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Review

Influence of microRNAs and Long Non-Coding RNAs in Cancer Chemoresistance

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Abstract: Innate and acquired chemoresistance exhibited by most tumours exposed to conventional chemotherapeutic agents account for the majority of relapse cases in cancer patients. Such chemoresistance phenotypes are of a multi-factorial nature from multiple key molecular players. The discovery of the RNA interference pathway in 1998 and the widespread gene regulatory influences exerted by microRNAs (miRNAs) and other non-coding RNAs have certainly expanded the level of intricacy present for the development of any single physiological phenotype, including cancer chemoresistance. This review article focuses on the latest research efforts in identifying and validating specific key molecular players from the two main families of non-coding RNAs, namely miRNAs and long non-coding RNAs (lncRNAs), having direct or indirect influences in the development of cancer drug resistance properties and how such knowledge can be utilised for novel theranostics in oncology.

Keywords: miRNA; lncRNA; cancer; chemoresistance; drug resistance; tumour; microRNA

1. Introduction

The discovery of the RNA interference pathway in 1998 and the widespread gene regulatory influences exerted by microRNAs (miRNAs) and other non-coding RNAs (ncRNAs) have certainly expanded the level of intricacy present for the development of any single physiological phenotype [1]. Such phenotypes can include clinical conditions of either an acute or a chronic nature. Undoubtedly, cancer best symbolizes clinical conditions relying on multifactorial influences for its development. Furthermore, the clinical presentation of any specific cancer condition in the patient can vary to great extents, depending on multiple tumour characteristics such as the degree of invasiveness, aggressiveness and angiogenesis. However, one of the most crucial cancer phenotypes that pose a major challenge to current conventional chemotherapeutic measures is the ability of the tumour to withstand the pharmacological effects of multiple cancer chemotherapy drugs, typically described as chemoresistance.

Since the influences of ncRNAs in the main facets of cancer development are described in great detail within the scientific literature, this review specifically places a spotlight on the emerging global research efforts that (in the authors' opinion) most effectively recognize the growing link pertaining to non-coding RNA activities with the regulation of cancer chemoresistance properties [2–6].

2. Cancer Chemoresistance Manifestations and Development Mechanisms

Tumours bearing a chemoresistance phenotype can irrevocably thwart the prognosis of the cancer patient, particularly when such characteristics evolve in relapse of the disease. This chemoresistance phenotype has two distinct development mechanisms, leading to the existence of innate and acquired chemoresistance phenotypes [7].

Innate chemoresistance refers to the scenario that an individual tumour can inherently possess unique genetic characteristics that render the tumour to withstand single (or multiple) chemotherapeutic agents, through various influences on drug cytotoxicity circumvention pathways, as described below [7].

In the case of acquired chemoresistance properties, the link between such cancer relapse phases and multi-drug resistant (MDR) tumours is predominantly due to the regular exposure of the tumour to conventional chemotherapeutic cyclical administration [7]. This essentially drives the tumour to evolve at the genetic level to a variant having increased withstanding potential against such conventional chemotherapeutic agents [7].

Since this article focuses specifically on the links identified so far between miRNAs/lncRNAs and cancer chemoresistance properties, it is important to highlight the main recognized mechanisms by which tumours can develop multi-drug resistance against conventional chemotherapeutic agents.

By far the most important and characterised mechanism for the emergence of cancer chemoresistance properties is the employment of drug efflux pumps that actively remove multiple drugs from the tumour cell cytoplasm, including conventional chemotherapeutic agents and eventually leading to MDR [8–12]. The key molecular players involved in drug efflux processes are primarily the ATP-dependent binding cassette (ABC) transporters such as ABCG2, ABCB1 (multidrug resistance 1 gene/P-glycoprotein) and ABCC1 (multidrug resistance-associated protein 1) [8–12]. Another important mechanistic branch leading to chemoresistance is the dysfunction or loss of p53-mediated apoptotic pathways typically triggered by DNA damage, with examples being dysfunctional activity of the mouse double minute 2 gene (Mdm2) and the p53 encoding gene (TP53) [13–15]. In a similar manner, other pro-apoptotic pathways that are typically triggered by cytotoxic drug activities can be hindered within chemoresistant tumour cells. Such pathway issues include cellular FADD-like interleukin 1 beta converting enzyme-inhibitory protein (c-FLIP) and the Bcl-2 protein family members [16–19]. Alternatively, triggering of proliferative/survival signalling pathways such as the ERK and PI3K pathways by means of protein tyrosine kinases, sirtulins, transcription factor kappa B (NFκB) or epidermal growth factor receptor (EGFR) family members can also lead to chemoresistance phenotypes within tumours [20–22]. Furthermore, increased efforts by key molecular components of the nucleotide excision repair pathway can take place as a means of limiting tumour cell DNA damage by cytotoxic drug activity [23–25]. Other mechanisms directing chemoresistance phenotypes in tumours include drug modulation through inactivation or attenuation of cytotoxic drug activity, modification of drug targets and inhibition of tumour suppressor genes that trigger DNA methylation pathways [26–28].

In essence, a particular tumour can be clinically recognized as MDR through the identification of a unique spectrum of dysregulated expression patterns of multiple mRNA biomarkers [29–33]. However, the discovery of the miRNA and long non-coding RNA (lncRNA) families have created additional layers of genomic regulatory functions [2,34–39]. Further insight into the roles conducted by miRNAs and lncRNAs in the development of innate and/or acquired chemoresistance properties by tumours is expected to lead to a more accurate depiction of the cancer patient's condition—both at diagnosis and during possible relapse condition.

The sections below represent a comprehensive summary of the global research efforts in delineating the influences and main mechanistic links of such non-coding RNA families on this specific tumour characteristic. Ultimately, the goal of developing novel theranostic measures for employment in the oncology clinic setting can be attained.

3. Influences of miRNAs in Cancer Chemoresistance

Each physiologically active, individual miRNA consists of a 19–22 nucleotide RNA duplex, bearing a guide strand that is fully or partially complementary to the target transcript to which it binds [40]. This binding, which is typically non-totally complementary, leads to either mRNA target cleavage or a hindering effect on the translational phase of protein synthesis by the ribosomal infrastructure. This has the ultimate effect of a reduction in protein level production for the affected target transcript, or effectively post-transcriptional gene regulation [40].

Since the discovery of the initial concept of miRNA-driven gene regulation in living organisms at the turn of the millennium, close to 2600 miRNAs have been identified and catalogued in human [41]. This large family of gene regulating molecular players leads to a myriad of possibilities to the degree of beneficial and detrimental physiological interactions within the cellular microenvironment, including cancer chemoresistance properties.

Table 1 and Supplementary Materials Table S1 comprise an exhaustive compendium of studies directly focusing on the influence, through dysregulated expression, of specific miRNAs on cancer chemoresistance in the past three years alone:

Table 1. Compendium of miRNAs identified to influence cancer chemoresistance since 2013, either as oncomiRs or as tumour suppressors. A details list of additional such miRNAs, identified prior to 2013, can be obtained through the open-access review publication by Garofalo and Croce [42]. Furthermore, due to recent changes in miRNA annotation and nomenclature, the putative miRNAs mentioned in the literature have been listed according to the latest annotation changes on the miRBase repository, using the miRBase tracker webtool (annotation history of mature miRNA searches) [43]. Table keys: u, Upregulated; d, Downregulated; nd, not described; +, Increase; −, Reduction.

miRNA/s Involved (Species—*Homo sapiens*)	Accession (MIMAT) Number	Cancer Model	Affected Chemotherapeutic Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
miR-34a-5p miR-100-5p miR-146b-5p miR-9-5p miR-193a-3p	0000255 0000098 0002809 0000441 0000459	bladder	neoadjuvant chemotherapy	nd	+	[44]
let-7c-5p	0000064	bladder	Platinum-based neoadjuvant chemotherapy	d	+	[45]
miR-1290 miR-138-5p let-7i-5p let-7b-5p	0005880 0000430 0000415 0000063	bladder	gemcitabine	u u d d	+ + + +	[46]
miR-193a-3p	0000459	bladder	MDR	u	+	[47–49]
miR-21-5p	0000076	breast	gemcitabine	u	+	[50]
miR-25-3p	0000081	breast		d	−	[51]
miR-125b-5p	0000423	breast		u	+	[52]
miR-149-5p	0000450	breast		d	+	[53]
miR-320a	0000510	breast		d	+	[54]
miR-29a-3p	0000086	breast	doxorubicin	u	+	[55]
miR-129-2-3p	0004605	breast	docetaxel	u	+	[56]
miR-139-5p	0000250	breast	docetaxel	d	+	[57]
miR-760	0004957	breast	doxorubicin	u	+	[58]
miR-484	0002174	breast		u	+	[59]

Table 1. *Cont.*

miRNA/s Involved (Species—*Homo sapiens*)	Accession (MIMAT) Number	Cancer Model	Affected Chemotherapeutic Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
miR-223-3p	0000280	breast		d	+	[60]
miR-489-3p	0002805	breast		u	-	[61]
miR-34a-5p miR-222-3p miR-452-5p miR-29a-3p	0000255 0000279 0001635 0000086	breast	doxorubicin docetaxel	u d d d	– – – –	[62]
let-7a-5p	0000062	breast	epirubicin	d	+	[63]
miR-181b-5p	0000257	breast	doxorubicin	u	+	[64]
miR-141-3p	0000432	breast	docetaxel	u	+	[65]
miR-145-5p	0000437	breast	doxorubicin	u	–	[66]
miR-100-5p miR-222-3p miR-30a-3p miR-30a-5p	0000098 0000279 0000088 0000087	breast	doxorubicin docetaxel	u u u u	+ + + +	[67]
miR-30c-5p	0000244	breast		u	–	[68]
miR-155-5p	0000646	breast	tamoxifen	u	+	[69]
miR-663a	0003326	breast	doxorubicin	u	+	[70]
miR-302a-3p miR-302b-3p miR-302c-3p miR-302d-3p	0000684 0000715 0000717 0000718	breast	doxorubicin	u u u u	– – – –	[71]
miR-200c-3p	0000617	breast	doxorubicin	u	–	[72]
miR-181a-5p	0000256	cervical	cisplatin	u	+	[73]
miR-125a-5p	0000443	cervical	paclitaxel	u	–	[74]
miR-100-5p	0000098	chondrosarcoma	cisplatin	u	–	[75]
miR-4299 miR-196b-5p	0016851 0001080	colon	capecitabine oxaliplatin	d u	– –	[76]

Table 1. *Cont.*

miRNA/s Involved (Species—*Homo sapiens*)	Accession (MIMAT) Number	Cancer Model	Affected Chemotherapeutic Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
miR-34a-5p	0000255	colon	5-fluorouracil	u	–	[77]
miR-122-5p	0000421	colon	5-fluorouracil	u	–	[78]
miR-409-3p	0001639	colon	oxaliplatin	u	–	[79]
miR-223-3p	0000280	colon		d	+	[60]
miR-494-3p	0002816	colon	5-fluorouracil	u	–	[80]
miR-125a-5p miR-125b-5p	0000443 0000423	colon	paclitaxel	u	–	[81]
miR-218-5p	0000275	colorectal	5-fluorouracil	u	–	[82]
miR-203a-3p	0000264	colorectal	paclitaxel 5-fluorouracil	u	–	[83,84]
miR-1914-3p miR-1915-3p	0007890 0007892	colorectal	capecitabine oxaliplatin	u u	– –	[85]
miR-204-5p	0000265	colorectal	5-fluorouracil	u	–	[86]
miR-139-5p	0000250	colorectal	5-fluorouracil	u	–	[87]
miR-205-5p miR-373-3p	0000266 0000726	colorectal		u u	+ +	[88]
miR-425-5p	0003393	colorectal	5-fluorouracil oxaliplatin	u	+	[89]
miR-429	0001536	colorectal	5-fluorouracil	u	+	[90]
miR-34a-5p	0000255	colorectal	5-fluorouracil	u	–	[91]
miR-519c-3p	0002832	colorectal	5-fluorouracil irinotecan	d	+	[92]
miR-520g-3p	0002858	colorectal	5-fluorouracil	u	+	[93]
miR-23a-3p	0000078	colorectal	5-fluorouracil	u	+	[94]
miR-96-5p	0000095	colorectal	5-fluorouracil	u	–	[95]
miR-587	0003253	colorectal	5-fluorouracil	u	+	[96]

Table 1. *Cont.*

miRNA/s Involved (Species—*Homo sapiens*)	Accession (MIMAT) Number	Cancer Model	Affected Chemotherapeutic Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
miR-218-5p	0000275	endometrial	paclitaxel	u	–	[97]
miR-125b-5p	0000423	ewing sarcoma	doxorubicin	u	+	[98]
miR-145-5p	0000437	gallbladder	cisplatin	u	–	[99]
miR-1284	0005941	gastric	vincristine	u	–	[100]
miR-375	0000728	gastric	cisplatin	u	–	[101]
miR-23b-3p	0000418	gastric	MDR	u	–	[102]
miR-20a-5p	0000075	gastric	cisplatin	u	+	[103]
miR-34c-5p	0000686	gastric	paclitaxel	d	+	[104]
miR-16-5p	0000069	gastric	etoposide 5-fluorouracil	u	–	[105]
miR-9-5p	0000441	glioblastoma	temozolomide	u	+	[106]
miR-20a-5p	0000075	glioblastoma	temozolomide	u	–	[107]
miR-21-5p	0000076	glioblastoma	doxorubicin	u	+	[108]
miR-873-5p	0004953	glioblastoma	cisplatin	u	–	[109]
miR-210-3p	0000267	glioblastoma	temozolomide	u	–	[110]
miR-138-5p	0000430	glioblastoma	temozolomide	u	+	[111]
miR-125b-5p	0000423	glioblastoma	temozolomide	u	–	[112]
miR-203a-3p	0000264	glioblastoma		d	+	[113]
let-7b-5p	0000063	glioblastoma	cisplatin	d	+	[114]
miR-181b-5p	0000257	glioma	temozolomide	u	–	[115]
miR-124-3p	0000422	glioma	temozolomide	u	–	[116]
miR-200a-3p	0000682	glioma	temozolomide	u	–	[117]
miR-136-5p	0000448	glioma	cisplatin	u	–	[118]
miR-10b-5p	0000254	head/neck squamous cell	cisplatin	u	+	[119]

Table 1. *Cont.*

miRNA/s Involved (Species—*Homo sapiens*)	Accession (MIMAT) Number	Cancer Model	Affected Chemotherapeutic Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
miR-21-5p	0000076	hepatocellular		u	+	[120]
miR-34a-5p	0000255	hepatocellular	sorafenib	u	–	[121]
miR-26b-5p	0000083	hepatocellular	doxorubicin	u	–	[122]
miR-106a-5p	0000103	hepatocellular	gemcitabine	d	+	[123]
miR-101-3p	0000099	hepatocellular	cisplatin	u	–	[124]
miR-125b-5p	0000423	hepatocellular	5-fluorouracil	u	–	[125]
miR-145-5p	0000437	hepatocellular	doxorubicin	u	–	[126]
miR-141-3p	0000432	hepatocellular	5-fluorouracil	u	+	[127]
miR-122-5p	0000421	hepatocellular	sorafenib	d	+	[128]
miR-340-5p	0004692	hepatocellular	cisplatin	u	–	[129]
miR-182-5p	0000259	hepatocellular	cisplatin	u	+	[130]
miR-215-5p	0000272	hepatocellular	doxorubicin	u	+	[131]
miR-135b-5p miR-196b-5p	0000758 0001080	leukaemia	genotoxic agent treatment (eg., etoposide, doxorubicin)	u u	+ +	[132]
miR-17-3p miR-17-5p miR-20a-5p	0000071 0000070 0000075	leukaemia		d d d	– – –	[133]
miR-21-5p	0000076	leukaemia	etoposide, doxorubicin	d	–	[134]
miR-181a-5p	0000256	leukaemia	doxorubicin	u	+	[135]
miR-181c-5p	0000258	leukaemia	chronic myelocytic leukaemia	u	–	[136]
let-7a-5p	0000062	leukaemia	cytarabine	d	+	[137]
let-7c-5p	0000064	lung	cisplatin	u	–	[138]
miR-1244	0005896	lung	cisplatin	u	–	[139]
miR-96-5p	0000095	lung	cisplatin	u	+	[140]

Table 1. *Cont.*

miRNA/s Involved (Species—*Homo sapiens*)	Accession (MIMAT) Number	Cancer Model	Affected Chemotherapeutic Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
miR-107	0000104	lung	cisplatin	u	–	[141]
miR-378a-3p	0000732	lung	cisplatin	u	–	[142]
miR-192-5p	0000222	lung	cisplatin	u	+	[143]
miR-205-5p	0000266	lung		u	+	[144]
miR-21-5p	0000076	lung	cisplatin	d	–	[145]
miR-24-3p	0000080	lung	etoposide, cisplatin	d	+	[146]
miR-299-3p	0000687	lung	doxorubicin	u	–	[147]
miR-27a-3p	0000084	lung	cisplatin	u	–	[148]
miR-551a	0003214	lung		u	+	[149]
miR-100-5p	0000098	lung		u	+	[150]
miR-146a-5p	0000449	lung	cisplatin	u	+	[151]
miR-182	(sequence not listed in paper)	lung	cisplatin	u	+	[152]
miR-650	0003320	lung	docetaxel	u	+	[153]
miR-224-5p	0000281	lung	cisplatin	u	+	[154]
miR-451a	0001631	lung	docetaxel	u	–	[155]
miR-15b-5p	0000417	lung	cisplatin	u	–	[156]
miR-148b-3p	0000759	lung	cisplatin	u	–	[157]
miR-205-5p miR-218-5p	0000266 0000275	lung	carboplatin	u u	+ +	[158]
miR-26b-5p	0000083	lung		d	–	[159]
miR-192-5p	0000222	lung	gemcitabine, cisplatin	u	–	[160]
miR-197-3p	0000227	lung	platinum-based	d	+	[161]
miR-7-5p	0000252	lung		u	–	[162]
miR-940	0004983	lung	cisplatin	d	+	[163]

Table 1. *Cont.*

miRNA/s Involved (Species—*Homo sapiens*)	Accession (MIMAT) Number	Cancer Model	Affected Chemotherapeutic Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
miR-200b-3p	0000318	lung	docetaxel	u	–	[164]
miR-200c-3p	0000617	lung	methotrexate	u	–	[165]
miR-494-3p	0002816	lung		u	–	[166]
miR-377-3p	0000730	lymphoma (b-cell)	venetoclax	u	+	[167]
miR-125b-5p miR-130a-3p	0000423 0000425	lymphoma (b-cell)	cyclophosphamide, doxorubicin, vincristine	u u	+ +	[168]
miR-21-5p	0000076	nasopharyngeal	cisplatin	u	+	[169]
miR-634	0003304	nasopharyngeal	paclitaxel	u	–	[170]
miR-214-3p	0000271	oesophageal (squamous cell)	cisplatin	u	–	[171]
miR-21-5p	0000076	oesophageal (squamous cell)	5-fluorouracil cisplatin (circulating miRnas)	u	+	[172]
miR-193a-3p	0000459	oesophageal	chemoradiation	u	–	[173]
miR-27a-3p	0000084	oesophageal	cisplatin	u	+	[174]
miR-221-3p	0000278	oesophageal	5-fluorouracil	u	+	[175]
miR-181a-5p	0000256	oral squamous cell	cisplatin	u	–	[176]
miR-23a-3p	0000078	oral squamous cell	cisplatin	u	+	[177]
miR-143-3p	0000435	osteosarcoma	doxorubicin	d	+	[178]
miR-101-3p	0000099	osteosarcoma	cisplatin doxorubicin methotrexate	u	–	[179]
miR-29b-1	MI00000105 (precursor)	osteosarcoma		u	–	[180]
miR-33a-5p	0000091	osteosarcoma	cisplatin	u	+	[181]
miR-34c-5p	0000686	osteosarcoma		u	–	[182]

Table 1. *Cont.*

miRNA/s Involved (Species—*Homo sapiens*)	Accession (MIMAT) Number	Cancer Model	Affected Chemotherapeutic Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
miR-301a-3p	0000688	osteosarcoma	doxorubicin	u	+	[183]
miR-22-3p	0000077	osteosarcoma		u	–	[184]
miR-382-5p	0000737	osteosarcoma		u	–	[185]
miR-193a-5p	0004614	osteo-/ewing sarcoma	cisplatin	u	–	[186]
miR-136-5p	0000448	ovarian	cisplatin	u	+	[187]
miR-30a-5p	0000087	ovarian	cisplatin	u	–	[188]
miR-149-5p	0000450	ovarian	paclitaxel	d	+	[189]
miR-9-5p	0000441	ovarian	paclitaxel	d	+	[190]
miR-21-3p	0004494	ovarian	cisplatin	u	+	[191]
miR-31-5p	0000089	ovarian	cisplatin	u	+	[192]
miR-31-5p	0000089	ovarian	taxane	u	–	[193]
miR-29b-3p	0000100	ovarian	paclitaxel	d	+	[194]
miR-200a-3p	0000682	ovarian	paclitaxel	u	–	[195]
miR-506-3p	0002878	ovarian	cisplatin olaparib	u	–	[196]
miR-433-3p	0001627	ovarian	paclitaxel	u	+	[197]
miR-186-5p	0000456	ovarian	cisplatin	u	–	[198]
miR-1307-3p	0005951	ovarian		u	+	[199]
miR-224-5p	0000281	ovarian	cisplatin	u	+	[200]
miR-130a-3p miR-374a-5p	0000425 0000727	ovarian	cisplatin	u u	– –	[201]
miR-106a-5p	0000103	ovarian	cisplatin	u	–	[202]
miR-106a-5p miR-591	0000103 0003259	ovarian	paclitaxel	u d	+ +	[203]

Table 1. *Cont.*

miRNA/s Involved (Species—*Homo sapiens*)	Accession (MIMAT) Number	Cancer Model	Affected Chemotherapeutic Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
miR-770-5p	0003948	ovarian	cisplatin	u	–	[204]
miR-21-5p	0000076	ovarian	paclitaxel; exosome-driven	u	+	[205]
miR-199b-5p	0000263	ovarian	cisplatin	d	+	[206]
miR-145-5p	0000437	ovarian	paclitaxel	u	–	[207]
let-7e-5p	0000066	ovarian	cisplatin	d	+	[208]
miR-152-3p	0000438	ovarian	cisplatin	u	–	[209]
miR-128-3p	0000424	ovarian	cisplatin	d	+	[210]
miR-484 miR-642a-5p miR-217	0002174 0003312 0000274	ovarian		d d d	+ + +	[211]
miR-23a-3p miR-27b-3p miR-424-5p miR-503-5p	0000078 0000419 0001341 0002874	ovarian		u u u u	+ + + +	[212]
miR-21-5p miR-214-3p	0000076 0000271	ovarian	carboplatin paclitaxel	u u	+ +	[213]
miR-182-5p	0000259	ovarian	cisplatin paclitaxel	u	+	[214]
miR-200c-3p	0000617	pancreatic		u	-	[215]
miR-33a-5p	0000091	pancreatic	gemcitabine	u	-	[216]
miR-17-92 cluster		pancreatic		d	+	[217]
miR-221-3p	0000278	pancreatic	5-fluorouracil	u	+	[218]
miR-1246	0005898	pancreatic		u	+	[219]
miR-181b-5p	0000257	pancreatic	gemcitabine	u	+	[220]
miR-494-3p	0002816	pancreatic		u	–	[221]

Table 1. *Cont.*

miRNA/s Involved (Species—*Homo sapiens*)	Accession (MIMAT) Number	Cancer Model	Affected Chemotherapeutic Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
miR-101-3p	0000099	pancreatic	gemcitabine	u	–	[222]
miR-100-5p	0000098	pancreatic (ductal)	gemcitabine	u	+	[223,224]
miR-21-5p	0000076			u	+	
miR-99a-5p	0000097			u	+	
miR-125b-5p	0000423			u	+	
miR-138-5p	0000430			u	+	
miR-210-3p	0000267			u	+	
miR-31-3p	0004504			d	+	
miR-330-3p	0000751			d	+	
miR-378-5p	0000731			d	+	
let-7a-5p	0000062	pancreatic	gemcitabine	u	–	[225]
miR-205-5p	0000266	pancreatic	gemcitabine	u	–	[226]
miR-506-3p	0002878	pancreatic		d	+	[227]
miR-3176	0015053	prostate	paclitaxel	d	+	[228]
miR-141-3p	0000432			d	+	
miR-5004-5p	0021027			d	+	
miR-16-5p	0000069			d	+	
miR-3915	0018189			d	+	
miR-488-3p	0004763			d	+	
miR-23c	0018000			d	+	
miR-3673	0018096			d	+	
miR-3654	0018074			d	+	
miR-32-5p	0000090			u	+	
miR-606	0003274			u	+	
miR-381-3p	0000736			u	+	
miR-429	0001536			u	+	
miR-708	0004926	renal	doxorubicin	u	–	[229]
let-7b-5p	0000063	renal	5-fluorouracil	u	–	[230]
let-7c-5p	0000064			u	–	
miR-200c-3p	0000617	renal	docetaxel	d	+	[231]

The list of scientific literature depicting the involvement of miRNAs in cancer chemoresistance, as described above, highlights specific trends that require chemoresistance biomarker investigators to delve further for enhanced insight.

In essence, over 10% of all reported research findings of miRNA influences in cancer chemoresistance demonstrated that such a phenotype modulation was effected through simultaneous dysregulation of multiple miRNAs, rather than an individual putative chemoresistance miRNA—though no specific miRNA combination was identified as most prevalent by the authors [44,46–49,62,67,71,76,81,85,88,132,133,158,168,201,203,211–213,217,223,224,228,230]. This suggests that miRNA influences on cellular functions also occur at a more complex level, whereby it is a signature dysregulated expression pattern of two (or more) miRNAs that trigger simultaneous downregulation of a specific set of target transcripts leading to an ultimate change in cellular/tissue phenotype. Further evidence for this can be concluded by previous efforts carried out by the authors, whereby a set of seven putative chemoresistance miRNAs were identified for neuroblastoma—a paediatric cancer model [232].

The mechanistic links between miRNA activity and chemoresistance development that have been identified so far reveal that miRNA dysregulated expression can indeed influence the main cellular pathways (described in Section 2 above) that are directly affecting chemoresistance emergence in tumour models.

In the first instance, miRNAs have been recognized to regulate MDR-related molecular players such as multidrug resistance-associated protein 1 (MRP-1) [66]. The study carried out by Gao and colleagues identified the gene regulatory effects of miR-145-5p on MRP-1, ultimately enhancing the level of chemosensitivity in the doxorubicin resistant MCF-7 breast cancer cell line [66]. Furthermore, the study performed by Zhan and colleagues identified that MRP-1 could also be downregulated through the overexpression of miR-145-5p in cisplatin-resistant gallbladder tumour models, resulting in sensitizing of the tumour cells to cisplatin activity [99]. Similarly, the study conducted by Zhao and colleagues revealed that a combination of four miRNAs, namely miR-302a-3p/b-3p/c-3p/d-3p, concomitantly provide similar effects in doxorubicin-resistant breast cancer MCF-7 cell lines [71]. This study confirmed through RT-qPCR and Western blotting techniques that over-expression of these miRNAs induced sensitization to doxorubicin through a reduction in the expression level of MAP/ERK kinase 1 (MEKK1), leading to an overall downregulation of P-glycoprotein (P-gp) expression [71].

Other studies have demonstrated miRNA influences on the p53 pathway status as a means of inducing chemoresistance properties. The study conducted by Shen and colleagues recognized the effect of up-regulated miR-29a-3p in exacerbating doxorubicin-resistance in breast cancer cell lines, through its regulatory function on PTEN and GSK3β, that are two major components of the PTEN/AKT/GSK3β signalling pathway providing feedback to TP53 [55]. Further evidence for such miRNA influences on p53 modulation include the study carried out by Qin and colleagues, who revealed that the over-expression of miR-182-5p can induce cisplatin chemoresistance in hepatocellular carcinoma HepG2-Rcells [130]. This exacerbation was found to occur through the direct regulatory effect of the miRNA on tumour protein 53-induced nuclear protein 1 (TP53INP1) [130].

Evidence for the mechanistic link between miRNA activity and apoptotic pathway dysfunction for the emergence of chemoresistance in cancer includes the study performed by Zhang and colleagues [89]. The outcome of this investigation identified the exacerbating effect of miR-425-5p on chemoresistance in colorectal cancer HCT116 cell lines as well as in xenograft models, through direct action on programmed cell death 10 (PCD10) [89]. In addition, Stojcheva and colleagues reported the acquisition of chemoresistance properties by glioblastoma to alkylators such as temozolomide due to miR-138-5p direct regulatory function on BIM, which is a Bcl-2 interacting mediator of apoptosis [111]. Furthermore, miR-182-5p was also identified as playing a key role in the development of chemoresistance in ovarian carcinomas due to its gene-regulating capacity on programmed cell death 4 (PDCD4) [214].

The influences of miRNA activity on cell proliferative function, as another mechanism for chemoresistance emergence, is described through the study performed by Ye and colleagues on

chemoresistant breast cancer cell line models [59]. This seminal investigation recognized the downregulatory effect of miR-484 on cytidine deaminase (CDA), which is a major molecular player in controlling cell proliferation through its suppressive function on cyclin E-CDK2 signalling, thereby inhibiting any cell-cycle progress [59]. Interestingly, the investigation conducted by Phatak and colleagues on oesophageal squamous cancer cell line models revealed that overexpression of miR-214-3p resulted in the sensitization of such tissue cultures to cisplatin [171]. Such a reduction in chemoresistance by miR-214-3p was mediated by direct regulation of surviving expression, together with indirect regulation by means of downregulation of CUG-BP1, leading to decreased mRNA stability in the targeted tumour cells [171].

Cytotoxic drug-induced DNA damage response pathway was also found to be affected by miRNA influence. The study performed by Li and colleagues identified that such a pathway can be activated by upregulation of the inhibitor of growth 5 (ING5) gene, which is in turn regulated by miR-193a-3p within the bladder cancer cell line 5637 [49]. In addition, inhibition of ING5 in this study resulted in a drastic reduction of the DNA damage response pathway within the same cell line [49].

Evidence for the modulation of cytotoxic drug targets by miRNAs can be reflected in the study performed by Liang and colleagues on gemcitabine resistant MiaPiaCa-2 pancreatic cell cancer models [216]. Results of this study led to the regulatory role of miR-33a in β-catenin downregulation, with the latter being a key molecular player in directing the expression levels of multiple genes including cyclin D1, surviving and MDR-1 [216].

In addition to the effect of multiple miRNAs on cancer chemoresistance, several studies reported the possible influences exhibited by circulating miRNAs (in blood), typically through extracellular vesicle or exosome transport [67,168,172,205,228].

Exosomes can be characterized as endocytic vesicles that can be secreted by multiple cell types within the human body, carrying a spectrum of molecular players, including miRNAs, for the purpose of cell-cell communication (e.g., antigen presentation) [233]. The transfer of genomic components such as mRNA and miRNAs between two individual cells of varying morphology, such as from bone marrow to mast cells, was also identified to lead to novel protein synthesis within the recipient cells [233]. Consequently, exosomal transfer can be reliably considered as an additional method of influence on multiple molecular pathways, since the desired physiological effect/s is induced from cellular populations situation within remote locations.

The effect of exosome activity can also be linked within the context of cancer chemoresistance, such as the findings described by Chen and colleagues [67]. This study highlighted the effect of exosomes on chemoresistant breast cancer cell lines, focusing on the transfer of miR-222-3p from doxorubicin resistant MCF-7 cell line to a chemosensitive MCF-7 cell line model [67]. This exosomal transfer ultimately rendered the recipient breast carcinoma cell line more resistant to doxorubicin activity following post-transfer functional assays [67].

Furthermore, the study carried out by Au Yeung and colleagues identified and validated the effect of exosomal transfer of miRNAs in drug resistant ovarian cancer models [205]. This study identified the exosomal transfer of miR-21-5p from cancer-associated adipocytes (within the omental stroma) into ovarian carcinoma cell populations [205]. This transfer ultimately conferred paclitaxel chemoresistance properties to the recipient ovarian carcinoma cells due to the direct regulatory effect of miR-21-5p on the transcript for apoptotic protease activating factor 1 (APAF1) [205].

Exosome transfer was also identified as being implicated in chemoresistance conferring to prostate cancer, as highlighted by the investigation by Li and colleagues [228]. The study identified 29 dysregulated miRNAs within exosomes derived from two paclitaxel resistant prostate cancer cell line models [228].

4. Influences of lncRNAs in Cancer Chemoresistance

Notwithstanding the myriad of networking interactions leading to miRNA directed gene regulatory effects within cellular populations, the more recent discovery of a separate family of

non-coding RNAs, namely lncRNAs, leads to the identification of an additional level of gene regulation within the human body. According to the latest version of LNCipedia, there are over 60,000 members of the lncRNA family that have been catalogued [234,235]. LncRNAs are non-coding RNA genes of at least 200 nucleotides long. LncRNAs can either act as positive or negative regulators of target gene expression, with this activity being directed either on transcripts originating from the same locus as the lncRNA itself (cis-acting) or directed on target transcripts originating on other loci (trans-acting) [6].

Table 2 and Supplementary Materials Table S2 highlight in detail the currently reported scientific evidence for the influence of multiple lncRNAs on varying cancer models. Interestingly, previous studies have highlighted the detrimental effects of one individual lncRNA, known as homeobox transcript antisense RNA (HOTAIR), having an elevated prevalence within multiple tumour chemoresistance phenotypes [236–238].

The investigation carried out by Fang and colleagues focused on the possible effects of HOTAIR on chemoresistance in small cell lung cancer, mainly through knock-down of the lncRNA in chemoresistant and parental cell line models, followed by viability assays [236]. Apart from confirming HOTAIR knock-down with enhanced chemosensitivity of the affected cell lines to doxorubicin, cisplatin and etoposide, the study also recognized the chemoresistance phenotype was additionally linked to increased methylation of homeobox A1 (HOXA1), suggesting HOTAIR influences in affecting such a methylation status [236]. The study also confirmed that HOTAIR inhibition, through short hairpin RNA antagonist employment in murine tumour xenograft models for small cell lung cancer, led to a reduction in tumour growth [236].

In a similar study conducted by Liu and colleagues, HOTAIR expression was discovered to be up-regulated in the cisplatin-resistant A549 lung adenocarcinoma cell line model, with consequent re-sensitisation of the cell line to cisplatin exposure following HOTAIR knock-down [237]. This short interfering RNA (siRNA)-induced HOTAIR knock-down effect was also linked to enhanced cell cycle arrest and apoptosis, together with a reduction in cell proliferation, through control of $p21^{WAF1/CIP1}$ expression [237].

Furthermore, the study performed by Ozes and colleagues investigated the possible influences of HOTAIR on ovarian cancer chemoresistance properties, specifically for platinum-based chemotherapeutic agent chemoresistance [238]. The results of the study highlighted exacerbated HOTAIR expression within platinum drug resistant ovarian tumour samples when compared to primary ovarian tumour counterpart samples [238]. The study also revealed that HOTAIR up-regulation allows for prolonged NF-*K*B expression, leading to extended DNA damage response mechanisms to take place, following platinum-based drug exposure and therefore contributing to the chemoresistance phenotype development [238].

In addition to HOTAIR, another putative chemoresistance lncRNA of particular interest is MRUL (NR_024549), since the chromosomal locus for MRUL is in close proximity to the locus for the Multi Drug Resistance 1 (MDR1) gene—the latter being recognised as the most important gene to induce cancer chemoresistance phenotypes [239]. Such a study highlights the unique properties of lncRNAs in their capacity to perform cis-regulatory functions on neighbouring transcripts of clinical relevance.

Evidence for the regulatory role of lncRNAs in directing both cell proliferative signalling and drug modulation mechanisms affecting chemoresistance can be found in the study performed by Dong and colleagues [240]. This particular study recognised the effect of GAS5 in enhancing apoptosis due to gefitinib activity within innate EGFR tyrosine-kinase inhibitor (TKI) resistant lung adenocarcinomas (A549 cell line), through the gene regulating role of GAS5 on insulin-like growth factor 1 receptor (IGF-1R) [240]. Interestingly, the investigation conducted by Cheng and colleagues identified UCA1 as being upregulated in acquired (non T790M) EGFR-TKI resistant non-small cell lung cancer [241]. UCA1 knockdown assays confirmed that this lncRNA, when downregulated, allowed for increased gefitinib sensitivity and furthermore inhibited AKT/mTOR functions [241].

Table 2. Compendium of lncRNAs identified to influence cancer chemoresistance, either as oncogenic lncRNAs or as tumour suppressors. Table keys: u, Upregulated; d, Downregulated; +, Exacerbation; −, Inhibition.

lncRNA/s involved (Species—*Homo sapiens*)	gene ID (LNCipedia.org—Where Applicable)	Cancer Model	Affected Chemo-Therapy Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
UCA1	UCA1	bladder	cisplatin, gemcitabine	u	+	[242,243]
NONHSAT028712 NONHSAT057282 NONHSAG023333	lnc-DGKA-1 lnc-RP11-677O4.1.1-7 lnc-TXNDC2-7	breast	doxorubicin	u u u	+ + +	[244]
ARA	lnc-ALG13-7	breast	doxorubicin	u	+	[245]
ATB	lncRNA-AL589182	breast	trastuzumab	u	+	[246]
GAS5	GAS5	breast	trastuzumab	d	+	[247]
XIST 53BP1	XIST Lnc-TP53BP1-1	breast	alkylating agents	u d	+ +	[248]
CCAT2	lnc-POU5F1B-8	breast	5-fluorouracil	u	+	[249]
snaR	lnc-BSPH1-1/2	colon	5-fluorouracil	u	+	[250]
LINC00152	LINC00152	colon	oxaliplatin	u	+	[251]
SLC25A25-AS1	SLC25A25-AS1	colorectal		d	+	[252]
MRUL	(NR_024549)	gastric	MDR	u	+	[239]
AK022798	lnc-TRAF3IP3-3	gastric	cisplatin	u	+	[253]
PVT1	PVT1	gastric	MDR	u	+	[254]
LINC-ROR	LINC-ROR	hepatocellular	sorafenib, doxorubicin	u	+	[255]
CCAT1	lnc-TMEM75-3	lung	docetaxel	u	+	[256]
AK126698	(LINC00969)	lung	cisplatin	d	+	[257]
HOTAIR	HOTAIR	lung	MDR	u	+	[236,237]
GAS5	GAS5	lung	EGFR-tyrosine kinase inhibitors	u	−	[240]
UCA1	UCA1	lung	EGFR-tyrosine kinase inhibitors	u	+	[241]
MEG3	MEG3	lung	cisplatin	u	+	[258]
GAS5	GAS5	lymphoma (mantle cell)	mTOR inhibitors	u	−	[259]

Table 2. *Cont.*

lncRNA/s involved (Species—*Homo sapiens*)	gene ID (LNCipedia.org—Where Applicable)	Cancer Model	Affected Chemo-Therapy Drugs	Dysregulation Status	Effect on Chemo-Resistance Phenotype	Ref.
N375709	(lnc-SRCIN1-1)	nasopharyngeal	paclitaxel	d	–	[260]
LINC-ROR	LINC-ROR	nasopharyngeal		u	+	[261]
TUG1	TUG1	oesophageal		u	+	[262]
LINC00161	LINC00161	osteosarcoma	cisplatin	u	–	[263]
ODRUL	FOXC2-AS1	osteosarcoma	doxorubicin	u	+	[264]
ODRUL	FOXC2-AS1	osteosarcoma	doxorubicin	u	+	[265]
HOTAIR	HOTAIR	ovarian	platinum-based drugs	u	+	[238]
PVT1	PVT1	ovarian	cisplatin	u	+	[266]
UCA1	UCA1	ovarian		u	+	[267]
HOTTIP	BCYRN1	ovarian	carboplatin	d	+	[268]
HOTTIP	BCYRN1	pancreatic	gemcitabine	u	+	[269]
PVT1	PVT1	pancreatic	gemcitabine	u	+	[270]
MALAT-1	MALAT1	pancreatic		u	+	[271]
GAS5	GAS5	prostate	mTOR inhibitors	u	–	[272]
UCA1	UCA1	breast	tamoxifen	u	+	[273]

5. Conclusions and Perspectives

In essence, it can be stated that ncRNAs do have a place in regulating cancer chemoresistance properties, merely based on the body of evidence described above. Furthermore, the recent scientific literature on this niche research reveals that both miRNAs and lncRNAs have important roles in affecting the main mechanisms currently known to lead to the development of cancer chemoresistance phenotypes (see Figure 1).

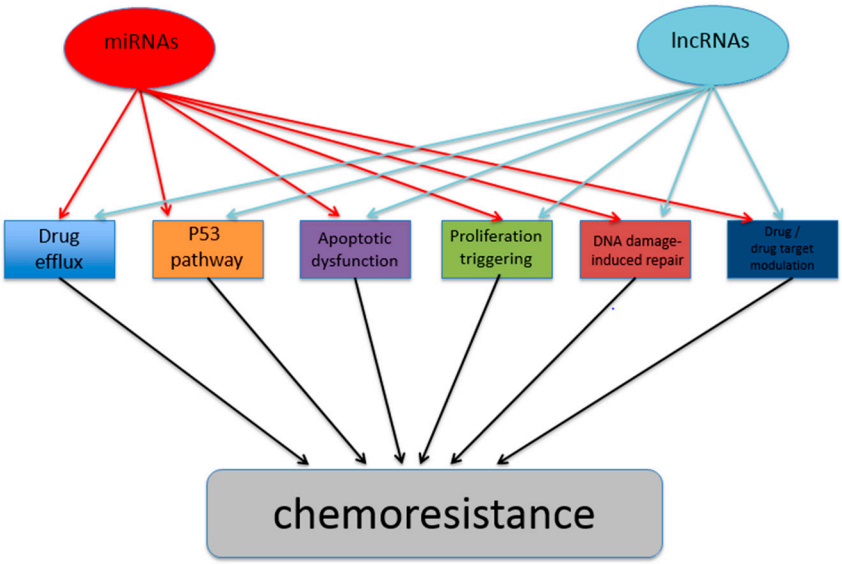

Figure 1. Model of miRNA and lncRNA influences on varying molecular pathway mechanisms leading to downstream effects on cancer chemoresistance phenotypes.

Undoubtedly, the recent progress in molecular analytical and sequencing technologies has advanced to the levels that the entire miRnome/lncRNome can be quantified in a rapid and reliable manner, facilitating investigators' efforts to identify unique expression profiles that are linked with defined tumour chemoresistance properties.

Such breakthroughs in technology are proving to be essential for biomarker researchers since evermore studies are leading to the paradigm that tumour clinical characteristics such as chemoresistance are the result of influence by multiple miRNAs and/or lncRNAs acting in a simultaneous manner, and not merely the outcome of one individual non-coding RNA's dysregulated expression. The issue with this paradigm is the degree of complexity and resource consumption in carrying out detailed functional analyses to validate each permutation of non-coding RNA influences from an identified expression profile comprising just a handful of miRNAs/lncRNAs. Hopefully, further advances in bioinformatics and analytical technologies can permit more accurate trawling efforts to pinpoint such biomarkers and/or possibly allow for high throughput functional analyses for the entire miRnome/lncRNome in a rapid and effective manner.

The clinical importance for all global research efforts to identify and validate novel non-coding RNA biomarkers for cancer chemoresistance must certainly not be underestimated. The validation of reliable miRNA and/or lncRNA biomarkers for individual cancer chemoresistance (be it innate or acquired) can lead to the exploitation of such biomarkers as novel drug targets. Ultimately, antagonists and/or mimics (depending whether the miRNA/lncRNA is up- or down-regulated) for each non-coding RNA drug target can be developed and safely delivered as adjunct therapy together with conventional chemotherapeutic drugs. The adjuvant therapy leads to enhanced tumour sensitivity for the conventional chemotherapeutic drugs, therefore markedly enhancing chemotherapy effectiveness.

Alternatively, in patients who are particularly prone to the dose limiting adverse effects of conventional chemotherapy, the doses for the latter can be reduced due to the addition of the novel non-coding RNA-directed therapy. This leads to a great reduction in dose-limiting adverse effects and consequent discomfort in the cancer patient.

Finally, such chemoresistance biomarker expression profiles can be easily quantified from tumour biopsy through real time quantitative polymerase chain reaction (RT-qPCR) assays. The additional clinical information regarding the chemoresistance properties can provide the oncologist with valuable pre-emptive knowledge. Such additional information aids in developing a bespoke chemotherapy drug combination for the cancer patient that maximizes therapeutic efficacy and therefore minimises "trial and error" chemotherapy regimes, since the tumour would be exposed only to the chemotherapeutic agents to which it is fully sensitive.

However, efforts to render such a powerful theranostic technology is confronted with two main issues for it to become commonplace within global reach.

Firstly, the most effective technologies for accurate quantitative analysis of ncRNAs remain to be real-time, reverse transcription quantitative PCR (RT-qPCR) and next-generation sequencing. Both such technologies require sophisticated equipment and highly skilled staff dedicated to the processing of clinical samples for miRNA and lncRNA expression profiling. Eventually, these technologies can be miniaturized and simplified to the level of the development of a cost-effective point-of-care diagnostic apparatus that can be utilised by healthcare professionals with limited experience in the analytical technologies being employed.

Secondly, the issues regarding safe and effective drug delivery of novel miRNA and lncRNA therapeutics still pose a hurdle to rapid development of such translational medicine and effective availability for use by the individual cancer patient. Notwithstanding this issue however, the pharmaceutical industry are currently focusing hard on multiple circumvention methods for effectively providing efficient drug delivery options. These efforts are concentrated in pharmaceutical companies that are entirely dedicated to the research and development of miRNA and lncRNA-based therapeutics.

However, the authors sincerely believe that, despite such challenges, the advent of such novel clinical oncology drug treatment/management protocols will become a reality within the hospital setting in the not too distant future.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4425/8/3/95/s1, Table S1: Frequency chart depicting prevalence of individual miRNAs in specific cancer models reported in the literature (as depicted in Table 1 above) and from the data reported in the review article by Garofalo and Croce [42], Table S2: Frequency chart depicting prevalence of individual lncRNAs in specific cancer models reported in the literature (as depicted in Table 2 above).

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

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