miR-573/*E2F3* [69]	↑ (C33A/SiHa)	↑ (C33A/SiHa)	-	-	↑ (C33A/SiHa)	-	- *
TUSC8/miR-641/*PTEN* [70] ***	-	-	-	↓ (HeLa)	↓ (HeLa)	-	-
WT1-AS/miR-203a-5p/*FOXN2* [71] ***	↓ (CaSki/SiHa)	-	-	↓ (CaSki/SiHa)	↓ (CaSki/SiHa)	-	- **
XIST/miR-140-5p/*ORC1* [73]	↑ (C33A/HeLa)	-	↑ (C33A/HeLa)	-	-	↓ (C33A/HeLa)	-
XIST/miR-200a/*FUS* [72]	↑ (HeLa/SiHa)	↑ (HeLa/SiHa)	-	-	↑ (HeLa/SiHa)	↓ (HeLa/SiHa)	-
ZNF667-AS1/miR-93-3p/*PEG3* [74] ***	-	-	↓ (C33A/HeLa)	-	↓ (C33A/HeLa)	-	- **

CeRNA = competing endogenous RNA; [ref] = reference; - = not performed. The final biological effects are presented as general results of the respective involved ceRNA axis based on the different performed experiments. For example, some references investigated the silencing of the respective lncRNA implicated in decreasing or increasing cellular proliferation, while others investigated such an effect using both strategies of silencing and overexpressing the involved lncRNA. Differences like these were observed within strategies to evaluate lncRNA action over these different biological parameters as well as, in some cases, of the different miRNAs and/or mRNAs effects. In general, the authors present such effects as a consequence of the respective lncRNA, although, sometimes, the observed effects are presented as a consequence of the respective miRNA (such as for DANCR/miR-665/*TGFBR1* and SNHG12/miR-125b/*STAT3*) or mRNA (such as for MALAT1/miR-202-3p/*POSTN*)). Despite that, based on all adopted experiments and strategies, we may consider the whole ceRNA axis involved. The arrows represent cellular proliferation and apoptosis (↑ = increases; ↓ decreases); for colony formation, cell cycle progression, migration, invasion, and metastasis (↑ = promotes; ↓ inhibits). * Some references mentioned that the respective lncRNA had an influence over metastasis based on in vitro experiments, although such effects were not fully demonstrated by the performed experiments. ** Studies providing evidence that metastasis is, in fact, occurring (based on patients with lymph node metastasis occurrence and/or in vivo evidence). *** The observed biological effects were related to the overexpression of the involved lncRNAs. Those ceRNA axes seem not to be occurring in CC cell lineages since these lncRNAs and mRNAs are downregulated in such context; contrarily, they seem to be predominantly occurring in normal cell lines. [1] Cell proliferation was also evaluated in ME180 and SiHa cells. [2] Cell proliferation was also evaluated in CaSki, and C33A cells. Here, miRNA nomenclature was reproduced exactly as mentioned by the author in the respective article (thus, not all follow miRBase's most recent IDs). For further information, consult the miRBase database. All the abovementioned miRNAs are hsa-miRNAs (*Homo sapiens* miRNAs). The lncRNA nomenclature applied here was reproduced exactly as mentioned by the author in the respective article and is better described in the list of abbreviations (except for some lncRNAs such as RP11-552-M11.4 and TCONS_0026907, which correspond to transcript codes).

Further on, it is important to mention that the capability of inducing metastasis—another hallmark of cancer—is another evaluated biological parameter, although this is not quite correct in some cases. Several authors reported that 'the respective lncRNA stimulated invasion and migration and also increased metastasis', although the performed in vitro experiments did not fully support such effect. In fact, because some of the involved ncRNAs (and their respective axes) presented a pattern of expression of epithelial–mesenchymal transition (EMT)-related proteins consistent with the occurrence of this biologic process, the authors inferred their effect over metastasis. Such inference should be presented as a suggestion since the deregulated expression of EMT-related components may indeed suggest their influence over metastasis but not as a closed statement supporting such an effect. Some references provided proper evidence that metastasis is, in fact, occurring (based on lymph node metastasis occurrence in patients and/or in vivo evidence, using appropriate animal models of metastasis) [31,42,43] or is somehow prevented by tumor-suppressive lncRNA-mediated axes [56,65,71,74].

Finally, in vivo experiments have confirmed the involvement of the respective ceRNA axes in modulating cell proliferation, cell cycle, apoptosis, and tumor growth. The observed expression patterns of classical proliferation-related (such as Ki-67), cell-cycle-related (such as C-Fos, Cyclin D1, and Bcl-2), and apoptosis-related (such as cleaved caspase-3) markers corroborated such effects. For instance, an increased percentage of Ki-67-positive cells was observed in tumors induced by the SC injection of cells overexpressing the respective lncRNA (or silencing the involved target miRNA) [57,67,73]. Likewise, different lncRNA-mediated ceRNA axes were found to promote tumor growth in vivo, both independently as well as through common molecular networks. Additionally, the expression of different EMT-related (such as VEGF, vimentin, E-cadherin) markers was also evaluated, suggesting the involvement of some lncRNA-mediated axes in inducing EMT. Details on the investigated targets as well as the adopted strategies and the main findings are provided in Table S3.

Overall, HOTAIR was the most described lncRNA promoting CC growth, 'leading' different ceRNA axes [37,39,40]. Likewise, NEAT1 and XIST also promoted tumor growth in vivo [50,73]. In contrast, the overexpression of GAS5, WT1-AS, and ZNF667-AS1 led to opposite effects, suppressing tumor growth [35,71,74]. We hypothesize that as GAS5, WT1-AS, and ZNF667-AS1 are downregulated in CC, the endogenous competition between the components of the GAS5-, WT1-AS-, and ZNF667-AS1-mediated ceRNA axes are somehow impaired, preventing them from exerting their tumor-suppressive roles.

4.3. Evaluating Patients: Corroborating the Involvement of lncRNA-Mediated ceRNA Networks in Cervical Carcinogenesis

In general, the aforementioned strategies are worthy to better propose potentially involved ceRNA axes and confirm the direct interaction(s) among their components but have no clinical value if the obtained results are not somehow confirmed in the patients' biological samples. Therefore, experiments involving patients' samples—such as methods evaluating the expression profiles of the involved ncRNAs—represent an important strategy to ultimately suggest and/or confirm the involvement of the lncRNA–miRNA (or ceRNA axis) in cervical carcinogenesis. Almost all references adopted this strategy. Table 3 is an overview of sample description, performed methods, and major results.

In general, all ncRNAs participating in different axes were found deregulated at the tissular level in comparison to their matched controls, corroborating the patterns previously observed in vitro and in vivo. Overall, almost all evaluated lncRNAs were found upregulated. HOTAIR was one of the mostly described lncRNAs, reported to participate in different ceRNA axes: HOTAIR/miR-23b/*MAPK1* [37], HOTAIR/miR-206/*MKL1* [38], HOTAIR/miR-148a/*HLA-G* [39], and HOTAIR/miR-143-3p/*BCL2* [40].

In agreement, the respective involved mRNAs were found upregulated under the same conditions, while their 'matching' miRNAs were found downregulated. Consequently, a significantly positive correlation between the involved lncRNA and mRNA as well as a negative correlation between the lncRNA and miRNA (or between the miRNA and mRNA, when applicable) were also reported through experiments involving patient's samples. On

the other hand, GAS5, PTENP1, STXBP5-AS1, TUSC8, WT1-AS, and ZNF667-AS1 were downregulated in CC samples in comparison to NTT [35,56,65,70,71,74], and opposing patterns/correlations between them and the components of the different ceRNA axes that they take part in were observed in comparison to the ones mentioned above. Therefore, this, once again, highlights their tumor-suppressive role.

Table 3. Studies validating the involvement of the lncRNA-mediated ceRNA networks in patients with CC.

	Sample Description							Observed Results
LncRNA-Mediated ceRNA Networks [Ref]	**Population**	**CC (n)**	**SCC (n)**	**AD (n)**	**NTT (n)**	**Normal (n)**	**SIL/CIN (n)**	**Expression Levels of Target Molecules (RNAs by RT-qPCR/Proteins by WB)**
BBOX1-AS1/miR-361-3p/*HOXC6* [29]	C	100	-	-	100	-	-	BBOX1-AS1 (Up), miR-361-3p (Down), HOXC6 (Up)
C5orf66-AS1/miR-637/*RING1* * [30]	C	20	-	-	20	-	-	C5orf66-AS1 (Up), miR-637 (Down)
CTS/miR-505/*ZEB2* [31] **	C	-	50	-	-	50	-	CTS (Up), miR-505 (Down)
DANCR/miR-335-5p/*ROCK1* [32]	C	65	-	-	65	-	-	DANCR (Up), miR-335-5p (Down), *ROCK1* (Up)
DANCR/miR-665/*TGFBR1* [33]	C	33	-	-	33	-	-	DANCR (Up), miR-665 (Down), *TGFBR1* mRNA (Up)
DLG1-AS1/miR-107/*ZHX1* [34]	C	112	-	-	112	-	-	DLG1-AS1 (Up), miR-107 (Down), *ZHX1* mRNA (Up)
GAS5/miR-196a/*FOXO1* [35] ***	C	41	-	-	41	-	-	GAS5 (Down)
GAS5/miR-205/*PTEN* [35] ***	C	41	-	-	41	-	-	GAS5 (Down)
HCP5/miR-15a/*MACC1* [36]	C	48	-	-	48	-	-	HCP5 (Up), miR-15a (Down), *MACC1* mRNA (Up)
HOTAIR/miR-23b/*MAPK1* * [37]	C	33	-	-	33	-	-	HOTAIR (Up), miR-23b (Down)
HOTAIR/miR-206 */*MKL1* [38]	C	31	-	-	31	-	-	HOTAIR (Up), *MKL1* mRNA (Up)
HOTAIR/miR-148a/*HLA-G* [39]	C	59	50	09	59	-	-	HOTAIR (Up), miR-148a (Down), *HLA-G* mRNA (Up), HLA-G protein (Up)
HOTAIR/miR-143-3p/*BCL2* [40]	C	22	-	-	22	-	-	HOTAIR (Up), miR-143-3p (Down)
LINC00152/miR-216b-5p/*HOXA1* [41]	C	20	-	-	20	-	-	LINC00152 (Up), miR-216b-5p (Down), *HOXA1* (Up)
LINC00467/miR-107/*KIF23* [42]	C	54	-	-	54	-	-	LINC00467 (Up), miR-107 (Down), *KIF23* mRNA (Up), KIF23 protein (Up)
LINC00483/miR-508-3p/*RGS17* [43]	C	40	38	02	40	-	-	LINC00483 (Up), miR-508-3p (Down), *RGS17* (Up)
LINC01128/miR-383-5p/*SFN* [44]	C	33	10	23	33	-	-	LINC01128 (Up), miR-383-5p (Down), *SFN* (Up)
LINC01535/miR-214/*EZH2* [45]	C	80	55	25	80	-	-	LINC01535 (Up), miR-214 (Down)
MALAT1/miR-202-3p/*POSTN* [46]	C	23	-	-	23	-	-	MALAT1 (Up), miR-202-3p (Down), *POSTN* mRNA (Up), Periostin (Up)
MALAT1/miR-124/*GRB2* [47]	C	22	-	-	-	22	-	MALAT1 (Up), miR-124 (Down)
NEAT1/miR-9-5p/*POU2F1* [48]	C	50	-	-	50	-	-	NEAT1 (Up), miR-9-5p (Down)
NEAT1/miR-9-5p/*PTEN* [48]	C	50	-	-	50	-	-	NEAT1 (Up), miR-9-5p (Down)
NEAT1/miR-101/*FOS* [49]	C	68	50	18	68	-	-	NEAT (Up), miR-101 (Down)
NORAD/miR-590-3p/*SIP1* [52]	C	47	34	13	47	-	-	NORAD (Up), miR-590-3p (Down)
OIP5-AS1/miR-143-3p/*SMAD3* [53]	C	16	-	-	15			OIP5-AS1 (Up), miR-143-3p (Down), *SMAD3* (Up)
OIP5-AS1/miR-143-3p/*ROCK1* [54]	C	20	-	-	20	-	-	OIP5-AS1 (Up), *GAPDH* (Up)
POU3F3/miR-127-5p/*FOXD1* [55]	C	36	-	-		36	-	POU3F3 (Up)
PTENP1/miR-106b/*PTEN* [56] ***	C	54	-	-	54	-	-	PTENP1 (Down), miR-106b (Up), *PTEN* mRNA (Down), PTEN protein (Down)
RP11-552M11.4/miR-3941/*ATF1* [57]	C	92	44	48	92	-	-	RP11-552M11.4 (Up), mir-3941 (Down), *ATF1* mRNA (Up)
RSU1P2/let-7a/*IGF1R* [58]	C	14	-	-	14	-	-	RSU1P2 (Up), let-7a (Down), *IGF1R* (Up)
RSU1P2/let-7a/*NMYC* [58]	C	14	-	-	14	-	-	RSU1P2 (Up), let-7a (Down), *NMYC* (Up)
RSU1P2/let-7a/*EPHA4* [58]	C	14	-	-	14	-	-	RSU1P2 (Up), let-7a (Down), *EPHA4* (Up)
SBF2-AS1/miR-361-5p/*FOXM1* [59]	C	66	-	-	66	-	-	SBF2-AS1 (Up), miR-361-5p (Down), *FOXM1* mRNA (Up)
SNHG4/miR-148a-3p/*MET 1* [60]	R	-	27	-	27	-	-	SNHG4 (Up), miR-148a-3p (Down)
SNHG14/miR-206/*YWHAZ* [62]	C	80	46	34	80	-	-	SNHG14 (Up), miR-206 (Down), *YWHAZ* mRNA (Up)
SNHG20/miR-140-5p/*ADAM10* [63]	C	93	-	-	93	-	-	SNHG20 (Up), miR-140-5p (Down), *ADAM10* mRNA (Up)
SOX21-AS1/miR-7/*VDAC1* [64]	C	160	-	-	160	-	-	SOX21-AS1 (Up)
STXBP5-AS1/miR-96-5p/*PTEN* [65] ***	C	37	-	-	37	-	-	STXBP5-AS1 (Down), miR-96-5p (Up), *PTEN* (Down)
TCONS_00026907/miR-143-5p/*ELK1* [66]	C	83	56	27	83	-	-	TCONS_00026907 (Up)
TDRG1/miR-326/*MAPK1* [67]	C	30	-	-	-	30	-	TDRG1 (Up), miR-326 (Down), *MAPK1* mRNA (Up), MAPK1 protein (Up)
TP73-AS1/miR-329-3p/*SMAD2* [68]	C	30	-	-	-	30	-	TP73-AS1 (Up), miR-329-3p (Down)
TTN-AS1/miR-573/*E2F3* [69]	C	45	34	11	45	-	-	TTN-AS1 (Up), miR-573 (Down), *E2F3* mRNA (Up)
TUSC8/miR-641/*PTEN* [70] ***	C	40	-	-	40	-	-	TUSC8 (Down), miR-641 (Up), *PTEN* mRNA (Down), PTEN protein (Down)
WT1-AS/miR-203a-5p/*FOXN2* [71] ***	C	47	-	-	47	-	-	*WT1-AS* mRNA (Down), WT1-AS protein (Down) [1]
XIST/miR-200a/*FUS* [72]	C	52	-	-	52	-	-	XIST (Up), miR-200a (Down), *FUS* mRNA (Up)
XIST/miR-140-5p/*ORC1* [73]	C	30	14	16	30	-	-	XIST (Up), miR-140-5p (Down), *ORC1* mRNA (Up)
ZNF667-AS1/miR-93-3p/*PEG3* [74] ***	C	64	43	21	64	-	-	ZNF667-AS1 (Down), miR-93-3p (Up), *PEG3* (Down)

C = Chinese; R = Russian; ceRNA = competing endogenous RNA; [ref] = reference; - or X = not performed; ✓ = performed; CC = cervical cancer; RT-qPCR = reverse transcription quantitative polymerase chain reaction; WB = Western blotting; SCC = squamous cell carcinoma; AD = adenocarcinoma; NTT = nontumor tissues; SIL/CIN = squamous intraepithelial lesion/cervical intraepithelial neoplasia; Up = upregulated; Down = downregulated. Some references do not use adjacent NTT but, instead, normal cervix (or healthy controls). * Other candidate RNAs were tested by RT-qPCR, although not validated. No reference has evaluated the expression of the involved RNAs at the serum/plasmatic level (nor in any other biofluid). ** The article mentions a serum measurement, although not clearly explained/presented. *** Those ceRNA axes seem not to be occurring in CC tissue since these lncRNAs and mRNAs are downregulated in such context; contrarily, they seem to be predominantly occurring in NTT. [1] The expression of WT1-AS in cervical cancer tissues was checked by in situ hybridization. Here, miRNA nomenclature was reproduced exactly as mentioned by the author in the respective article (thus, not all follow miRBase's most recent IDs). For further information, consult the miRBase platform. All the abovementioned miRNAs are hsa-miRNAs (*Homo sapiens* miRNAs). The lncRNA nomenclature applied here was reproduced exactly as mentioned by the author in the respective article and is better described in the list of abbreviations (except for some lncRNAs such as RP11-552-M11.4 and TCONS_0026907, which correspond to transcript codes).

Interestingly, some references also measured the final 'mRNA product'—the expression of the respective protein. In CC samples, in comparison to NTT, HLA-G [39], KIF23 [42], MAPK1 [67], and periostin (POST) [46] were found overexpressed, while PTEN was found underexpressed [56,70], at the protein level, in agreement with what had been seen at the mRNA level. No reference assessed the serum/plasma expression level of the involved lncRNA in the CC cases and age-matched controls.

Collectively, we observed that different lncRNA-mediated ceRNA axes seem to be closely associated with CC. Together, such observations demonstrate the abnormal patterns of gene expression of the different molecular components involved in the diverse lncRNA-mediated ceRNA networks described here, suggesting their important role in cervical carcinogenesis.

5. Important Cancer-Related RNAs Working through Different lncRNA-Mediated Axes in CC

Apart from unveiling important ceRNA networks involved in cervical carcinogenesis, we also aimed to highlight some important molecules that work through distinct lncRNA-mediated ceRNA networks. Some are very well described oncogenic RNAs in different cancers, while others have emerged as novel cancer-related RNAs, highly deregulated in a variety of cancers. Table 4 summarizes important details about the involved RNAs.

Table 4. Main biological roles, pathways, and the oncogenic/tumor-suppressive status of important RNAs involved in lncRNA-mediated axes in CC.

Molecule	Biological Role	Oncogene or TS Role		Reference
		Cancer	CC	
LncRNA				
HOTAIR	HOTAIR binds LSD1 and PRC2 and serves as a scaffold to assemble these regulators at the *HOXD* gene cluster, thereby promoting epigenetic repression of *HOXD*	Oncogene	Oncogene	[77–82]
MALAT1	MALAT1 is retained in the nucleus, where it is thought to form molecular scaffolds for ribonucleoprotein complexes. It may act as a transcriptional regulator for numerous genes, including some genes involved in cancer metastasis and cell migration, and it is involved in cell cycle regulation.	Oncogene	Oncogene	[77,83–85]
NEAT1	NEAT1 is retained in the nucleus, where it forms the core structural component of the paraspeckle suborganelles. It may act as a transcriptional regulator for numerous genes, including some genes involved in cancer progression.	Oncogene	Oncogene	[84,86,87]
OIP5-AS1	OIP5-AS1 maintains cell proliferation in embryonic stem cells and can bind to and negatively regulate the activity of multiple cellular RNAs and microRNAs, including cyclin G associated kinase and HuR	Oncogene	Oncogene	[84,88]
XIST	Besides regulating X chromosome inactivation, XIST is a classic example of how lncRNAs can exert multilayered and fine-tuned regulatory functions by acting as a molecular scaffold for the recruitment of distinct protein factors as well as acting as a transcriptional regulator for numerous genes	Oncogene	Oncogene	[84,89,90]
miRNA				
miR-140-5p	Inhibition of cell proliferation, migration, and invasion, as well as induction of apoptosis	TS	TS	[63,73,91–95]
miR-143-3p	Inhibition of cell proliferation, migration, and invasion, as well as induction of apoptosis	TS	TS	[40,54,96–102]
miR-148a-3p *	Inhibition of cell proliferation, migration, and invasion, as well as induction of apoptosis/promotion of cell proliferation	Oncogene/TS	TS	[39,60]
miR-206	Inhibition of cell proliferation, migration, and invasion, as well as induction of apoptosis	TS	TS	[62,103–105]
mRNA/Protein				
***MAPK1*/MAPK1**	MAPK1 is part of the MAPK pathway—an important bridge in the switch from extracellular signals to intracellular responses—that is ultimately involved in stimulating cell proliferation and differentiation as well as modulating transcription regulation and development	Oncogene	Oncogene	[106,107]
***PTEN*/PTEN**	PTEN is a very well-described tumor-suppressive protein, regulating proliferation and cell survival	TS	TS/Oncogene **	[108–110]
***ROCK1*/ROCK1**	ROCK1 is part of the ROCK family, which plays a central role in the organization of the actin cytoskeleton and is involved in a wide range of fundamental cellular functions. Stimulates tumor growth, angiogenesis, and metastasis.	Oncogene	Oncogene	[111–113]

CC = cervical cancer; LSD1 = lysine-specific demethylase 1; PRC2 = polycomb repressive complex 2; *HOXD* = homeobox D Cluster; HuR = ELAV-like RNA-binding protein 1; ROCK = Rho-associated coiled-coil kinase; TS = tumor suppressor. * miR-148a and miR-148a-3p represent the same miRNA. ** PTEN's overexpression (as a consequence of NEAT1 sponging miR-9-5p) ultimately promoted CC cell growth, therefore presenting an oncogenic role. Despite its classical ability to regulate proliferation and cell survival, PTEN also seems to play different intriguing roles under different cellular contexts, which may, in part, explain such contradictory patterns. However, as only one

study reported such an effect, more experiments are necessary in order to corroborate this result. Here, miRNA nomenclature was reproduced exactly as mentioned by the author in the respective article (thus, not all follow miRBase's most recent IDs). For further information, consult the miRBase platform. All the abovementioned miRNAs are hsa-miRNAs (*Homo sapiens* miRNAs). The lncRNA nomenclature applied here was reproduced exactly as mentioned by the author in the respective article and is better described in the list of abbreviations (except for some lncRNAs such as RP11-552-M11.4, and TCONS_0026907, which correspond to transcript codes).

5.1. HOTAIR, MALAT1, NEAT1, OIP5-AS1, and XIST

Among several lncRNAs, HOTAIR, MALAT1, NEAT1, OIP5-AS1, and XIST stood out as important players in different lncRNA-mediated ceRNA networks in CC. Interestingly, HOTAIR was the most described lncRNA, leading different ceRNA axes. All references investigating HOTAIR's role in CC performed in silico predictions and pointed to interesting molecular targets, which were confirmed by in vitro experiments. Furthermore, HOTAIR overexpression was found to increase cell proliferation [37,39,40], migration/invasion [37,38], and prevent apoptosis [37,39,40] through different ceRNA axes. In vivo experiments also confirmed HOTAIR's ability to promote CC tumor growth [37,39,40]. Additionally, HOTAIR expression in CC tissues, in comparison to adjacent normal tissues, was found upregulated in all studies. Therefore, HOTAIR seems to be closely related to CC development. In fact, HOTAIR is a very well-described oncogenic lncRNA in different cancers [114] and by far the most studied lncRNA involved in CC [79,84,115].

NEAT1 and XIST were also reported by independent studies as participating in more than one ceRNA network, exerting protumorigenic effects. NEAT1 has emerged as a novel cancer-related lncRNA [86], highly de/upregulated in a variety of cancers [87]. Similarly, the high expression of XIST has been associated with poor prognosis and metastasis in different cancer types, representing a predictive factor of poor prognosis in human cancers [89,90]. In fact, both have been described as crucial modulators in several cellular processes, influencing cervical oncogenesis [84]. Through in silico predictions and in vitro experiments, the molecular interactions between NEAT1- and XIST-mediated axes were confirmed. As for HOTAIR, such interactions were associated with an increase in cell proliferation, colony formation, and invasion and/or migration [48–50,72,73], together with the inhibition of apoptosis [49,50,72,73]. NEAT1 and XIST also promoted CC tumor growth [50,73] in vivo and were found upregulated in CC tissues in comparison with adjacent normal tissues [48,49,72,73], confirming the oncogenic role of both lncRNAs in CC.

Additionally, MALAT1 and OIP5-AS1 also stood out as important lncRNAs involved in different lncRNA-mediated ceRNA axes. Likewise, they were found to stimulate cell proliferation, invasion and/or migration [46,47,53,54], and prevent apoptosis [47,54] through different ceRNA axes, and were found upregulated in CC tissues in comparison with adjacent normal tissues [46,47,53,54]. Both seem to have an important role in cancer [88,116] and cervical carcinogenesis [84]. Differently from HOTAIR, NEAT1 and XIST, the protumorigenic effects of MALAT1 and OIP5-AS1 on cancer, in general, and on CC are still emerging.

5.2. MiR-140-5p, miR-143-3p, miR-148a-3p, and miR-206

In the same manner, shared miRNAs such as miR-140-5p, miR-143-3p, miR-148a-3p, and miR-206 take part in different lncRNA-mediated ceRNA networks. MiR-140-5p is a well-known tumor-suppressive miRNA, presenting the ability to inhibit cell proliferation, migration, and invasion as well as to induce apoptosis in different cancers [91–95]. Accordingly, a decreased expression of miR-140-5p has been described in cancer clinical samples in comparison to adjacent normal tissues [91–94]. In CC, miR-140-5p was also found downregulated [63,73,117], and sponged by different lncRNAs [63,73] and, therefore, hindered from negatively regulating *ADAM10* and *ORC1* expression.

Another important tumor-suppressive miRNA, impaired from regulating crucial target mRNAs (such as *BCL2*, *ROCK1*, and *SMAD3*), is miR-143-3p. Sponged by several lncRNAs in CC, miR-143-3p was found downregulated in cervical tumor samples in comparison to adjacent normal tissues [40,53,54]. Similarly, miR-143-5p was downregulated in CC, sponged by TCONS_00026907 [66]. Therefore, both miR-143 strands seem to present tumor-suppressive abilities in CC as well as in different cancer types [97–102]. Likewise,

miR-206 takes part in different ceRNA axes [38,62], being impaired from negatively regulating important target mRNAs such as *MKL1*. MiR-206 was found to inhibit cell proliferation, migration, and/or invasion in CC through different molecular interactions [104,105,118].

Similarly, mir-148a-3p (or miR-148a) was reported as an important molecular target of HOTAIR and SNHG4, consequently blocking *HLA-G* and *MET* expression modulation [39,60], which ultimately led to CC progression. Despite its tumor-suppressive role in CC, mir-148a-3p was found to be aberrantly expressed in various cancers, having been identified as a tumor suppressor and also as an oncogenic miRNA, depending on the molecular context [119]. Other miRNAs such as let-7a, and miR-9-5p were involved in distinct ceRNA axes, although this was investigated by the same reference [48,58]. Despite the evidence, the role of such miRNAs in CC development is not quite established.

5.3. MAPK1, PTEN, and ROCK1

Likewise, coinciding mRNAs participating in more than one ceRNA axis were also observed, such as *MAPK1*, *PTEN*, and *ROCK1*. For instance, *MAPK1* was reported as competing for different miRNAs with HOTAIR [37] and TDRG1 [67]. As HOTAIR and TDRG1 sponge miR-23b and miR-326, respectively, *MAPK1* translation was expected to be stimulated. In fact, MAPK1 was upregulated (at both the mRNA and protein levels) in CC in comparison to matched controls [67]. Similarly, *ROCK1* also caught our attention, taking part in two different ceRNA networks and being upregulated in CC in comparison to normal samples [32,54]. Accumulating evidence supports MAPK1 and ROCK1 oncogenic roles, which corroborates the results previously presented.

Additionally, *PTEN* was reported as participating in different axes [35,48,56,65,70]. As for MAPK1, PTEN was also deregulated at both the mRNA and protein levels, although exhibiting a different expression pattern (*PTEN* mRNA/PTEN protein were downregulated in CC in comparison to their matched controls) [56,70], suggesting that such ceRNA axes occurs primarily in normal tissue (see Section 6). Classically, PTEN is a well-described tumor-suppressive protein [108–110], and PTEN underexpression in CC cells/tissue corroborates such a statement. Intriguingly, PTEN overexpression (as a consequence of NEAT1 sponging miR-9-5p) ultimately promoted CC cell growth [48]. Despite its classical ability to regulate proliferation and cell survival, PTEN also seems to play different intriguing roles under different cellular contexts [120], which may, in part, explain such opposing patterns. However, as only one study reported such an effect, more experiments are necessary in order to corroborate this result.

6. Protumorigenic and Tumor-Suppressive lncRNA-Mediated ceRNA Axes Involved in Cervical Carcinogenesis

Ultimately, after carefully looking at individual lncRNA-mediated ceRNA networks as well as important molecules working through those axes, it is also relevant to define general patterns. Although quite a challenge, after carefully gathering all the results, two major patterns were observed: one with particular molecular endogenous competitions occurring predominantly in CC, highly associated with a protumorigenic final effect (Figure 2), and another with such molecular interactions most likely occurring in a normal cervical cell, with the lack of such competitions being associated with CC (Figure 3).

Mainly, we observed lncRNA-mediated axes with a protumorigenic role, with their respective lncRNAs (and mRNAs) being significantly upregulated in CC cell lines in comparison to control cell lineages, while their ‘matching’ miRNA was significantly downregulated under the same conditions. Predominantly, such lncRNA-mediated ceRNA axes led to a final state of sustained proliferative signaling, allowed replicative immortality, resisted cell death, and showed ‘signs’ of presenting the ability to activate (or somehow being associated with) migration/invasion and metastasis—classical cancer hallmarks. Furthermore, they were found to stimulate cell proliferation and cervical tumor growth (in vivo) and were ultimately detected in patients’ biological samples. HOTAIR-, MALAT-1-NEAT1-, OIP5-AS1, and XIST-mediated ceRNA axes were widely reported as presenting protumorigenic roles in CC.

Contrarily, some axes led by GAS5 [35], PTENP1 [56], STXBP5-AS1 [65], TUSC8 [70], WT1-AS [71], and ZNF667-AS1 [74] seemed to be 'inactive' in CC cells/tissue/patients' samples. In fact, such lncRNAs (and mRNAs participating in their respective ceRNA axes, when applicable) were scarce in CC cells, impairing the 'endogenous competition'. Overall, when overexpressed, they inhibited cell proliferation and/or colony formation and/or invasion/migration and increased apoptosis. In addition, GAS5, WT1-AS, and ZNF667-AS1 were found to inhibit tumor growth in vivo [35,71,74]. The patterns of correlation between the involved molecules were the same as for 'protumorigenic' axes, as expected, considering the ceRNA hypothesis. Together, such results suggest that these particular molecular competitions have the potential to occur, although they do not seem to be occurring (or broadly occurring) in CC cells/tissue/patients' samples since the involved lncRNAs are downregulated (and consequently 'unable' to sponge their 'matching' miRNAs). Accordingly, such specific endogenous competitions seem to primarily take place in normal tissue, being particularly important for cervical homeostasis.

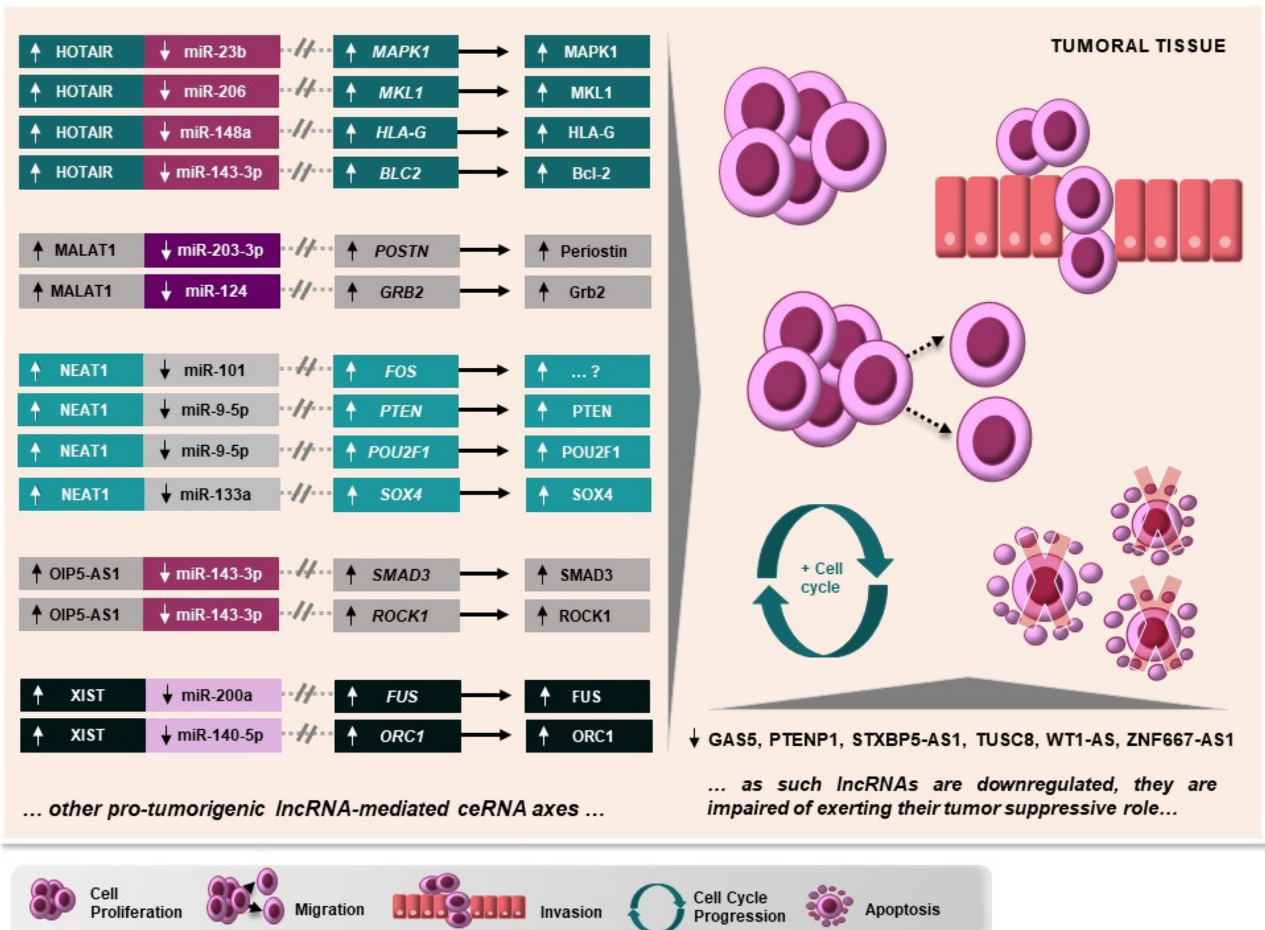


Figure 2. LncRNA-mediated ceRNA crosstalk in tumoral cervical tissue. Some lncRNA-mediated ceRNA axes (led by upregulated lncRNAs, as HOTAIR, MALAT1, NEAT1, OIP5-AS1, and XIST) seem to primarily take place in tumoral tissue, leading to a state of constant cell proliferation and cell cycle progression, inducing migration/invasion, and preventing apoptosis. Note that as tumor-suppressive lncRNAs such as GAS5, PTENP1, STXBP5-AS1, TUSC8, WT1-AS, and ZNF667-AS1 are downregulated in cervical tumoral tissue, they are impaired from exerting a final tumor-suppressive effect through different lncRNA-mediated ceRNA axes. The protein FOS is represented by a question mark (?) in order to emphasize that, although it has not yet been investigated, it probably presents a deregulated pattern of expression, as observed for the respective gene that codes this specific protein.

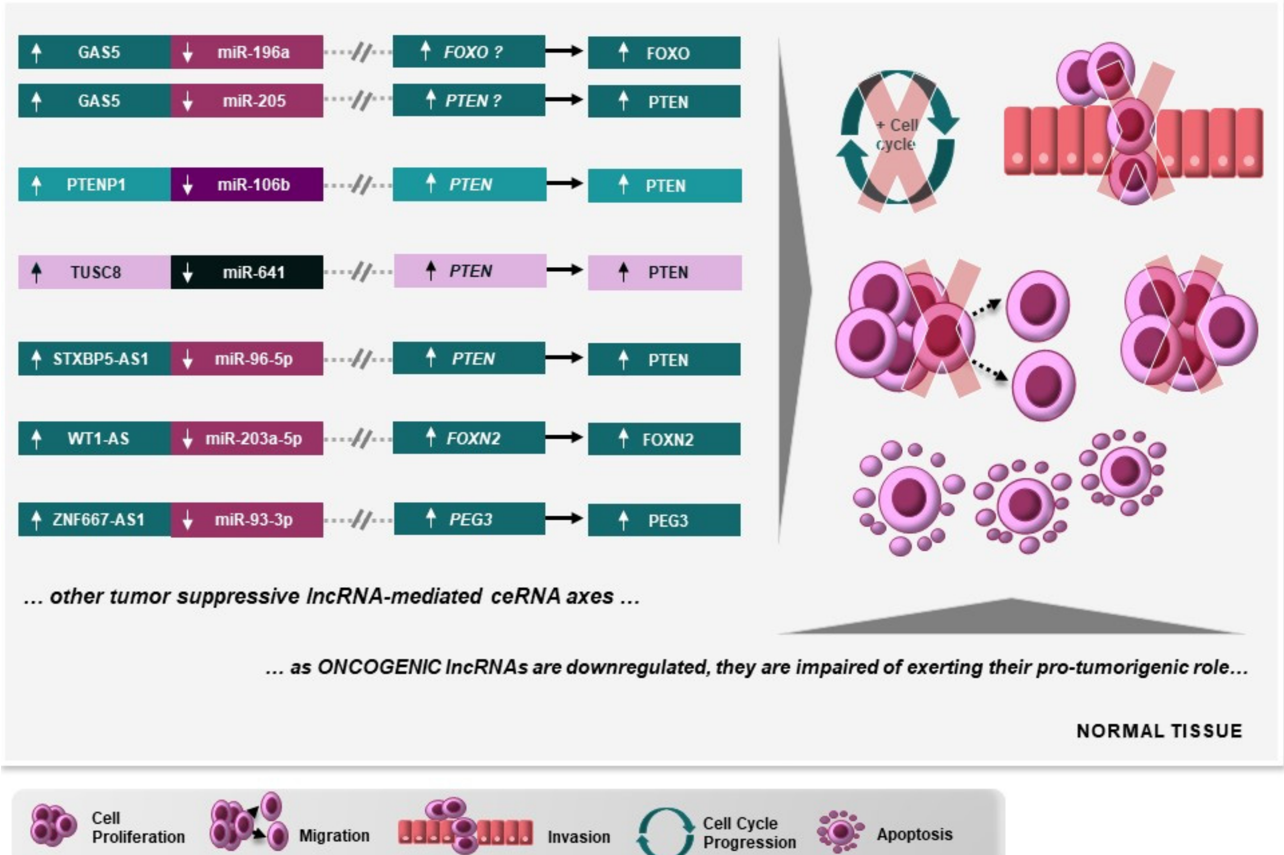


Figure 3. LncRNA-mediated ceRNA crosstalk in normal cervical tissue. Some lncRNAs, such as GAS5, PTENP1, STXBP5-AS1, TUSC8, WT1-AS, and ZNF667-AS1, are abundant in a normal cervical cell and may compete for 'matching' miRNA(s), acting as molecular sponges, indirectly regulating protein-coding gene expression by increasing translation. Consequently, through such interactions, they seem to inhibit abnormal cell proliferation and migration/invasion and to stimulate apoptosis, ultimately maintaining cervical tissue homeostasis. Note that as oncogenic lncRNAs such as HOTAIR, MALAT1, NEAT1, OIP5-AS1, and XIST are downregulated in normal cervical tumoral tissue, they are impaired from exerting a protumorigenic effect through different lncRNA-mediated ceRNA networks. Potential target mRNAs are represented by a question mark (?) in order to emphasize that, although they have not yet been investigated by the included references, they probably present a deregulated pattern of expression, as observed for the respective proteins coded by these genes.

Additionally, despite primarily occurring in tumoral tissue or nontumoral tissue, driving the development of CC or guaranteeing cervical homeostasis, we understand that different intensities of endogenous competition may occur in different cellular microenvironments since we are not dealing with a 'binary condition'. Thus, intermediate patterns of expression may be associated with greater or lesser competition, considering different ceRNA axes. In such a context, the relative concentration of the involved ceRNAs and their target miRNAs seem to be crucial for the occurrence (or not) of a particular ceRNA network [8]. Moreover, depending on the molecules involved, different responses may also occur (as a consequence of the similarity between the molecules and their availability to allow for such competition). It is important to consider aspects such as the available number and sets of MREs (since different transcripts may host different numbers and types of MREs in their 3′UTR) and the accessibility of those MREs (for instance, lncRNAs may present different structural forms with different binding partners, which may also influence the accessibility of specific miRNA molecules). Another interesting observation is the fact that different axes are comprised of different components. Such diversity is already expected once one ncRNA may regulate different other ncRNAs and/or mRNAs (proteins).

At the cellular level, an influence of the subcellular localization of the involved ceRNAs and miRNAs may be of great importance. Since different ceRNAs and miRNAs present different patterns of expression between different subcellular compartments in a given cell type at a given moment [121–124], subcellular localization stands as one of the many important factors influencing the occurrence (or not) of different ceRNA networks.

7. Remarks and Perspectives

Despite the recent advances toward understanding the molecular basis of CC, solid knowledge on the role of ncRNAs in such context and their involvement in important molecular networks and biological processes is still scarce. Once considered 'junk' sequences, ncRNAs have recently emerged as 'treasure' [125], standing as important key players in gene regulatory networks. Such molecules work in integrated networks, together with other biomolecules, including coding and other ncRNAs, DNA, and proteins [24]. Among them, ceRNAs have emerged as important post-transcriptional regulators that alter gene expression through a miRNA-mediated mechanism [13], playing a crucial role in both homeostasis and tumorigenesis [25]. In fact, the disruption of the equilibrium of ceRNAs and miRNAs seems to be critical for the activity of multiple ceRNA networks, influencing the outcome of several diseases, including cancer [126].

In the present review, we have comprehensively summarized different lncRNA-mediated ceRNA axes and promising ceRNA networks involved in cervical carcinogenesis as well as highlighted their major impacts on dynamic molecular changes over important cellular processes. Despite such effort, we emphasize the urgent need for more studies investigating ceRNA networks in CC. Collectively, with new studies investigating overlapping ncRNAs (and mRNAs) and consolidating the molecular basis of the ceRNA theory, it will be possible to reinforce some of the evidence presented here and better understand the importance of these networks in CC development and/or progression.

Consequently, the potential application of such molecules in CC screening (diagnosis, prognosis) will become more achievable. Indeed, it is important to highlight that the ceRNA model not only suggests the existence of a complex regulatory network in cancer but also implies the possibility of using a panel of network molecules to diagnose and predict cancer [127]. Additionally, the future use of such targets, focusing on therapeutic strategies for CC treatment, is also likely to occur. Different RNA-based strategies have emerged in the past few years [128], with several RNA-based products, mostly ncRNAs, successfully approved for clinical use [129,130]. Therefore, the use of the ceRNA concept, focusing on therapeutics, is also a reasonable possibility. For example, the use of artificial miRNA sponges containing various miRNA binding sites, mimicking the characteristics of ceRNAs as miRNA inhibitors, could be an interesting strategy for 'silencing' axes with upregulated miRNAs. Depending on the final desired effect, different strategies might be adopted. Together, they could represent new platforms for RNA-based therapeutic applications.

Finally, as limitations observed through the careful analysis of the included articles, it is important to mention that, with the exception of one, all other studies included patients' samples from the Chinese population. This represents an important limitation in the field of ceRNAs in CC. For sure, it is of great importance to study different populations, especially considering the existence of differential genetic backgrounds among them. Genetic variants may lead to different individual responses that may impact the course of the disease. Additionally, not discriminating among CC histological types, as well as the involved HPV type, may also be of important concern since we understand that different ceRNA axes may be associated with these different parameters. The lack of information on the ceRNAs' and miRNAs' subcellular localization and their relative abundance (i.e., the molecular ratio between them) also represents a limitation; it would be very enlightening to access such parameters. Overall, we observed problems concerning the adequate description of the employed methods and samples. All the abovementioned problems may be easily addressed, and we encourage future studies to more carefully present methods/results. This is important in order to standardize the included strategies, facilitating a better overview of the topic.

8. Conclusions

The involvement of ceRNA networks in cancer is an emerging topic, and their role in CC progression/development is becoming clearer. In the ceRNA hypothesis, lncRNAs and mRNAs act as 'players' competing for their common pair(s)—their 'matching' miRNA(s). Subsequently, changes in gene expression at the mRNA level may occur, affecting the overall activity and functional balance of gene networks in a cell. Essentially, this is a recent research field, with few studies investigating some of the many possible ceRNA axes involved. Despite that, the importance of these ceRNA networks in cervical carcinogenesis has already been demonstrated. Through an extensive literature search, we summarized previously described functional interactions between lncRNAs and miRNAs, focusing on lncRNA-mediated ceRNA networks involved in CC. Several axes seem to contribute to CC progression/development, while others seem to be important for cervical homeostasis maintenance. In the future, such molecular networks may present a potential application in CC screening (diagnosis, prognosis), and they may become important therapeutic targets for CC. Despite the enthusiasm, it is still an enormous challenge to fully understand the ceRNA regulatory networks in CC, and it will be quite a long journey, although a worthy and exciting one.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/pr9060991/s1. Table S1: Quality assessment form used to evaluate the quality of the included studies. Table S2: Molecular interactions of different lncRNA-mediated ceRNA networks involved in CC (in vitro strategies). Table S3: Biological effects promoted by different lncRNA-mediated ceRNA networks (in vivo strategies).

Author Contributions: Conceptualization, F.C.B.B., G.A.C., and D.M.; Methodology, F.C.B.B., C.d.F.O.-T., and P.S.d.A.-S.; Formal Analysis, F.C.B.B., S.C.L.-A., C.d.F.O.-T., A.S.-S., K.B.d.O., P.S.d.A.-S., G.A.C., and D.M.; Data, Curation, F.C.B.B. and S.C.L.-A.; Writing—Original Draft Preparation, F.C.B.B., S.C.L.-A., and J.K.P.; Writing—Review and Editing, P.S.d.A.-S., J.K.P.; G.A.C., and D.M.; Supervision, G.A.C. and D.M.; Project Administration, F.C.B.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES/PROAP—Finance Code 001) and a National Research Foundation of Korea (NRF) grant by the Korea government (MSIT) (2019R1A2C1089710).

Institutional Review Board Statement: Ethical review and approval were waived for this study, due to the fact that the present work is a review article, and approval has already being declared in each of the particular studies cited here.

Informed Consent Statement: Patient consent was waived due to the fact that the present work is a review article, and formal consent has already being obtained and declared in each of the particular studies cited here.

Data Availability Statement: The data presented in this study are available in the supplementary material.

Acknowledgments: We thank the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES/PROAP—Finance Code 001) for their financial support and the scholarships provided to F.C.B.B., C.d.F.O.T., and G.A.C. (postdoctoral scholarship, CAPES protocol 88882.306040/2018-01) and the Korean government for their financial support.

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

Abbreviations

ADAM10, ADAM Metallopeptidase Domain 10; AD, adenocarcinoma; ATF1, Activating Transcription Factor 1; BACE1, Beta-Secretase 1; BACE1-AS, BACE1 Antisense RNA; BBOX1-AS1, BBOX1 Antisense RNA 1; BCL2, B-cell lymphoma 2; C5orf66-AS1, C5orf66 Antisense RNA 1; CC, cervical cancer; ceRNA, competing (or competitive) endogenous RNA; ChIP, Chromatin Immunoprecipitation assay; CIN, Cervical intraepithelial neoplasia; CTS, lncRNA cancer-associated by transforming

growth factor (TGF)-β stimulation; DANCR, Differentiation Antagonizing Non-Protein Coding RNA; DLG1-AS1, DLG1 antisense RNA 1; E2F3, E2F Transcription Factor 3; ELK1, ETS Transcription Factor ELK1; End1/E6E7, Human epithelial HPV-16 E6/E7 transformed cells; EPHA4; EPH Receptor A4; EMT, epithelial–mesenchymal transition; ERK, extracellular signal-regulated kinase; EZH2, Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit; FOS, Fos Proto-Oncogene, AP-1 Transcription Factor Subunit; FOXD1, Forkhead Box D1; FOXM1, Forkhead Box M1; FOXN2, Forkhead box protein N2; FOXO, Forkhead Box O; FUS, FUS RNA Binding Protein; GAPDH, Glyceraldehyde-3-Phosphate Dehydrogenase; GAS5, Growth Arrest Specific 5; GRB2, Growth Factor Receptor Bound Protein 2; H19, H19 Imprinted Maternally Expressed Transcript; HCP5, HLA Complex P5; HPV, Human Papillomavirus; HR-HPV, High-risk Human Papillomavirus; HLA-G, Major Histocompatibility Complex, Class I, G; HOTAIR, HOX Transcript Antisense RNA; HOXC6, Homeobox C6; HOXD = Homeobox D Cluster; HuR, ELAV like RNA binding protein 1; IGF1R, Insulin Like Growth Factor 1 Receptor; IHC, Immunohistochemistry; KIF23, kinesin family member 23; LINC00152, Long intergenic non-coding RNA 152; LINC00467, Long intergenic non-coding RNA 467; LINC00483, Long intergenic non-coding RNA 483; LINC01128, Long intergenic non-coding RNA 1128; LINC01535, Long Intergenic Non-Protein Coding RNA 1535; lncRNA, long noncoding RNA; LSD1 = lysine specific demethylase 1; LUC, Luciferase Reporter assay; MACC1, MET Transcriptional Regulator MACC1; MALAT1, Metastasis Associated Lung Adenocarcinoma Transcript 1; MET, MET Proto-Oncogene, Receptor Tyrosine Kinase; MMP2, matrix metalloproteinase-2; MMP9, matrix metalloproteinase-9; MAPK, Mitogen-Activated Protein Kinase; MAPK1, Mitogen-Activated Protein Kinase 1; mRNA, messenger RNAs; miRNA, microRNA; MRE, miRNA recognition elements; MKL1, Megakaryoblastic leukemia protein-1; MTA1, metastasis-associated protein 1; NEAT1, Nuclear Paraspeckle Assembly Transcript 1; NMYC, MYCN Proto-Oncogene, BHLH Transcription Factor; NOC2L, NOC2 like nucleolar Associated Transcriptional Repressor; ncRNA, non-coding RNA; NTT, non-tumor tissues; NORAD, Non-coding RNA Activated By DNA Damage; ORC1, Origin Recognition Complex Subunit 1; PCNA, Proliferating cell nuclear antigen; PEG3, Paternally-expressed gene 3 protein; POSTN, Periostin; POU2F1, POU Class 2 Homeobox 1; POU3F3, POU Class 3 Homeobox 3; PRC2 = Polycomb repressive complex 2; PTEN, Phosphatase And Tensin Homolog; RING1, Ring Finger Protein 1; RIP, RNA Immunoprecipitation assay; RGS17, Regulator Of G Protein Signaling 17; ROCK1, Rho-associated coiled-coil containing protein kinase; RPD, RNA Pull-down assay; RSU1P2, Ras Suppressor Protein 1 Pseudogene 2; RT-qPCR, Reverse transcription quantitative polymerase chain reaction; SC, subcutaneous; SMAD2, SMAD Family Member 2; SMAD3, SMAD Family Member 3; SCC, Squamous cell carcinoma (SCC); SOX4, SRY-Box Transcription Factor 4; SBF2-AS1, SBF2 Antisense RNA 1; SFN, Stratifin; SIL, Squamous intraepithelial lesion; SNHG4, Small Nucleolar RNA Host Gene 4; SNHG12, Small Nucleolar RNA Host Gene 12; SNHG14, Small Nucleolar RNA Host Gene 14; SNHG20, Small Nucleolar RNA Host Gene 20; SOX21-AS1, SRY-Box Transcription Factor 21 Antisense Divergent Transcript 1; SIP1, Sp1 Transcription Factor; STA3, Signal Transducer And Activator Of Transcription 3; TDRG1, Testis Development Related 1; TGF-β, Transforming growth factor beta; TGFBR1, Transforming Growth Factor Beta Receptor 1; TP73-AS1, TP73 Antisense RNA 1; TTN-AS1, TTN Antisense RNA 1; TUSC8, Tumor Suppressor Candidate 8; VDAC1, Voltage Dependent Anion Channel 1; VEGF, Vascular Endothelial Growth Factor; WB, Western Blotting; WT1-AS, Wilms tumor 1 Antisense RNA; XIST, X Inactive Specific Transcript; YAP1, Yes Associated Protein 1; YWHAZ, Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein Zeta; ZEB2, Zinc Finger E-Box Binding Homeobox 2; ZHX1, Zinc Fingers And Homeoboxes 1; ZNF667-AS1, Zinc finger protein 667-antisense RNA 1.

References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA. Cancer J. Clin.* **2018**, *68*, 394–424. [CrossRef] [PubMed]
2. Tota, J.E.; Isidean, S.D.; Franco, E.L. Defining benchmarks for tolerable risk thresholds in cancer screening: Impact of HPV vaccination on the future of cervical cancer screening. *Int. J. Cancer* **2020**, *147*, 3305–3312. [CrossRef] [PubMed]
3. Jansen, E.E.L.; Zielonke, N.; Gini, A.; Anttila, A.; Segnan, N.; Vokó, Z.; Ivanuš, U.; McKee, M.; de Koning, H.J.; de Kok, I.M.C.M.; et al. Effect of organised cervical cancer screening on cervical cancer mortality in Europe: A systematic review. *Eur. J. Cancer* **2020**, *127*, 207–223. [CrossRef] [PubMed]

4. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2019. *CA. Cancer J. Clin.* **2019**, *69*, 7–34. [CrossRef]
5. Mandal, R.; Basu, P. Cancer screening and early diagnosis in low and middle income countries: Current situation and future perspectives. *Bundesgesundheitsblatt Gesundheitsforsch. Gesundh.* **2018**, *61*, 1505–1512. [CrossRef]
6. Anastasiadou, E.; Jacob, L.S.; Slack, F.J. Non-coding RNA networks in cancer. *Nat. Rev. Cancer* **2017**, *18*, 5–18. [CrossRef] [PubMed]
7. López-Urrutia, E.; Bustamante Montes, L.P.; Ladrón de Guevara Cervantes, D.; Pérez-Plasencia, C.; Campos-Parra, A.D. Crosstalk Between Long Non-coding RNAs, Micro-RNAs and mRNAs: Deciphering Molecular Mechanisms of Master Regulators in Cancer. *Front. Oncol.* **2019**, *9*, 669. [CrossRef] [PubMed]
8. Salmena, L.; Poliseno, L.; Tay, Y.; Kats, L.; Pandolfi, P.P. A ceRNA hypothesis: The rosetta stone of a hidden RNA language? *Cell* **2011**, *146*, 353–358. [CrossRef]
9. Thomson, D.W.; Dinger, M.E. Endogenous microRNA sponges: Evidence and controversy. *Nat. Rev. Genet.* **2016**, *17*, 272–283. [CrossRef]
10. Tay, Y.; Rinn, J.; Pandolfi, P.P. The multilayered complexity of ceRNA crosstalk and competition. *Nature* **2014**, *505*, 344–352. [CrossRef]
11. Su, X.; Xing, J.; Wang, Z.; Chen, L.; Cui, M.; Jiang, B. MicroRNAs and ceRNAs: RNA networks in pathogenesis of cancer. *Chin. J. Cancer Res.* **2013**, *25*, 235–239.
12. Liu, Y.; Xue, M.; Du, S.; Feng, W.; Zhang, K.; Zhang, L.; Liu, H.; Jia, G.; Wu, L.; Hu, X.; et al. Competitive endogenous RNA is an intrinsic component of EMT regulatory circuits and modulates EMT. *Nat. Commun.* **2019**, *10*, 1–12. [CrossRef] [PubMed]
13. Du, H.; Chen, Y. Competing endogenous RNA networks in cervical cancer: Function, mechanism and perspective. *J. Drug Target.* **2019**, *27*, 709–723. [CrossRef]
14. Cai, X.; Cullen, B.R. The imprinted H19 noncoding RNA is a primary microRNA precursor. *RNA* **2007**, *13*, 313–316. [CrossRef]
15. Leucci, E.; Patella, F.; Waage, J.; Holmstrøm, K.; Lindow, M.; Porse, B.; Kauppinen, S.; Lund, A.H. MicroRNA-9 targets the long non-coding RNA MALAT1 for degradation in the nucleus. *Sci. Rep.* **2013**, *3*. [CrossRef] [PubMed]
16. Faghihi, M.A.; Zhang, M.; Huang, J.; Modarresi, F.; Van der Brug, M.P.; Nalls, M.A.; Cookson, M.R.; St-Laurent, G.; Wahlestedt, C. Evidence for natural antisense transcript-mediated inhibition of microRNA function. *Genome Biol.* **2010**, *11*, R56. [CrossRef]
17. Bartel, D.P. MicroRNAs: Target Recognition and Regulatory Functions. *Cell* **2009**, *136*, 215–233. [CrossRef] [PubMed]
18. Thomas, M.; Lieberman, J.; Lal, A. Desperately seeking microRNA targets. *Nat. Struct. Mol. Biol.* **2010**, *17*, 1169–1174. [CrossRef]
19. Barrett, L.W.; Fletcher, S.; Wilton, S.D. Regulation of eukaryotic gene expression by the untranslated gene regions and other non-coding elements. *Cell. Mol. Life Sci.* **2012**, *69*, 3613–3634. [CrossRef]
20. Selbach, M.; Schwanhäusser, B.; Thierfelder, N.; Fang, Z.; Khanin, R.; Rajewsky, N. Widespread changes in protein synthesis induced by microRNAs. *Nature* **2008**, *455*, 58–63. [CrossRef]
21. Seitz, H. Redefining MicroRNA Targets. *Curr. Biol.* **2009**, *19*, 870–873. [CrossRef]
22. Novikova, I.V.; Hennelly, S.P.; Sanbonmatsu, K.Y. Sizing up long non-coding RNAs: Do lncRNAs have secondary and tertiary structure? *Bioarchitecture* **2012**, *2*, 189–199. [CrossRef]
23. Marchese, F.P.; Raimondi, I.; Huarte, M. The multidimensional mechanisms of long noncoding RNA function. *Genome Biol.* **2017**, *18*, 1–13. [CrossRef] [PubMed]
24. Zhang, P.; Wu, W.; Chen, Q.; Chen, M. Non-Coding RNAs and their Integrated Networks. *J. Integr. Bioinform.* **2019**, *16*. [CrossRef] [PubMed]
25. Qi, X.; Lin, Y.; Chen, J.; Shen, B. Decoding competing endogenous RNA networks for cancer biomarker discovery. *Brief. Bioinform.* **2019**. [CrossRef] [PubMed]
26. Ala, U. Competing Endogenous RNAs, Non-Coding RNAs and Diseases: An Intertwined Story. *Cells* **2020**, *9*, 1574. [CrossRef]
27. Gong, J.; Jiang, H.; Shu, C.; Hu, M.Q.; Huang, Y.; Liu, Q.; Li, R.F.; Wei, Y.Z. Integrated analysis of circular RNA-associated ceRNA network in cervical cancer: Observational Study. *Medicine* **2019**, *98*, e16922. [CrossRef] [PubMed]
28. Wang, Y.; Wang, L.; Wang, W.; Guo, X. Overexpression of circular RNA hsa_circ_0001038 promotes cervical cancer cell progression by acting as a ceRNA for miR-337-3p to regulate cyclin-M3 and metastasis-associated in colon cancer 1 expression. *Gene* **2020**, *733*. [CrossRef]
29. Xu, J.; Yang, B.; Wang, L.; Zhu, Y.; Zhu, X.; Xia, Z.; Zhao, Z.; Xu, L. LncRNA BBOX1-AS1 upregulates HOXC6 expression through miR-361-3p and HuR to drive cervical cancer progression. *Cell Prolif.* **2020**, *53*. [CrossRef]
30. Rui, X.; Xu, Y.; Jiang, X.; Ye, W.; Huang, Y.; Jiang, J. Long non-coding RNA C5orf66-AS1 promotes cell proliferation in cervical cancer by targeting miR-637/RING1 axis. *Cell Death Dis.* **2018**, *9*. [CrossRef]
31. Feng, S.; Liu, W.; Bai, X.; Pan, W.; Jia, Z.; Zhang, S.; Zhu, Y.; Tan, W. LncRNA-CTS promotes metastasis and epithelial-to-mesenchymal transition through regulating miR-505/ZEB2 axis in cervical cancer. *Cancer Lett.* **2019**, *465*, 105–117. [CrossRef] [PubMed]
32. Liang, H.; Zhang, C.; Guan, H.; Liu, J.; Cui, Y. LncRNA DANCR promotes cervical cancer progression by upregulating ROCK1 via sponging miR-335-5p. *J. Cell. Physiol.* **2019**, *234*, 7266–7278. [CrossRef] [PubMed]
33. Cao, L.; Jin, H.; Zheng, Y.; Mao, Y.; Fu, Z.; Li, X.; Dong, L. DANCR-mediated microRNA-665 regulates proliferation and metastasis of cervical cancer through the ERK/SMAD pathway. *Cancer Sci.* **2019**, *110*, 913–925. [CrossRef]
34. Rui, X.; Xu, Y.; Huang, Y.; Ji, L.; Jiang, X. LncRNA DLG1-AS1 Promotes Cell Proliferation by Competitively Binding with miR-107 and Up-Regulating ZHX1 Expression in Cervical Cancer. *Cell. Physiol. Biochem.* **2018**, *49*, 1792–1803. [CrossRef]

35. Yang, W.; Hong, L.; Xu, X.; Wang, Q.; Huang, J.; Jiang, L. LncRNA GAS5 suppresses the tumorigenesis of cervical cancer by downregulating miR-196a and miR-205. *Tumor Biol.* **2017**, *39*, 1–10. [CrossRef] [PubMed]
36. Yu, Y.; Shen, H.M.; Fang, D.M.; Meng, Q.J.; Xin, Y.H. LncRNA HCP5 promotes the development of cervical cancer by regulating MACC1 via suppression of microRNA-15a. *Eur. Rev. Med. Pharmacol. Sci.* **2018**, *22*, 4812–4819. [CrossRef]
37. Li, Q.; Feng, Y.; Chao, X.; Shi, S.; Liang, M.; Qiao, Y.; Wang, B.; Wang, P.; Zhu, Z. HOTAIR contributes to cell proliferation and metastasis of cervical cancer via targetting miR-23b/MAPK1 axis. *Biosci. Rep.* **2018**, *38*. [CrossRef] [PubMed]
38. Zheng, P.; Yin, Z.; Wu, Y.; Xu, Y.; Luo, Y.; Zhang, T.C. LncRNA HOTAIR promotes cell migration and invasion by regulating MKL1 via inhibition miR206 expression in HeLa cells. *Cell Commun. Signal.* **2018**, *16*, 5. [CrossRef]
39. Sun, J.; Chu, H.; Ji, J.; Huo, G.; Song, Q.; Zhang, X. Long non-coding RNA HOTAIR modulates HLA-G expression by absorbing miR-148a in human cervical cancer. *Int. J. Oncol.* **2016**, *49*, 943–952. [CrossRef] [PubMed]
40. Liu, M.; Jia, J.; Wang, X.; Liu, Y.; Wang, C.; Fan, R. Long non-coding RNA HOTAIR promotes cervical cancer progression through regulating BCL2 via targeting miR-143-3p. *Cancer Biol. Ther.* **2018**, *19*, 391–399. [CrossRef]
41. Zheng, J.J.; Du, X.J.; Wang, H.P.; Zhou, L.Y.; Wang, Y.J.; Zhang, L.; Xu, H.; Zhang, J.; Hu, Z.F. Long non-coding RNA 00152 promotes cell proliferation in cervical cancer via regulating miR-216b-5p/HOXA1 axis. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 3654–3663. [CrossRef]
42. Li, G.C.; Xin, L.; Wang, Y.S.; Chen, Y. Long Intervening Noncoding 00467 RNA Contributes to Tumorigenesis by Acting as a Competing Endogenous RNA against miR-107 in Cervical Cancer Cells. *Am. J. Pathol.* **2019**, *189*, 2293–2310. [CrossRef]
43. Hu, P.; Zhou, G.; Zhang, X.; Song, G.; Zhan, L.; Cao, Y. Long non-coding RNA Linc00483 accelerated tumorigenesis of cervical cancer by regulating miR-508-3p/RGS17 axis. *Life Sci.* **2019**, *234*. [CrossRef]
44. Hu, Y.; Ma, Y.; Liu, J.; Cai, Y.; Zhang, M.; Fang, X. LINC01128 expedites cervical cancer progression by regulating miR-383-5p/SFN axis. *BMC Cancer* **2019**, *19*. [CrossRef]
45. Song, H.; Liu, Y.; Jin, X.; Liu, Y.; Yang, Y.; Li, L.; Wang, X.; Li, G. Long non-coding RNA LINC01535 promotes cervical cancer progression via targeting the miR-214/EZH2 feedback loop. *J. Cell. Mol. Med.* **2019**, *23*, 6098–6111. [CrossRef]
46. Han, X.; Wang, Q.; Wang, Y.; Hu, B.; Dong, X.; Zhang, H.; Wang, W. Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1/microRNA-202-3p/periostin axis modulates invasion and epithelial–mesenchymal transition in human cervical cancer. *J. Cell. Physiol.* **2019**, *234*, 14170–14180. [CrossRef]
47. Liu, S.; Song, L.; Zeng, S.; Zhang, L. MALAT1-miR-124-RBG2 axis is involved in growth and invasion of HR-HPV-positive cervical cancer cells. *Tumour Biol.* **2016**, *37*, 633–640. [CrossRef] [PubMed]
48. Xie, Q.; Lin, S.; Zheng, M.; Cai, Q.; Tu, Y. Long noncoding RNA NEAT1 promotes the growth of cervical cancer cells via sponging miR-9-5p. *Biochem. Cell Biol.* **2019**, *97*, 100–108. [CrossRef] [PubMed]
49. Wang, L.; Zhu, H. Long non-coding nuclear paraspeckle assembly transcript 1 acts as prognosis biomarker and increases cell growth and invasion in cervical cancer by sequestering microRNA-101. *Mol. Med. Rep.* **2018**, *17*, 2771–2777. [CrossRef] [PubMed]
50. Yuan, L.Y.; Zhou, M.; Lv, H.; Qin, X.; Zhou, J.; Mao, X.; Li, X.; Xu, Y.; Liu, Y.; Xing, H. Involvement of NEAT1/miR-133a axis in promoting cervical cancer progression via targeting SOX4. *J. Cell. Physiol.* **2019**, *234*, 18985–18993. [CrossRef] [PubMed]
51. Wang, Q.; Ding, J.; Nan, G.; Lyu, Y.; Ni, G. LncRNA NOC2L-4.1 functions as a tumor oncogene in cervical cancer progression by regulating the miR-630/YAP1 pathway. *J. Cell. Biochem.* **2019**, *120*, 16913–16920. [CrossRef] [PubMed]
52. Huo, H.; Tian, J.; Wang, R.; Li, Y.; Qu, C.; Wang, N. Long non-coding RNA NORAD upregulate SIP1 expression to promote cell proliferation and invasion in cervical cancer. *Biomed. Pharmacother.* **2018**, *106*, 1454–1460. [CrossRef]
53. Chen, X.; Xiong, D.; Yang, H.; Ye, L.; Mei, S.; Wu, J.; Chen, S.; Shang, X.; Wang, K.; Huang, L. Long noncoding RNA OPA-interacting protein 5 antisense transcript 1 upregulated SMAD3 expression to contribute to metastasis of cervical cancer by sponging miR-143-3p. *J. Cell. Physiol.* **2019**, *234*, 5264–5275. [CrossRef]
54. Song, L.; Wang, L.; Pan, X.; Yang, C. LncRNA OIP5-AS1 targets ROCK1 to promote cell proliferation and inhibit cell apoptosis through a mechanism involving miR-143-3p in cervical cancer. *Braz. J. Med. Biol. Res.* **2020**, *53*. [CrossRef] [PubMed]
55. Chang, S.; Sun, L.; Feng, G. SP1-mediated long noncoding RNA POU3F3 accelerates the cervical cancer through miR-127-5p/FOXD1. *Biomed. Pharmacother.* **2019**, *117*. [CrossRef] [PubMed]
56. Fan, Y.; Sheng, W.; Meng, Y.; Cao, Y.; Li, R. LncRNA PTENP1 inhibits cervical cancer progression by suppressing miR-106b. *Artif. Cells Nanomed. Biotechnol.* **2020**, *48*, 393–407. [CrossRef] [PubMed]
57. Xu, Y.; Zhou, W.; Zhang, C.; Liu, X.; Lv, J.; Li, X.; Zhao, L.; Li, W.; Li, J.; Ren, Y.; et al. Long non-coding RNA RP11-552M11.4 favors tumorigenesis and development of cervical cancer via modulating miR-3941/ATF1 signaling. *Int. J. Biol. Macromol.* **2019**, *130*, 24–33. [CrossRef]
58. Liu, Q.; Guo, X.; Que, S.; Yang, X.; Fan, H.; Liu, M.; Li, X.; Tang, H. LncRNA RSU1P2 contributes to tumorigenesis by acting as a ceRNA against let-7a in cervical cancer cells. *Oncotarget* **2017**, *8*, 43768–43781. [CrossRef]
59. Gao, F.; Feng, J.; Yao, H.; Li, Y.; Xi, J.; Yang, J. LncRNA SBF2-AS1 promotes the progression of cervical cancer by regulating miR-361-5p/FOXM1 axis. *Artif. Cells Nanomed. Biotechnol.* **2019**, *47*, 776–782. [CrossRef]
60. Li, H.; Hong, J.; Wijayakulathilaka, W.S.M.A. Long non-coding RNA SNHG4 promotes cervical cancer progression through regulating c-Met via targeting miR-148a-3p. *Cell Cycle* **2019**, *18*, 3313–3324. [CrossRef]
61. Jin, X.J.; Chen, X.J.; Zhang, Z.F.; Hu, W.S.; Ou, R.Y.; Li, S.; Xue, J.S.; Chen, L.L.; Hu, Y.; Zhu, H. Long noncoding RNA SNHG12 promotes the progression of cervical cancer via modulating miR-125b/STAT3 axis. *J. Cell. Physiol.* **2019**, *234*, 6624–6632. [CrossRef]

62. Ji, N.; Wang, Y.; Bao, G.; Yan, J.; Ji, S. LncRNA SNHG14 promotes the progression of cervical cancer by regulating miR-206/YWHAZ. *Pathol. Res. Pract.* **2019**, *215*, 668–675. [CrossRef]
63. Guo, H.; Yang, S.; Li, S.; Yan, M.; Li, L.; Zhang, H. LncRNA SNHG20 promotes cell proliferation and invasion via miR-140-5p-ADAM10 axis in cervical cancer. *Biomed. Pharmacother.* **2018**, *102*, 749–757. [CrossRef]
64. Zhang, X.; Zhao, X.; Li, Y.; Zhou, Y.; Zhang, Z. Long noncoding RNA SOX21-AS1 promotes cervical cancer progression by competitively sponging miR-7/VDAC1. *J. Cell. Physiol.* **2019**, *234*, 17494–17504. [CrossRef]
65. Shao, S.; Wang, C.; Wang, S.; Zhang, H.; Zhang, Y. LncRNA STXBP5-AS1 suppressed cervical cancer progression via targeting miR-96-5p/PTEN axis. *Biomed. Pharmacother.* **2019**, *117*. [CrossRef]
66. Jin, X.; Chen, X.; Hu, Y.; Ying, F.; Zou, R.; Lin, F.; Shi, Z.; Zhu, X.; Yan, X.; Li, S.; et al. LncRNA-TCONS_00026907 is involved in the progression and prognosis of cervical cancer through inhibiting miR-143-5p. *Cancer Med.* **2017**, *6*, 1409–1423. [CrossRef] [PubMed]
67. Jiang, H.; Liang, M.; Jiang, Y.; Zhang, T.; Mo, K.; Su, S.; Wang, A.; Zhu, Y.; Huang, G.; Zhou, R. The lncRNA TDRG1 promotes cell proliferation, migration and invasion by targeting miR-326 to regulate MAPK1 expression in cervical cancer. *Cancer Cell Int.* **2019**, *19*, 152. [CrossRef] [PubMed]
68. Guan, M.M.; Rao, Q.X.; Huang, M.L.; Wang, L.J.; Lin, S.D.; Chen, Q.; Liu, C.H. Long noncoding RNA TP73-AS1 targets microRNA-329-3p to regulate expression of the SMAD2 gene in human cervical cancer tissue and cell lines. *Med. Sci. Monit.* **2019**, *25*, 8131–8141. [CrossRef] [PubMed]
69. Chen, P.; Wang, R.; Yue, Q.; Hao, M. Long non-coding RNA TTN-AS1 promotes cell growth and metastasis in cervical cancer via miR-573/E2F3. *Biochem. Biophys. Res. Commun.* **2018**, *503*, 2956–2962. [CrossRef]
70. Zhu, Y.; Liu, B.; Zhang, P.; Zhang, J.; Wang, L. LncRNA TUSC8 inhibits the invasion and migration of cervical cancer cells via miR-641/PTEN axis. *Cell Biol. Int.* **2019**, *43*, 781–788. [CrossRef]
71. Dai, S.G.; Guo, L.L.; Xia, X.; Pan, Y. Long non-coding RNA WT1-AS inhibits cell aggressiveness via miR-203a-5p/FOXN2 axis and is associated with prognosis in cervical cancer. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 486–495. [CrossRef]
72. Zhu, H.; Zheng, T.; Yu, J.; Zhou, L.; Wang, L. LncRNA XIST accelerates cervical cancer progression via upregulating Fus through competitively binding with miR-200a. *Biomed. Pharmacother.* **2018**, *105*, 789–797. [CrossRef]
73. Chen, X.; Xiong, D.; Ye, L.; Wang, K.; Huang, L.; Mei, S.; Wu, J.; Chen, S.; Lai, X.; Zheng, L.; et al. Up-regulated lncRNA XIST contributes to progression of cervical cancer via regulating miR-140-5p and ORC1. *Cancer Cell Int.* **2019**, *19*, 45. [CrossRef] [PubMed]
74. Li, Y.J.; Yang, Z.; Wang, Y.Y.; Wang, Y. Long noncoding RNA ZNF667-AS1 reduces tumor invasion and metastasis in cervical cancer by counteracting microRNA-93-3p-dependent PEG3 downregulation. *Mol. Oncol.* **2019**, *13*, 2375–2392. [CrossRef]
75. Lewis, B.P.; Shih, I.H.; Jones-Rhoades, M.W.; Bartel, D.P.; Burge, C.B. Prediction of Mammalian MicroRNA Targets. *Cell* **2003**, *115*, 787–798. [CrossRef]
76. Hanahan, D.; Weinberg, R.A. Hallmarks of Cancer: The Next Generation. *Cell* **2011**, *144*, 646–674. [CrossRef]
77. Peng, L.; Yuan, X.; Jiang, B.; Tang, Z.; Li, G.-C. LncRNAs: Key players and novel insights into cervical cancer. *Tumour Biol.* **2016**, *37*, 2779–2788. [CrossRef] [PubMed]
78. Clancy, J.L.; Nousch, M.; Humphreys, D.T.; Westman, B.J.; Beilharz, T.H.; Preiss, T. Methods to Analyze Mi-croRNA-Mediated Control of mRNA Translation. *Methods Enzymol.* **2007**, *431*, 83–111.
79. Tornesello, M.L.; Faraonio, R.; Buonaguro, L.; Annunziata, C.; Starita, N.; Cerasuolo, A.; Pezzuto, F.; Tornesello, A.L.; Buonaguro, F.M. The Role of microRNAs, Long Non-coding RNAs, and Circular RNAs in Cervical Cancer. *Front. Oncol.* **2020**, *10*. [CrossRef] [PubMed]
80. Rajagopal, T.; Talluri, S.; Akshaya, R.L.; Dunna, N.R. HOTAIR LncRNA: A novel oncogenic propellant in human cancer. *Clin. Chim. Acta* **2020**, *503*, 1–18. [CrossRef] [PubMed]
81. Hajjari, M.; Salavaty, A. HOTAIR: An oncogenic long non-coding RNA in different cancers. *Cancer Biol. Med.* **2015**, *12*, 1–9.
82. Qu, X.; Alsager, S.; Zhuo, Y.; Shan, B. HOX transcript antisense RNA (HOTAIR) in cancer. *Cancer Lett.* **2019**, *454*, 90–97. [CrossRef] [PubMed]
83. Liu, H.; Fang, L.; Cheng, Y.; Sun, Q. LncRNA PVT1 regulates prostate cancer cell growth by inducing the methylation of miR-146a. *Cancer Med.* **2016**, *5*, 3512–3519. [CrossRef] [PubMed]
84. Aalijahan, H.; Ghorbian, S. Long non-coding RNAs and cervical cancer. *Exp. Mol. Pathol.* **2019**, *106*, 7–16. [CrossRef] [PubMed]
85. Fu, S.; Wang, Y.; Li, H.; Chen, L.; Liu, Q. Regulatory networks of lncrna malat-1 in cancer. *Cancer Manag. Res.* **2020**, *12*, 10181–10198. [CrossRef] [PubMed]
86. Yu, X.; Li, Z.; Zheng, H.; Chan, M.T.V.; Wu, W.K.K. NEAT1: A novel cancer-related long non-coding RNA. *Cell Prolif.* **2017**, *50*. [CrossRef] [PubMed]
87. Klec, C.; Prinz, F.; Pichler, M. Involvement of the long noncoding RNA NEAT1 in carcinogenesis. *Mol. Oncol.* **2019**, *13*, 46–60. [CrossRef] [PubMed]
88. Li, Y.; Han, X.; Feng, H.; Han, J. Long noncoding RNA OIP5-AS1 in cancer. *Clin. Chim. Acta* **2019**, *499*, 75–80. [CrossRef]
89. Zhou, Q.; Hu, W.; Zhu, W.; Zhang, F.; Lin-lin, L.; Liu, C.; Songyang, Y.-y.; Sun, C.-c.; Li, D. Long non coding RNA XIST as a prognostic cancer marker—A meta-analysis. *Clin. Chim. Acta* **2018**, *482*, 1–7. [CrossRef]
90. Weakley, S.M.; Wang, H.; Yao, Q.; Chen, C. Expression and function of a large non-coding RNA gene XIST in human cancer. *World J. Surg.* **2011**, *35*, 1751–1756. [CrossRef]

91. Zhao, Z.; Liu, W.; Li, J. MiR-140-5p inhibits cell proliferation and invasion in colorectal carcinoma by targeting SOX4. *Oncol. Lett.* **2019**, *17*, 2215–2220. [CrossRef]
92. Lu, Y.; Qin, T.; Li, J.; Wang, L.; Zhang, Q.; Jiang, Z.; Mao, J. MicroRNA-140-5p inhibits invasion and angiogenesis through targeting VEGF-A in breast cancer. *Cancer Gene Ther.* **2017**, *24*, 386–392. [CrossRef]
93. Zhou, W.; Wang, X.; Yin, D.; Xue, L.; Ma, Z.; Wang, Z.; Zhang, Q.; Zhao, Z.; Wang, H.; Sun, Y.; et al. Effect of miR-140-5p on the regulation of proliferation and apoptosis in NSCLC and its underlying mechanism. *Exp. Ther. Med.* **2019**, *18*. [CrossRef] [PubMed]
94. Wang, Z.Y.; Zhu, Z.; Wang, H.F.; Qin, B.; Liu, J.; Yao, X.H.; Li, W.C.; Chen, K.S. Downregulation of circDYNC1H1 exhibits inhibitor effect on cell proliferation and migration in hepatocellular carcinoma through miR-140-5p. *J. Cell. Physiol.* **2019**, *234*, 17775–17785. [CrossRef] [PubMed]
95. Wu, Y.; Li, J.; Chen, S.; Yu, Z. The effects of miR-140-5p on the biological characteristics of ovarian cancer cells through the Wnt signaling pathway. *Adv. Clin. Exp. Med.* **2020**, *29*, 777–784. [CrossRef]
96. Yang, J.; Jiang, B.; Hai, J.; Duan, S.; Dong, X.; Chen, C. Long noncoding RNA opa-interacting protein 5 antisense transcript 1 promotes proliferation and invasion through elevating integrin α6 expression by sponging miR-143-3p in cervical cancer. *J. Cell. Biochem.* **2019**, *120*, 907–916. [CrossRef] [PubMed]
97. Shi, H.; Shen, H.; Xu, J.; Zhao, S.; Yao, S.; Jiang, N. MiR-143-3p suppresses the progression of ovarian cancer. *Am. J. Transl. Res.* **2018**, *10*, 866–874.
98. Xie, F.; Li, C.; Zhang, X.; Peng, W.; Wen, T. MiR-143-3p suppresses tumorigenesis in pancreatic ductal adenocarcinoma by targeting KRAS. *Biomed. Pharmacother.* **2019**, *119*. [CrossRef] [PubMed]
99. Xia, C.; Yang, Y.; Kong, F.; Kong, Q.; Shan, C. MiR-143-3p inhibits the proliferation, cell migration and invasion of human breast cancer cells by modulating the expression of MAPK7. *Biochimie* **2018**, *147*, 98–104. [CrossRef] [PubMed]
100. He, M.; Zhan, M.; Chen, W.; Xu, S.; Long, M.; Shen, H.; Shi, Y.; Liu, Q.; Mohan, M.; Wang, J. MiR-143-5p Deficiency Triggers EMT and Metastasis by Targeting HIF-1α in Gallbladder Cancer. *Cell. Physiol. Biochem.* **2017**, *42*, 2078–2092. [CrossRef]
101. Sanada, H.; Seki, N.; Mizuno, K.; Misono, S.; Uchida, A.; Yamada, Y.; Moriya, S.; Kikkawa, N.; Machida, K.; Kumamoto, T.; et al. Involvement of dual strands of miR-143 (miR-143-5p and miR-143-3p) and their target oncogenes in the molecular pathogenesis of lung adenocarcinoma. *Int. J. Mol. Sci.* **2019**, *20*, 4482. [CrossRef] [PubMed]
102. Yang, C.; Shen, S.; Zheng, X.; Ye, K.; Sun, Y.; Lu, Y.; Ge, H. Long noncoding RNA HAGLR acts as a microRNA-143-5p sponge to regulate epithelial-mesenchymal transition and metastatic potential in esophageal cancer by regulating LAMP3. *FASEB J.* **2019**, *33*, 10490–10504. [CrossRef]
103. Li, T.; Qin, Y.; Zhen, Z.; Shen, H.; Cong, T.; Schiferle, E.; Xiao, S. Long non-coding RNA HOTAIR/microRNA-206 sponge regulates STC2 and further influences cell biological functions in head and neck squamous cell carcinoma. *Cell Prolif.* **2019**, *52*. [CrossRef] [PubMed]
104. Wang, Y.; Tian, Y. MiR-206 inhibits cell proliferation, migration, and invasion by targeting BAG3 in human cervical cancer. *Oncol. Res.* **2018**, *26*, 923–931. [CrossRef] [PubMed]
105. Yan, Q.; Tian, Y.; Hao, F. Downregulation of lncRNA UCA1 inhibits proliferation and invasion of cervical cancer cells through miR-206 expression. *Oncol. Res. Featur. Preclin. Clin. Cancer Ther.* **2018**. [CrossRef]
106. Braicu, C.; Buse, M.; Busuioc, C.; Drula, R.; Gulei, D.; Raduly, L.; Rusu, A.; Irimie, A.; Atanasov, A.G.; Slaby, O.; et al. A comprehensive review on MAPK: A promising therapeutic target in cancer. *Cancers* **2019**, *11*, 1618. [CrossRef] [PubMed]
107. Dhillon, A.S.; Hagan, S.; Rath, O.; Kolch, W. MAP kinase signalling pathways in cancer. *Oncogene* **2007**, *26*, 3279–3290. [CrossRef]
108. Li, A.; Qiu, M.; Zhou, H.; Wang, T.; Guo, W. PTEN, Insulin Resistance and Cancer. *Curr. Pharm. Des.* **2017**, *23*. [CrossRef] [PubMed]
109. Naderali, E.; Khaki, A.A.; Rad, J.S.; Ali-Hemmati, A.; Rahmati, M.; Charoudeh, H.N. Regulation and modulation of PTEN activity. *Mol. Biol. Rep.* **2018**, *45*, 2869–2881. [CrossRef]
110. Chen, C.Y.; Chen, J.; He, L.; Stiles, B.L. PTEN: Tumor suppressor and metabolic regulator. *Front. Endocrinol. (Lausanne)* **2018**, *9*, 338. [CrossRef]
111. Wei, L.; Surma, M.; Shi, S.; Lambert-Cheatham, N.; Shi, J. Novel Insights into the Roles of Rho Kinase in Cancer. *Arch. Immunol. Ther. Exp. (Warsz)* **2016**, *64*, 259–278. [CrossRef] [PubMed]
112. Li, J.; Wang, J.; Jiao, H.; Liao, J.; Xu, X. Cytokinesis and cancer: Polo loves ROCK'n' Rho(A). *J. Genet. Genom.* **2010**, *37*, 159–172. [CrossRef]
113. Shahbazi, R.; Baradaran, B.; Khordadmehr, M.; Safaei, S.; Baghbanzadeh, A.; Jigari, F.; Ezzati, H. Targeting ROCK signaling in health, malignant and non-malignant diseases. *Immunol. Lett.* **2020**, *219*, 15–26. [CrossRef] [PubMed]
114. Tang, Q.; Hann, S.S. HOTAIR: An oncogenic long non-coding RNA in human cancer. *Cell. Physiol. Biochem.* **2018**, *47*, 893–913. [CrossRef] [PubMed]
115. Zhou, Y.H.; Cui, Y.H.; Wang, T.; Luo, Y. Long non-coding RNA HOTAIR in cervical cancer: Molecular marker, mechanistic insight, and therapeutic target. *Adv. Clin. Chem.* **2020**, *97*, 117–140. [PubMed]
116. Li, Z.X.; Zhu, Q.N.; Zhang, H.B.; Hu, Y.; Wang, G.; Zhu, Y.S. MALAT1: A potential biomarker in cancer. *Cancer Manag. Res.* **2018**, *10*, 6757–6768. [CrossRef]
117. Su, Y.; Xiong, J.; Hu, J.; Wei, X.; Zhang, X.; Rao, L. MicroRNA-140-5p targets insulin like growth factor 2 mRNA binding protein 1 (IGF2BP1) to suppress cervical cancer growth and metastasis. *Oncotarget* **2016**, *7*, 68397–68411. [CrossRef]

118. Cui, J.; Pan, Y.; Wang, J.; Liu, Y.; Wang, H.; Li, H. MicroRNA-206 suppresses proliferation and predict poor prognosis of HR-HPV-positive cervical cancer cells by targeting G6PD. *Oncol. Lett.* **2018**, *16*, 5946–5952. [CrossRef]
119. Li, Y.; Deng, X.; Zeng, X.; Peng, X. The role of Mir-148a in cancer. *J. Cancer* **2016**, *7*, 1233–1241. [CrossRef]
120. Milella, M.; Falcone, I.; Conciatori, F.; Incani, U.C.; Del Curatolo, A.; Inzerilli, N.; Nuzzo, C.M.A.; Vaccaro, V.; Vari, S.; Cognetti, F.; et al. PTEN: Multiple functions in human malignant tumors. *Front. Oncol.* **2015**, *5*, 24. [CrossRef]
121. Cabili, M.N.; Dunagin, M.C.; McClanahan, P.D.; Biaesch, A.; Padovan-Merhar, O.; Regev, A.; Rinn, J.L.; Raj, A. Localization and abundance analysis of human lncRNAs at single-cell and single-molecule resolution. *Genome Biol.* **2015**, *16*, 1–16. [CrossRef]
122. Cipolla, G.A. A non-canonical landscape of the microRNA system. *Front. Genet.* **2014**, *5*, 337. [CrossRef] [PubMed]
123. Leung, A.K.L. The Whereabouts of microRNA Actions: Cytoplasm and Beyond. *Trends Cell Biol.* **2015**, *25*, 601–610. [CrossRef]
124. Wang, P.; Guo, Q.; Hao, Y.; Liu, Q.; Gao, Y.; Zhi, H.; Li, X.; Shang, S.; Guo, S.; Zhang, Y.; et al. LnCeCell: A comprehensive database of predicted lncRNA-associated ceRNA networks at single-cell resolution. *Nucleic Acids Res.* **2021**, *49*, D125–D133. [CrossRef] [PubMed]
125. Knowling, S.; Morris, K.V. Non-coding RNA and antisense RNA. Nature's trash or treasure? *Biochimie* **2011**, *93*, 1922–1927. [CrossRef] [PubMed]
126. Sen, R.; Ghosal, S.; Das, S.; Balti, S.; Chakrabarti, J. Competing endogenous RNA: The key to posttranscriptional regulation. *Sci. World J.* **2014**, *2014*. [CrossRef]
127. Nagahashi, M.; Shimada, Y.; Ichikawa, H.; Kameyama, H.; Takabe, K.; Okuda, S.; Wakai, T. Next generation sequencing-based gene panel tests for the management of solid tumors. *Cancer Sci.* **2019**, *110*, 6–15. [CrossRef]
128. Burnett, J.C.; Rossi, J.J. RNA-based therapeutics: Current progress and future prospects. *Chem. Biol.* **2012**, *19*, 60–71. [CrossRef]
129. Matsui, M.; Corey, D.R. Non-coding RNAs as drug targets. *Nat. Rev. Drug Discov.* **2017**, *16*, 167–179. [CrossRef]
130. Rupaimoole, R.; Slack, F.J. MicroRNA therapeutics: Towards a new era for the management of cancer and other diseases. *Nat. Rev. Drug Discov.* **2017**, *16*, 203–221. [CrossRef]