Review

Current insights into the molecular systems pharmacology of lncRNA-miRNA regulatory interactions and implications in cancer translational medicine

Sujit Nair *

Amrita Cancer Discovery Biology Laboratory, Amrita Vishwa Vidyapeetham University, Amritapuri, Clappana P.O., Kollam, Kerala - 690525, India

* **Correspondence:** Email: sujit108@gmail.com.

Abstract: In recent times, the role(s) of microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) in the pathogenesis of various cancers has received great attention. Indeed, there is also a growing recognition of regulatory RNA cross-talk, i.e., lncRNA-miRNA interactions, that may modulate various events in carcinogenesis and progression to metastasis. This review summarizes current evidence in the literature of lncRNA-miRNA interactions in various cancers such as breast, liver, stomach, lung, prostate, bladder, colorectal, blood, brain, skin, kidney, cervical, laryngeal, gall bladder, and bone. Further, the potential prognostic and theragnostic clinical applications of lncRNA-miRNA interactions in cancer are discussed along with an overview of noncoding RNA (ncRNA)-based studies that were presented at the American Society of Clinical Oncology (ASCO) 2015. Interestingly, the last decade has seen tremendous innovation, as well as increase in complexity, of the cancer biological network(s) from mRNA- to miRNA- and lncRNA-based networks. Thus, biological networks devoted to understanding regulatory interactions between these ncRNAs would be the next frontier in better elucidating the contributions of lncRNA-miRNA interactions in cancer. Herein, a cancer biological network of lncRNA-miRNA interactions is presented wherein "edges" connect interacting lncRNA-miRNA pairs, with each ncRNA serving as a discrete "node" of the network. In conclusion, the untapped potential of lncRNA-miRNA interactions in terms of its diagnostic, prognostic and therapeutic potential as targets for clinically actionable intervention as well as biomarker validation in discovery pipelines remains to be explored. Future research will likely harness this potential so as to take us closer to the goal of "precision" and "personalized medicine" which is tailor-made to the unique needs of each cancer patient, and is clearly the way forward going into the future.

1. Introduction

MicroRNAs (miRNAs) are small RNA molecules, about 22 nucleotides in length, that regulate gene expression via translational inhibition or degradation of mRNA transcripts, while long noncoding RNAs (lncRNAs) are larger RNA molecules (longer than 200 nucleotides) that have been shown to play a role in multiple cellular maintenance functions such as protein scaffolding, chromatin looping, and regulation of mRNA stability [1]. Competing endogenous RNAs (ceRNAs) [2] are RNA transcripts which can communicate with each other by decreasing target concentration of miRNA with the derepression of other messenger RNAs (mRNAs) having common miRNA response elements (MREs). Oncocers [2] are ceRNAs taking crucial roles in oncogenic pathways, and oncocer-mediated cross-talk are analyzed by sponging miRNAs in these pathways.

The role(s) of miRNAs or lncRNAs have recently been elucidated, and continue to be studied, in multiple cancers especially in the last decade. The importance of miRNA signatures in chemoresistance to therapeutic intervention and in chemoprevention has been discussed earlier [3]. The role(s) of lncRNAs in malignant disease affecting several different organs of the body are receiving great attention in recent times [4-8] to cite a few examples. Interestingly, there is also a growing recognition of regulatory RNA cross-talk, i.e., lncRNA-miRNA interactions, that may modulate various events in carcinogenesis and progression to metastasis. Jalali et al. [9] reported a systematic transcriptome-wide analysis of lncRNA-miRNA interactions and reconstructed a genome-wide map of miRNA interactions with lncRNAs as well as mRNAs.

In this review, lncRNA-miRNA interactions that have been identified in various cancer phenotypes, as well as the diagnostic, prognostic and therapeutic implications of the same, are delineated. Further, the network biology of lncRNA-miRNA interactions in cancer, and the potential of harnessing this knowledge for achieving the goal of "precision" or "personalized medicine" in oncology, is also discussed. Indeed, with the data emerging on non-coding RNAs (ncRNAs), it is now clear that biomarker methodologies applicable to individual miRNAs and/or lncRNAs will also be applicable to lncRNA-miRNA interacting ncRNAs once the interaction has been functionally established. Thus, it may be possible in the future to profile circulating lncRNA-miRNAs or tissue-based lncRNA-miRNAs or to perform a liquid biopsy of these ncRNAs in clinical samples from individual patients in a rapid, efficient molecular diagnostic test platform. This would have positive implications for the future of "personalized medicine" to titrate the right dose of the drug intervention necessary to ameliorate the clinical status of these patients and improve patient prognosis.

Indeed, the field of lncRNA-miRNA interaction is very nascent and in its infancy. Thus, knowledge of specific lncRNA-miRNA regulation is only emerging and it will take the global research community some time to generate more functional data that will enable a "go/no-go" decision on therapeutic intervention targeted against lncRNA-miRNA in cancer. Existing reviews on miRNA and lncRNA in cancer, to the best of knowledge, are not devoted primarily to lncRNA-miRNA interactions but are devoted to role(s) of either miRNA or lncRNA individually in cancer, except for the excellent review by Yoon, Abdelmohsen and Gorospe [10] on functional lncRNA-miRNA interactions that the reader is referred to. The *raison d'etre* of this review manuscript is to focus on cancer lncRNA-miRNA

interactions, notwithstanding the fact that this field is nascent and data is only evolving. Thus, this review has the potential to be a roadmap of existing information that can stimulate thought processes in the global research community to take up more studies that are devoted to studying cancer lncRNA-miRNA interactions specifically, not just miRNA or lncRNA individually. The jury is still out on how the specific interaction between these ncRNAs can specifically modulate cancer therapy, and the years ahead will surely give us the answer to this question in more definitive terms.

2. lncRNA-miRNA interactions in cancer

The following sub-sections will be devoted to evidence in the literature of lncRNA-miRNA interactions that have been reported by primary studies in various cancers such as breast, liver, gastric, lung, prostate, bladder, colorectal, blood, brain, skin, kidney and other cancers. Figure 1 is a schematic representation of major lncRNA-miRNA interactions implicated in cancers affecting these various organs.
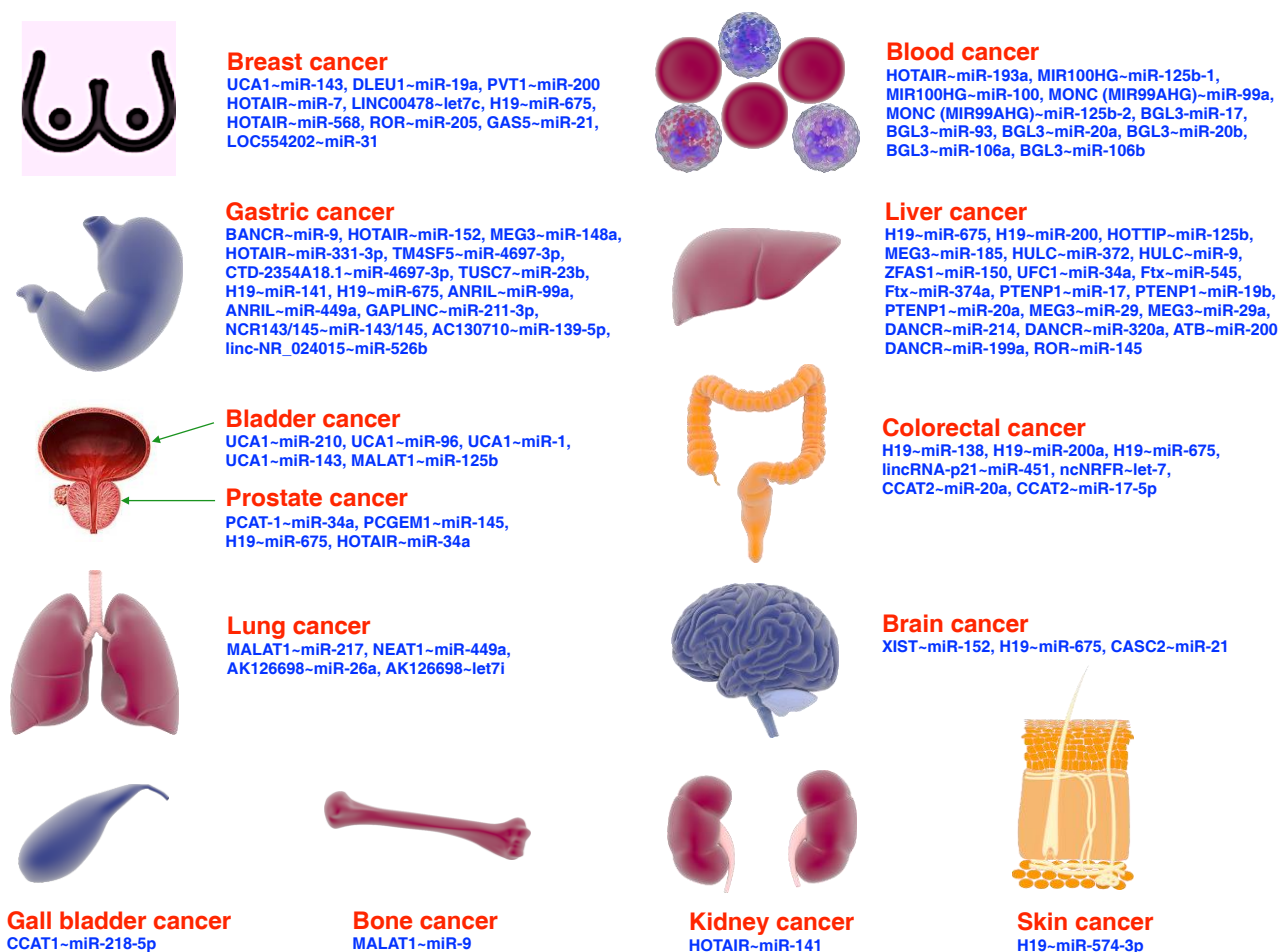

Breast cancer
UCA1~miR-143, DLEU1~miR-19a, PVT1~miR-200, HOTAIR~miR-7, LINC00478~let7c, H19~miR-675, HOTAIR~miR-568, ROR~miR-205, GAS5~miR-21, LOC554202~miR-31

Gastric cancer
BANCR~miR-9, HOTAIR~miR-152, MEG3~miR-148a, HOTAIR~miR-331-3p, TM4SF5~miR-4697-3p, CTD-2354A18.1~miR-4697-3p, TUSC7~miR-23b, H19~miR-141, H19~miR-675, ANRIL~miR-99a, ANRIL~miR-449a, GAPLINC~miR-211-3p, NCR143/145~miR-143/145, AC130710~miR-139-5p, linc-NR_024015~miR-526b

Bladder cancer
UCA1~miR-210, UCA1~miR-96, UCA1~miR-1, UCA1~miR-143, MALAT1~miR-125b

Prostate cancer
PCAT-1~miR-34a, PCGEM1~miR-145, H19~miR-675, HOTAIR~miR-34a

Lung cancer
MALAT1~miR-217, NEAT1~miR-449a, AK126698~miR-26a, AK126698~let7i

Blood cancer
HOTAIR~miR-193a, MIR100HG~miR-125b-1, MIR100HG~miR-100, MONC (MIR99AHG)~miR-99a, MONC (MIR99AHG)~miR-125b-2, BGL3-miR-17, BGL3~miR-93, BGL3~miR-20a, BGL3~miR-20b, BGL3~miR-106a, BGL3~miR-106b

Liver cancer
H19~miR-675, H19~miR-200, HOTTIP~miR-125b, MEG3~miR-185, HULC~miR-372, HULC~miR-9, ZFAS1~miR-150, UFC1~miR-34a, Ftx~miR-545, Ftx~miR-374a, PTENP1~miR-17, PTENP1~miR-19b, PTENP1~miR-20a, MEG3~miR-29, MEG3~miR-29a, DANCR~miR-214, DANCR~miR-320a, ATB~miR-200, DANCR~miR-199a, ROR~miR-145

Colorectal cancer
H19~miR-138, H19~miR-200a, H19~miR-675, lincRNA-p21~miR-451, ncNRFR~let-7, CCAT2~miR-20a, CCAT2~miR-17-5p

Brain cancer
XIST~miR-152, H19~miR-675, CASC2~miR-21

Gall bladder cancer
CCAT1~miR-218-5p

Bone cancer
MALAT1~miR-9

Kidney cancer
HOTAIR~miR-141

Skin cancer
H19~miR-574-3p

Figure 1. lncRNA-miRNA interactions in various cancers. Current knowledge of interactions between lncRNAs and miRNAs in malignancies affecting various organs is summarized in the figure. The ~ sign denotes an interaction between the particular lncRNA and miRNA.

2.1. Breast cancer

Cai et al. [11] showed by quantitative real-time PCR (qPCR) that lncRNA CCAT2 is highly expressed in breast cancer tissues and breast cancer cell lines and that abnormal expression of CCAT2 could influence Wnt signaling. Tuo et al. [12] used miRNA microarray and qPCR and reported that lncRNA urothelial carcinoma-associated 1 (UCA1) is significantly upregulated, while miR-143 is significantly downregulated, in breast tumor tissues than in adjacent normal tissues. In addition, dual luciferase and RNA binding protein immunoprecipitation (RIP) assays were performed and it was confirmed that UCA1 can directly interact with miR-143, lower its expression and affect its downstream regulation, thus, UCA1-miR-143 axis constitutes a part of the oncogenic role of UCA1 in breast cancer [12]. Using lncRNA + mRNA microarray, and miRNA microarray, with qPCR, Wu et al. [13] reported that there is a co-expression relationship between *ESR1*, the gene coding for estrogen receptor (ER), and lncRNA DLEU1, and that miR-19a and DLEU1 are both located on human chromosome 13q leading the authors to speculate that miR-19a might be co-expressed with lncRNA DLEU1 to coregulate the expression of *ESR1*. Various miRNAs and lncRNAs associated with breast cancer stem cells (CSCs) including let-7, miR-200 family, miR-205, miR-200b, miR-200c, miR-141, miR-22, HOTAIR, HOTAIR/miR-7, Linc-ROR, Lnc-H19, Lnc-H19/miR-675, Lnc-ATB have been tabulated elsewhere earlier [14].

Bailey et al. [15] used NanoString technology to profile the expression of 800 miRNAs in the estrogen-dependent human breast cancer MCF-7 cell line and its estrogen-independent derivative MCF7:2A and identified 78 differentially expressed miRNAs including a cluster comprising let-7c, miR-99a, and miR-125b, which is encoded in an intron of the lncRNA LINC00478. It has been shown [16] that tumor suppressor miR-7 is inhibited indirectly by lncRNA HOTAIR (HOX antisense intergenic RNA) and directly inhibits the oncogene SETDB1 as well as reverses the EMT of breast CSCs by downregulating the STAT3 pathway in MCF-7 and MDA-MB-231 human breast cancer cell lines and xenograft tumors. Li et al. [17] found that nuclear factor of activated T cells 5 (NFAT5) is directly targeted by miR-568, which in turn is suppressed by lncRNA HOTAIR, and upregulates S100 calcium binding protein A4 to promote breast cancer metastasis. Hou et al. [18] reported that the lncRNA linc-ROR (regulator of reprogramming) induces EMT and contributes to breast cancer tumorigenesis and metastasis by functioning as a ceRNA to miR-205 and preventing the degradation of miR-205 target genes including the EMT inducer ZEB2. A negative regulation of GAS5 (growth arrest-specific 5) by miR-21 has been observed [19] in breast tumor specimens. Augoff et al. [20] demonstrated that miR-31 and its host gene lncRNA LOC554202 were regulated by promoter hypermethylation in triple negative breast cancer (TNBC) cells, particularly of the basal subtype.

Matouk et al. [21] reported that lncRNA H19 promotes tumor metastasis by suppressing the expression of E-cadherin and upregulating Slug expression through miR-675 in female CD1 nude mouse breast cancer model. Paci et al. [22] used computational analyses to elucidate a sponge interaction network that explained the ability of lncRNAs to act as ceRNAs by protecting mRNAs from miRNA repression using breast cancer expression data from The Cancer Gene Atlas (TCGA) and highlighted the role of the lncRNA PVT1/miR-200 family axis. Li et al. [23] used GWAS-based association analyses to demonstrate that a polymorphism rs12325489C>T in the lincRNA-ENST00000515084 exon was found to modulate breast cancer risk in the Chinese population. In this particular study, biochemical analysis demonstrated that the C to T base change at rs12325489C>T disrupts the binding site for miRNA-370, thereby influencing the transcriptional activity of lincRNA-

ENST00000515084 in vitro and in vivo, and affecting breast cancer cell proliferation and tumor growth [23].

2.2. Liver cancer

Zhang et al. [24] studied 372 hepatocellular carcinoma (HCC) tumors and 48 adjacent non-tumor liver tissues from TCGA and NCBI GEO databases using bioinformatics analyses and identified a complex, cancer-specific ceRNA network which includes 14 lncRNAs and 17 miRNAs in HCC including six lncRNAs (CECR7, LINC00346, MAPKAPK5-AS1, LOC338651, FLJ90757, and LOC283663) that were found to be significantly associated with overall survival. miR-675 has been reported [25] to upregulate lncRNA H19 through the activation of early growth response protein 1 (EGR1) in HCC. It has been shown [26] that downregulation of lncRNA H19 and miR-675 promotes migration and invasion of human HCC cells through Akt/GSK-3ß/Cdc25A signaling pathway. Zhang et al. [27] showed that epigenetic activation of the miR-200 family contributed to lncRNA H19-mediated mesenchymal-to-epithelial (MET) transition and the suppression of tumor metastasis in HCC. Zamani et al. [28] observed that dendrosomal curcumin increases the expression of tumor suppressor lncRNA MEG3 via upregulation of miR-29a and miR-185 as well as downregulation of DNMT1, 3A and 3B in HCC. Wang et al. [29] showed that CREB upregulates the expression of lncRNA HULC (highly upregulated in liver cancer) through interaction with miR-372 in vivo in human patient liver tissues and in vitro in liver cancer cell lines Huh-1, Huh-4, Huh-7, Hep3B, HepG2, SNU-449, and SNU-475, with the highest in vitro HULC expression seen in Hep3B cells. Cui et al. [30] demonstrated that lncRNA HULC modulated abnormal lipid metabolism in hepatoma cells through an miR-9-mediated retinoid receptor (RXRA) signaling pathway.

Li et al. [31] reported that amplification of lncRNA ZFAS1 promotes intrahepatic and extrahepatic metastasis in HCC by binding miR-150 and abrogating its tumor-suppressive function and by upregulating ZEB1, MMP14, and MMP16 resulting in a poor prognosis of HCC. Cao et al. [32] observed that the long intergenic noncoding RNA UFC1 (lincRNA-UFC1), a target of miR-34a, promotes proliferation and growth of xenografted tumors, and interacts with the mRNA stabilizing protein HuR to increase levels of beta-catenin in experiments using human tumor specimens, BALB/c nude mice, and SK-Hep1, Huh-7, and MHCC-97H human HCC cells. Zhao et al. [33] investigated the miR-545/374a cluster encoded in the lncRNA Ftx and found that this cluster is overexpressed in Hepatitis B (HBV)-related HCC and promotes tumorigenesis and tumor progression. Chen et al. [34] successfully demonstrated the suppression of HCC by the use of a Sleeping Beauty-based hybrid baculovirus vector for sustained expression of lncRNA PTENP1 resulting in subsequent "decoy" of oncomirs miR-17, miR-19b, and miR-20a and elevation of PTEN which suppressed the oncogenic PI3K/Akt pathway. Braconi et al. [35] reported that miR-29 can regulate the expression of lncRNA MEG3 in HepG2, Huh-7, PLC/PRF-5, and Hep-3B human HCC cell lines. Yuan et al. [36] found that lncRNA DANCR increases stemness feature of HCC by blocking the repressing effect of miR-214, miR-320a, miR-199a on beta-catenin (CTNNB1). Tsang et al. [37] reported that lncRNA HOTTIP is upregulated in HCC and is negatively regulated by tumor suppressor miR-125b.

Molecular profiling of mouse livers during 13 weeks of phenobarbital-mediated liver promotion identified the Dlk1-Dio3 imprinted gene cluster noncoding RNAs as novel candidate biomarkers for liver tumor promotion [38]. Tang et al. [39] showed that miR-642 acts as a ceRNA in regulating two lncRNAs Linc00974 and KRT19 which interact with each other to promote proliferation and

metastasis in HCC by activation of Notch and TGF-ß pathways. Based on previous findings that HCC cell-derived extracellular vesicles contain miRNAs that can modulate transformed cell behavior in target cells, Takahashi et al. [40] hypothesized that intercellular signaling by extracellular vesicle RNA in response to TGFβ could mediate chemoresistance. Thus, Takahashi et al. [40] reported that TGF-ß increased expression of tumor-resistant CD133+ cells and selectively enriched lncRNA linc-ROR within extracellular vesicles resulting in chemoresistance of HCC cells to sorafenib or doxorubicin, whereas knockdown of linc-ROR enhanced the chemosensitivity of HCC cells. In another study, it was shown [41] that linc-RoR is a hypoxia-responsive lncRNA that is functionally linked to hypoxia signaling in HCC through a miR-145-HIF-1α signaling module. Yuan et al. [42] reported that the lncRNA-activated by TGF-β (lncRNA-ATB) was upregulated in HCC metastases and associated with poor prognosis through upregulation of ZEB1 and ZEB2 by competitively binding the miR-200 family to promote the invasion-metastasis cascade in HCC.

2.3. Gastric cancer

Li et al. [43] performed microarray analyses and reported that expression levels of 3732 lncRNAs were altered in gastric cancer tissues as compared to controls, and that the pathophysiology of gastric cancer may involve a disruption of lncRNAs TM4SF5 and CTD-2354A18.1 as well as miR-4697-3p. Xia et al. [44] studied lncRNA microarray data and concluded that eight lncRNAs (AC009499.1, GACAT1, GACAT3, H19, LINC00152, AP000288.2, FER1L4, and RP4-620F22.3) and nine miRNAs (miR-18a-5p, miR-18b-5p, miR-19a-3p, miR-20b-5p, miR-106a-5p, miR-106b-5p, miR-31-5p, miR-139-5p, and miR-195-5p) were involved in gastric cancer. In this particular study, the results suggested that lncRNAs harbor miRNA response elements (MREs); for instance, through its MREs to compete for miR-106a-5p, lncRNA-FER1L4 regulates the expression of PTEN, RB1, RUNX1, VEGFA, CDKN1A, E2F1, HIPK3, IL-10, and PAK7 [44]. Zhang et al. [45] showed that the lncRNA BANCR (BRAF activated non-coding RNA) was highly expressed in gastric tumor tissues, and in MGC803 and BGC823 human gastric cancer cell lines, and promoted gastric cancer proliferation via regulation by NFkappaB1 and miR-9. Song et al. [46] observed that lncRNA HOTAIR promoted human leukocyte antigen (HLA)-G expression by inhibition of miR-152 in gastric cancer tissues. Lie et al. [47] demonstrated that lncRNA HOTAIR may act as a ceRNA, effectively becoming a sink for miR-331-3p, thereby modulating the derepression of HER2 in advanced gastric cancer. Qi et al. [48] used microarray profiling, loss-of-function, and gain-of-function approaches, and observed that the lncRNA TUSC7 (tumor suppressor candidate 7) was a p53-regulated tumor suppressor that was downregulated in gastric cancer tissues as well as repressed miR-23b and may be a key regulatory hub in gastric cancer.

Zhou et al. [49] reported that miR-141 and lncRNA H19 could compete with each other and affect their target genes, thus, regulating cell proliferation and migration in gastric cancer. It has been previously shown that lncRNA H19 gives rise to miR-675-3p and miR-675-5p [50]. Zhuang et al. [51] reported that lncRNA H19-derived miR-675 was positively correlated with lncRNA H19 and was a pivotal mediator in H19-induced human gastric cancer cell proliferation by targeting tumor suppressor RUNX1 (Runt Domain Transcription Factor 1). In this study, rescue assays indicated that RUNX1 mediated the H19/miR-675-induced gastric cancer cell phenotypic changes [51]. Li et al. [52] reported that the overexpression of lncRNA H19 enhances metastasis of gastric cancer, an effect that is mediated by the direct upregulation of ISM1 and the indirect suppression of CALN1 expression via miR-675. Hu et al. [53], based on the use of global microarrays, reported that the novel lncRNA GAPLINC

(gastric adenocarcinoma predictive long intergenic noncoding RNA) is highly expressed in gastric cancer tissues. In this study [53], the effects of GAPLINC on cell migration and proliferation were neutralized by suppressing CD44 expression, and GAPLINC was found to regulate CD44 as a molecular decoy for miR-211-3p, a miRNA that targets both CD44 and GAPLINC. Moreover, tissue in situ hybridization analyses suggested that GAPLINC overexpression defines a subgroup of patients with gastric cancer with very poor survival [53]. It has been shown [54] that DEAD-box RNA helicase 6 (DDX6) post-transcriptionally downregulates miR-143/145 expression through noncoding RNA NCR143/145 in MKN45 human gastric cancer cells.

Yan et al. [55] demonstrated that lncRNA MEG3 was downregulated in human gastric cancer tissues as well as SGC-7901 and BGC-823 gastric cancer cell lines and was regulated by miR-148a by modulation of DNMT-1 (DNA methyltransferase 1). Fan et al. [56] showed using GWAS that a G to A base change at rs8506G>A disrupts the binding site for miR-526b, thereby influencing the transcriptional activity of long intergenic noncoding RNA lincRNA-NR_024015 and predisposes to gastric cancer risk in the Chinese population. Zhang et al. [57] observed that lncRNA ANRIL (CDKN2B-AS1) promotes tumor growth by epigenetic silencing of miR-99a/miR-449a and indicates a poor prognosis of gastric cancer. Xu et al. [58] reported that lncRNA AC130710 is upregulated in gastric cancer and associates with poor prognosis and is regulated by miR-139-5p.

2.4. Lung cancer

Lu et al. [59] established a mechanism for lung carcinogenesis by showing that post-transcriptional silencing of lncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) by miR-217 inhibits the epithelial-to-mesenchymal transition (EMT) via enhancer of zeste homolog 2 (*EZH2*) and H3K27me3 during the malignant transformation of human bronchial epithelial cells induced by cigarette smoke extract. Shao et al. [60] used a computational method to form a lung adenocarcinoma dysregulated ceRNA-ceRNA network (LDCCNet) and identified dysregulated ceRNA modules which are significantly enriched with known lung cancer miRNAs as well as gain and loss ceRNAs as topological key nodes in lung cancer. You et al. [61] showed that miR-449a inhibits cell growth and was downregulated in lung cancer tissues and regulates lncRNA NEAT 1 (nuclear enriched abundant transcript 1) in NL9980 and L9981 lung carcinoma cell lines. Nasser et al. [62] reported the downregulation of miR-1 in lung cancer and the suppression of tumorigenic property of A549 and H1299 lung cancer cells and their sensitization to doxorubicin-induced apoptosis by miR-1. Yang et al. [63] used microarray profiling and identified 1380 lncRNAs and 25 miRNAs that were differentially expressed in A549 and cisplatin-resistant A549/CDDP lung cancer cells, with key roles in cisplatin resistance for miR-26a and let-7i as well as lncRNA AK126698 that targeted the Wnt pathway.

2.5. Prostate cancer

Prensner et al. [64] described a role for the oncogenic lncRNA PCAT-1 in promoting prostate cancer cell proliferation through cMyc protein, and a role for PCAT-1 in the disruption of MYC-targeting miRNAs such as miR-34a at the MYC 3'-untranslated region (UTR). He et al. [65] identified a reciprocal regulation of the lncRNA prostate cancer gene expression marker 1 (PCGEM1) and miR-145 that promoted proliferation of LNCaP prostate cancer cells and regulated tumor growth in nu/nu mice. Zhu et al. [66] reported that lncRNA H19 and H19-derived miR-675 were significantly

downregulated in the metastatic prostate cancer cell line M12 compared with the non-metastatic prostate epithelial cell line P69, and that the H19-miR-675 axis suppresses prostate cancer metastasis by targeting transforming growth factor ß-induced protein (TGFBI) which is an extracellular matrix protein involved in cancer metastasis. Using PC-3 and DU-145 human prostate cancer cells and nude mice, Chiyomaru et al. [67] demonstrated that the soy isoflavone genistein inhibits prostate cancer cell growth through downregulation of oncogenic lncRNA HOTAIR that is also targeted by tumor suppressor miR-34a.

2.6. Bladder cancer

EZH2, which belongs to the polycomb repressive complex 2 (PRC2) as its catalytic subunit, and produces gene silencing through the trimethylation of H3 (Histone 3) on K27 (Lysine 27), is frequently found overexpressed in bladder cancer [68]. The *EZH2*-miRNA network in bladder cancer has been enumerated and includes miR-26a and miR-101 that regulate *EZH2* by interacting with its 3'UTR; and miR-200a, miR-200b, and miR-200c whose expressions are suppressed by *EZH2* [68]. In bladder cancer, *EZH2* has been shown to associate with both lncRNAs H19 [69] and HOTAIR [70] whereas linc-UBC1 (Upregulated in bladder cancer 1) is known to be associated with PRC2 complex [71]. Eissa et al. [72] reported a diagnostic panel of three epigenetic regulators of hyaluronoglucosaminidase 1 (*HYAL1*) including long non-coding RNA-urothelial cancer associated 1 (lncRNA-UCA1), miRNA-210, and miRNA-96 that were positively correlated with *HYAL1* in urine samples of bladder cancer patients and had good specificity and sensitivity for distinguishing bladder cancer patients from controls. Fu et al. [73] reported how synthetic artificial miRNAs targeting UCA1-MALAT1 or *c-Myc* can inhibit malignant phenotypes of T24 and 5637 bladder cancer cell lines and may represent a novel genetic device for treating bladder cancer. It has been reported [74] that downregulated miR-1 and upregulated lncRNA UCA1 were inversely expressed in bladder cancer cells with miR-1 playing a tumor suppressor role by decreasing the expression of UCA1 in an Ago2-slicer-dependent manner. Li et al. showed [75] that lncRNA UCA1 promoted glycolysis by upregulating hexokinase 2 through activation of mTOR and STAT3 and by repression of miR-143.

Han et al. observed [76] that miR-125b suppresses bladder cancer development by down-regulating oncogene SIRT7 and oncogenic lncRNA MALAT1. Interestingly, Andrew et al. [77] assessed the prognostic value of miR-34a by evaluating its expression levels in individual tumor cells in a large, population-based, prognostic study of bladder cancer in New Hampshire, USA. In this study [77], fluorescence-based in situ hybridization assays were performed on 229 urothelial carcinoma tissue specimens and it was found that a larger proportion of the nonmuscle invasive tumors had high levels of miR-34a within the carcinoma cells compared to those tumors that were muscle invasive, and that patients with high miR-34a expression were associated with a lower risk of bladder cancer recurrence. Indeed, further clinical studies of miR-34a as a guide for recurrence screening and as a possible candidate therapeutic target in the bladder are necessary [77].

2.7. Colorectal cancer

Wang et al. [78] reported that miR-451-regulated delivery of large intergenic non-coding RNA p21 (lincRNA-p21) suppresses ß-catenin signaling and tumorigenicity of colorectal CSCs. Next generation sequencing was used to identify 111 upregulated miRNAs, 95 downregulated miRNAs, 270

upregulated lncRNAs, and 123 downregulated lncRNAs in a study of p53-regulated networks in the SW480 colorectal cancer cell line [79]. Liang et al. [80] reported that lncRNA H19 was highly expressed in colorectal cancer tissues and promotes epithelial-to-mesenchymal (EMT) transition by functioning as miRNA sponges in colorectal cancer. In this study [80], it was shown that lncRNA H19 functioned as a ceRNA for miR-138 and miR-200a, antagonized their functions and led to the de-repression of their endogenous targets *vimentin, ZEB1* and *ZEB2*. Tsang et al. showed [81] that lncRNA H19-derived miR-675 through downregulation of its target tumor suppressor retinoblastoma (RB) regulates human colorectal cancer development. Franklin et al. [82] reported the malignant transformation of mouse colonic epithelial cells by a colon-derived lncRNA designated as non-coding Nras functional RNA (ncNRFR) which also appeared to inhibit the function of the tumor suppressor miRNA let-7. Ling et al. [83] demonstrated that lncRNA CCAT2 encompassing the rs6983267 SNP (mapping to 8q24) is highly overexpressed in microsatellite-stable colorectal cancer, promotes tumor growth, metastasis and chromosomal instability, and upregulates *MYC*, miR-17-5p, and miR-20a through TCF7L2-mediated transcriptional regulation, with CCAT2 itself being a WNT downstream target.

2.8. Blood cancer

Using a lncRNA cDNA microarray, Guo et al. [84] analyzed lncRNAs in K562 human chronic myeloid leukemia (CML) cells and leukemic cells derived from CML patients and identified lncRNA-BGL3 that acted as a key regulator of Bcr-Abl-mediated cellular transformation. Further, in transgenic mice expressing lncRNA-BGL3, it was found [84] that lncRNA-BGL3 was a target of miR-17, miR-93, miR-20a, miR-20b, miR-106a, and miR-106b all of which repress mRNA of phosphatase and tensin homolog (*PTEN*), and that lncRNA-BGL3 functioned as a ceRNA for binding these miRNAs to cross-regulate *PTEN* expression in CML. Emmrich et al. [85] reported that lncRNA hostgenes MONC (alias MIR99AHG) and MIR100HG within the intronic miRNA clusters miR-99a~125b-2 and miR-100~125b-1 are highly expressed in acute megakaryoblastic leukemia (AMKL), and that these two lncRNAs may serve as regulators of hematopoiesis and as oncogenes in the development of myeloid leukemia. Xing et al. [86] reported that lncRNA HOTAIR modulated c-KIT expression through sponging miR-193a in acute myeloid leukemia (AML) cell lines and primary AML blasts, and that AML patients with greater HOTAIR expression exhibited worse clinical outcome compared to patients with lower HOTAIR expression. Iosue et al. [87] reported that Argonaute 2 (Ago2) sustains the gene expression program driving human monocytic differentiation of AML cells. In this study [87], Ago2 was shown to be recruited on miR-155 host gene promoter and on the upstream region of an overlapping antisense RNA, determining their epigenetic silencing, and miR-155 downregulation.

2.9. Brain cancer

Yao et al. [88] showed that lncRNA XIST (X-inactive-specific transcript) is upregulated in glioma tissues and human glioblastoma stem cells and that there is a reciprocal repression between XIST and miR-152, with miR-152 mediating the tumor-suppressive effects that knockdown of XIST exerted. Using methylation-specific PCR, Cui et al. [89] showed that epigenetics may play a major role in the expression of miR-126 which was found to be downregulated in glioma tumors from 50 patients. Shi et al. [90] analyzed glioma gene expression datasets and identified that lncRNA H19/miR-675 signaling was critical for glioma progression with increased expression of H19 in high-grade gliomas

and a positive correlation between expression levels of H19 and miR-675. The interaction of lncRNAs with *EZH2* in gliomas has been discussed elsewhere [91]. Given that glioma stem cells are believed to be responsible for drug resistance, Shi et al. [92] showed that miR-125b was downregulated in human U251 glioma stem cells and that miR-125b regulated the proliferation of glioma stem cells through the cell cycle regulated proteins CDK6 and CDC25A. It has been reported [93] that lncRNA CASC2 plays a tumor suppressor role in human glioma via negative regulation of miR-21, with CASC2 exhibiting low expression in glioma tissues as well as in U251 and U87 glioma cell lines and a reciprocal repression with miR-21 in an Argonaute2-dependent manner.

2.10. Skin cancer

In a study of UVB-induced melanogenesis in primary melanocytes, it was found [94] that expression levels of three lncRNAs, viz., lnc-GKN2-1:1, lnc-CD1D-2:1, and lnc-SGSG-5:4 were significantly increased after UVB irradiation, and these may be involved in the UVB-induced stress response of melanocytes via reactive oxygen species (ROS)-mediated production of some of the lncRNAs. Soares et al. [95] investigated *IGF*2/*Apa*I and H19/*Rsa*I polymorphisms in 21 patients with hereditary melanoma by genotyping. In this study, although the *IGF2* and H19 genotypes/haplotypes were not significantly associated with melanoma, two of the most severe melanoma cases were heterozygous for both genes, and there was an overlap between *IGF*2/*Apa*I and miR-615-5p, and between H19/*Rsa*I and miR-574-3p [95].

2.11. Kidney cancer

It has been shown [96] that lncRNA HOTAIR is targeted and regulated by miR-141 in an Ago2-dependent manner in 786-O and ACHN human renal cell carcinoma (RCC). Slaby et al. [97] examined the expression of several miRNAs in 38 patient samples of RCC and reported that miR-155, miR-210, miR-106a, and miR-106b were significantly overexpressed in these tumors, whereas the expression of miR-141 and miR-200c were significantly decreased in RCC.

2.12. Other cancers

Liu et al. [98] reported that lncRNA MALAT1 can indirectly modulate *GRB2* expression via miR-124 and promotes growth and invasion of high-risk human papillomavirus (HR-HPV)-positive cervical cancer cells. Kwanhian et al. [99] performed miRNA profiling of diffuse large B-cell lymphoma and showed that there exists a mutation in the seed sequence of miR-142-3p and that miR-142 is mutated in about 20% of this lymphoma subtype probably leading to a loss rather than a gain of function. Wang et al. [100] showed that combined expression of serum exosomal miR-21 and lncRNA HOTAIR was significantly correlated with clinical parameters of laryngeal squamous cell carcinoma and could be used as prognostic and diagnostic biomarkers for the same. Ma et al. showed [101] that lncRNA CCAT1 was a driver of gall bladder malignancy via negative modulation, i.e., acting as a competitive sponge, of miR-218-5p. Fang et al. [102] demonstrated that 17β-estradiol regulates cell proliferation, colony formation, migration, invasion and promotes apoptosis by upregulating miR-9 and thus degrading MALAT1 in MG-63 osteosarcoma cells in an estrogen receptor-independent manner.

3. Prognostic and theragnostic applications in clinical oncology

Yoon, Abdelmohsen and Gorospe [10] observed that various lncRNA-miRNA regulatory paradigms modulate gene expression patterns that drive major cellular processes such as cell differentiation, proliferation, and cell death either by (i) reduction of lncRNA stability through the interaction of specific miRNAs; (ii) lncRNAs acting as miRNA decoys, with the sequestration of miRNAs favoring expression of repressed target RNAs; (iii) lncRNAs derepressing gene expression by competing with miRNAs for interaction with shared target mRNAs; and (iv) lncRNAs producing miRNAs, leading to repression of target mRNAs. In recent times, we have seen a heightened interest in miRNA- and lncRNA-based research in clinical oncology indications. However, the ncRNA interactions field is in its infancy especially in clinical oncology indications. Indeed, more data needs to emerge on lncRNA-miRNA interactions in animal models first and then in clinical scenarios in the oncology clinical care setting. Hence, at the present time, due to the limited literature already published, this section includes available ncRNA literature from ASCO, the American Society of Clinical Oncology, which is arguably one of the best forums for dissemination of clinical developments in cancer care. Indeed, a large number of RNA-based studies were presented at the 2015 Annual Meeting of American Society of Clinical Oncology (ASCO). To reiterate, although studies on lncRNA-miRNA interactions were not directly included given the nascent nature of the field with respect to clinical practice, there were several miRNA-based studies far too numerous to be all included here, as well as some lncRNA-based studies. In this section, some of the lncRNA- and miRNA-based studies with potential prognostic, diagnostic, and therapeutic applications in clinical oncology that were presented at ASCO are delineated. Of note, Malouf et al. [103] presented the identification of 592 (27.7%) lncRNAs that gained DNA methylation in clear-cell RCC which was associated with the repression of expression of 70 of them after analyzing TCGA molecular RNAseq profiles of 471 primary clear-cell RCC tumors. Wang et al. [104] reported that the lncRNA RUNXOR (RUNX1 overlapping promoter-derived noncoding RNA) acts as a tumor suppressor by epigenetic regulation of RUNX1, a master regulator of hematopoiesis, in acute myelocytic leukemia (AML). Hatziapostolou et al. [105] reported that lncRNA HOTAIR is significantly upregulated (>30-fold) in colon cancer and inversely correlates with patient survival, and that HOTAIR interacts with the histone acetyltransferase PCAF (p300 CBP-associated factor) to form a novel RNA-protein complex that is essential for colon oncogenesis via mTOR/insulin receptor/PI3K-Akt pathways. Crea et al. [106] reported the identification and functional characterization of lncRNA HORAS1 (hormone resistance associated sequence 1), a previously-uncharacterized regulator of the androgen receptor pathway, which is highly upregulated in patient-derived, prostate cancer xenografts and drives progression of hormone-independent prostate cancer.

Broto et al. [107] identified miRNA let-7e and miR-550 as the most downregulated and upregulated miRNAs respectively in gastrointestinal stromal tumors (GIST) and showed that let-7e was a statistically significant prognostic biomarker for relapse free survival in these patients. Ordonez et al. [108] reported that miR-21 may be a good biomarker for detection of different subpopulations of circulating tumor cells (CTCs) including CTCs with EMT phenotype. Ling and Mao [109] reported that circulating miR-125b is a potential marker for gefitinib sensitivity and correlated with EGFR mutational status in NSCLC thus having prognostic value in NSCLC patients. Mullane et al. [110] predicted outcome in metastatic urothelial cancer patients receiving docetaxel by using miRNA profiling both pre- and post-therapy, and showed that miR-200a correlated with a longer progression free survival in pre-docetaxel patients while miR-125 levels had a significant decrease from pre to post

samples in the good outcome cohort, thus rendering these two miRNAs as potentially useful biomarkers for docetaxel treatment optimization in metastatic urothelial malignancies. Yue et al. [111] reported that increased expression of miR-141 in docetaxel-resistant MCF7/DTX and MDA-MB-231/DTX breast cancer cells may be the mechanism for acquired resistance (possibly through direct interaction with EIF4E) thus providing a potential therapeutic target for treatment of docetaxel-resistant breast cancer. Espin et al. [112] studied the effect of trastuzumab on the antiproliferative effects of PI3K inhibitors in HER2+ breast cancer cells with de novo resistance to trastuzumab and suggested that miR-21, miR-221, and miR-30b may mediate the enhanced antiproliferative effects with combination drugs despite primary resistance in the HER2+ breast cells.

4. Network biology of lncRNA-miRNA interactions in cancer

Before the advent of the miRNA revolution, the primary focus of biological network studies was in the realm of mRNA profiling by microarray studies and generation of mostly static, and sometimes dynamic, networks therefrom. Thus, Nair et al. [113,114] have elucidated differential signaling gene regulatory networks in human prostate cancer tissue as well as human prostate cancer cell lines using the Ingenuity® application. With the recent advances in deep sequencing technology, Wang et al. [115] have reported an integrated analysis of a miRNA regulatory network in nasopharyngeal carcinoma using Illumina HiSeq2000 deep sequencing followed by Ingenuity® suite for regulatory miRNA network analysis. Recently, Nair and Kong [116] have described signature miRNA regulatory networks in cancer such as a network important for conferring chemoresistance to cancer on therapeutic intervention with chemotherapeutic drugs, a network for chemoprevention against cancer, and a novel bifunctional network consisting of miRNAs that potentially play dual roles in both chemoresistance and chemoprevention. Liu and Zhao [117] have described LnCaNet, a pan-cancer co-expression network for 9641 human lncRNAs and 2544 cancer genes in 2922 matched TCGA samples. Cao et al. [118] performed microarray profiling of bone marrow lncRNA expression in Chinese pediatric AML patients and used GO and KEGG pathways analyses to construct a lncRNA-mRNA co-expression network. The specific examples cited above show how the last decade has seen tremendous innovation, as well as increase in complexity, of the cancer biological network(s) from mRNA- to miRNA- and lncRNA-based networks. It follows logically, therefore, that biological networks devoted to understanding interactions between these ncRNAs would be the next frontier in elucidating the contributions of lncRNA-miRNA interactions in cancer. The preceding sections delineated herein have elucidated several lncRNA-miRNA interactions implicated in diverse cancers. Figure 2 represents a biological network of known lncRNA-miRNA interactions in the various cancers discussed herein that was constructed using the Cytoscape 3.3 [119] application. In this figure, "edges" connect interacting lncRNA-miRNA pairs (each ncRNA serving as a discrete "node" of the network), whereas individual miRNAs and lncRNAs that are known to be implicated in cancer, but whose interaction is not evidenced by primary studies in the literature, are depicted as isolated nodes in the bottom panel. This lncRNA-miRNA cancer network will likely expand greatly in the coming days with the explosion of data being reported in this field in current times which is testimony to the importance of lncRNA-miRNA interactions being recognized by cancer scientists for their diagnostic, prognostic, and therapeutic benefits as discussed earlier.
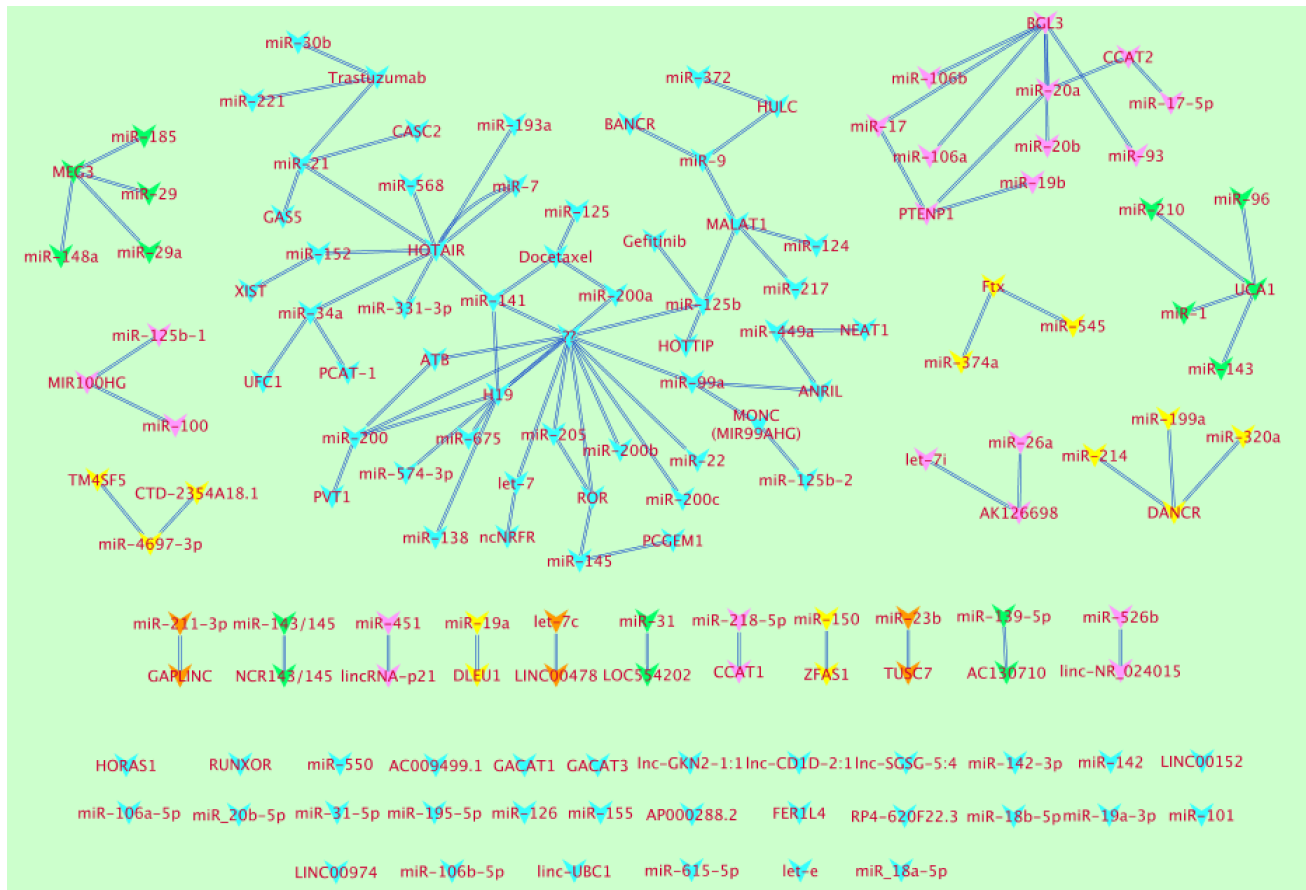
Figure 2. Regulatory cancer network of lncRNA-miRNA interactions. A regulatory cancer network of lncRNA-miRNA interactions is presented wherein each noncoding RNA (ncRNA) is represented as a "node" and interacting ncRNAs are joined by "edges". Nodes interacting within the same subset or subgraph of the regulatory network retain the same color in the figure. Nodes listed in the bottom panel without any edges represent lncRNAs or miRNAs that have been implicated in cancer but whose interacting partners are yet to be identified. A question mark (?) as a node label indicates that the node identity is uncharacterized. The figure was generated using Cytoscape 3.3 [119].

5. Conclusions

Indeed, lncRNA-miRNA interactions are increasingly being discovered in various cancer phenotypes, not limited only to those discussed in this review. Interestingly, the regulatory interaction between miRNAs and lncRNAs is very complex and may involve regulation of the miRNA by the lncRNA, or the converse regulation of the lncRNA by the miRNA, or both. Thus, each interaction pair has to be studied in isolation in a particular cancer microenvironment as there potentially exists spatial or organ-specific expression of certain ncRNAs. Thus, a lncRNA-miRNA interaction in one organ may differ markedly from that in another organ in which the same ncRNAs are expressed, with the "regulator" and "target" switching roles in the altered tumor milieu. However, despite the associated complexity, lncRNA-miRNA interactions are now gaining due attention by the scientific community worldwide. Indeed, the untapped potential of lncRNA-miRNA interactions in terms of its diagnostic,

prognostic and therapeutic potential as targets for clinically actionable intervention as well as biomarker validation in discovery pipelines remains to be explored and will necessitate more research in animal models as well as clinical patient samples in the days ahead.

Currently, there is great excitement over the success of immunotherapies such as anti-PD-1 (programmed death-1) monoclonal antibody nivolumab in cancer, but despite our knowledge of the remarkable clinical benefits of nivolumab in metastatic cancers, only subsets of patients respond to antibody-based therapies including nivolumab [120]. Hence, there is a need for identifying other biomarkers that can complement anti-PD-1 therapy. The role of ncRNAs such as miRNAs and particularly lncRNAs as regulators of innate immune cell development and inflammatory gene expression has been recently described [121]. Future research in the exciting domain of lncRNA-miRNA interactions concurrent with nivolumab intervention will likely unearth interesting information that may lead to successful integration of this knowledge in the clinical pharmacogenomics domain into the oncology clinical care setting. Indeed, this may harness the potential inherent in RNA biology of taking us closer to the goal of "precision" and "personalized medicine" which is tailor-made to the unique needs of each cancer patient, and is clearly the way forward going into the future.

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Conflict of interest

The author declares no conflict of interest.

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