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MicroRNAs as mediators of drug resistance mechanisms

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MicroRNAs are small RNA transcripts involved in fine-tuning of several cellular mechanisms and pathways crucial for maintaining cells' homeostasis like apoptosis, differentiation, inflammation and cell-cycle regulation. They act by regulation of gene expression at post-transcriptional level through fine-tuning of target proteins expression. Expression of microRNAs is cell-type specific and since their discovery they have been proven to be deregulated in various disorders including cancer. Several lines of evidence are emerging that link microRNAs to drug resistance mechanisms in tumours given their important role in modulating oncogenic and tumour suppressive mechanisms. This review will focus on latest knowledge of the roles and mechanisms of microRNAs as mediators to drug resistance and the implications for future therapies.

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Introduction

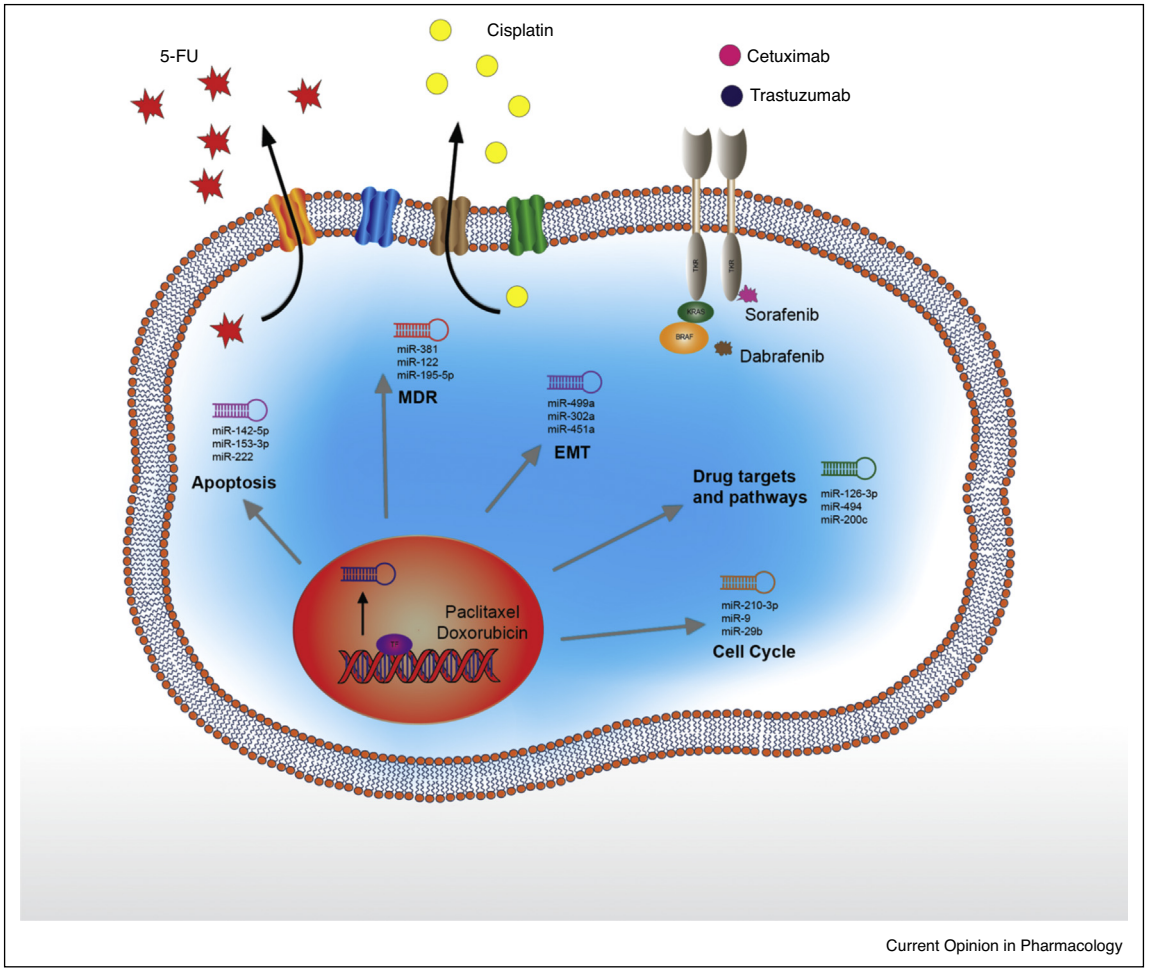
In the past decade chemotherapeutic treatments have become more successful in many types of cancers boosted by the contribution given by the discovery of biological compounds able to impair essential cell oncogenic pathways and the emerging of more specific compounds (i.e., small molecules; monoclonal antibodies) for targeted therapies. In parallel, increased knowledge about deregulated cancer molecular make-up helped to stratify patients who can benefit more from specific drugs [1,2]. Nevertheless, all these achievements have been continuously hampered by drug resistance to treatment that still remains one the major clinical hurdle to successful therapeutic outcome. Drug resistance arises from mechanisms that can be classified as primary or acquired. In general, resistance to standard chemotherapy and/or to biological compounds might reside on tumour primary molecular complexity as well as on intra-tumour heterogeneity driven by cancer initiating cells [3].

MicroRNAs (miRNAs) belong to a wide class of non-coding RNAs species that includes moreover long non-coding RNAs, and several of which involved in drugs resistance mechanisms. In particular, miRNAs are small (18–22 nucleotides) non-coding RNAs that act in most cases by binding to the 3′-untranslated region (3′-UTR) of their target messenger RNAs and mediating post-translational degradation and down modulation of proteins thus fine modulating several cells' pathways in maintenance of homeostasis [4,5]. Given their important role in regulation of cellular mechanisms, miRNAs have been constantly studied as one of the potential reasons for drug resistance mechanisms provided by the evidence of their involvement in virtually all hallmarks of cancer [6]. The main mechanisms through which miRNAs might mediate drug resistance have been related to different cellular functions like apoptosis, cell cycle modification, alteration in drug targets and regulation of drugs efflux transporters [7] (Figure 1). Furthermore, miRNAs are not only present within cells, but also detected in body fluids (i.e., plasma, urine) and are actively secreted from cells in extracellular vesicles like exosomes. These vesicles have been described as a way of inter-cellular communication and they are used by tumour cells to transport miRNAs to other sites in the body thus promoting and transferring resistance/sensitivity towards treatments [8–10]. This peculiar cells' communication mechanisms can be exploited for new miRNA-based therapeutics in order to overcome drug resistance.

MiRNAs and apoptosis

In the past few years new evidences supporting the role of miRNAs in mediating drug resistance to compounds that promote apoptosis have emerged [9–13]. One of the most common used drugs for treating different types of tumours is cisplatin and observed resistance mechanism are often dependent on miRNAs. Taking into account the previous observations of general low expression of miR-1208 in various cancers, *in vitro* experiments in kidney cancer cells, revealed that miR-1208 acts as tumour suppressor by directly targeting 3′-UTR of TBC1 domain

Figure 1



miRNAs involvement in mediation of cellular mechanism of drug resistance. Representation of the different cellular mechanisms of miRNAs in mediating drug resistance against commonly used tumour chemotherapeutics (i.e.: 5-Fluorouracil; cisplatin; cetuximab; trastuzumab; sorafenib; dabrafenib; paclitaxel; doxorubicin). MicroRNAs are important post-transcriptional regulators for several pathways (MDR = multidrug resistance; EMT = epithelial-mesenchymal-transition; apoptosis; drug targets and pathways; cell cycle) potentially resulting in therapy failure.

containing kinase (TBCK) a mediator of cisplatin and TNF-related apoptosis-induced ligand (TRAIL) sensitivity, thus mediating sensitivity to drugs through anti-apoptotic mechanisms involving activation of caspase-dependent pathway [11]. Mechanisms of cisplatin resistance have been also shown to be based on miRNA de-regulation in ovarian cancers: *in vitro* and *in vivo* experiments demonstrated that miR-338-3p is able to enhance cisplatin sensitivity through downregulation of WNTB2 and promote apoptosis while inhibiting proliferation and epithelial-mesenchymal-transition (EMT) [12]. Another report showed that miR-142-5p specifically targets five anti-apoptotic regulators (XIAP, BIRC3, BCL2, BCL2L2 and MCL1) in ovarian cancer cell lines and supported by clinical observation of dysregulation of these targets. Given the broad effect observed on apoptotic regulators, the authors suggested the potential use of miR-142-5p mimics for increasing cisplatin sensitivity as therapeutic option [13]. Interference with apoptotic mechanisms has been demonstrated in chronic myeloid leukaemia (CML) cancer where downregulation of miR-153-3p has been proved to modulate imatinib resistance by targeting BLC2 [14]. Recently, miR-122 overexpression has been confirmed to interfere with apoptotic mechanisms and mediate resistance to sorafenib by modulating caspase-3 expression in hepatocellular carcinoma [15].

In breast cancer, resistance to doxorubicin is based on miR-222 by direct targeting Bim, a known mediator of the intrinsic pathway of apoptosis activation. Inhibition of miR-222 resulted in restoring Bim levels as well as chemosensitivity to doxorubicin of MCF-7 resistant cancer cells [16], thus blocking of miR-222 could represent another therapeutic option.

MiRNAs and cell cycle

MiRNAs are also able to modulate pivotal transcription factors that regulate cell cycle through which they can then impair drugs effects. For instance, by overexpressing and silencing miR-210-3p in SKOV-3/DDP cells, E2F3, a key transcription factor that control cell cycle progression, was identified as a direct target and miR-210-3p overexpression was able to re-sensitize SKOV-3/DDP cells to cisplatin treatment [17]. Another mechanism for enhancing drug sensitivity was demonstrated in a recent report whereby, miR-451a by targeting the well-known transcription factor c-Myc in lung cancer cells, resulted in alteration of cell-cycle and EMT. Furthermore, in *in vivo* experiments miR-451a promoted sensitivity of tumours to doxorubicin treatments by downregulating c-Myc function [18]. Another report revealed that vulnerability of glioma cells to the drug temozolomide was enhanced by miR-9 overexpression. When miR-9 was overexpressed and cells treated with temozolomide, the apoptotic rate and percentage of cells in G2/M stage were significantly higher compared with any of the treatment alone thus suggesting an increased sensitivity of the cells to the drug. In addition, topoisomerase II expression was suppressed by miR-9 via NF-κB signalling pathway thus mediating observed effect for the enhanced drug sensitivity [19]. Similar observations were made for miR-29b overexpression, which improved temozolomide treatment by directly targeting STAT3, in glioma cells [20]. MiR-494 regulates p27 in hepatocellular carcinoma (HCC) cells and xenograft models by increasing cell cycle progression and cells' survival, resulting in enhanced invasive and clonogenic capabilities. Furthermore, miR-494 was able to increase resistance to sorafenib treatment by modulating all reported mechanisms, in particular through mTOR signalling [21•]. In lung cancer cells instead, overexpression of miR-381 significantly regulated cell proliferation *in vitro* and *in vivo*, but also arrested non-small cell lung cancer (NSCLC) cells at G0/G1 phase. This was also complemented by enhanced expression of p21 and p27 and reduction of cyclin D1 and CDK4. MiR-381 was also able to induce cisplatin chemosensitivity in NSCLC by downregulation of ID1 resulting in NF-κB inactivation [22].

MiRNAs and multidrug resistance (MDR)

One of the first recognised mechanisms through which miRNA can mediate resistance to several drugs (MDR) is represented by their control on drug transporters levels [7]. Recently new data are emerging that support the hypothesis that miRNAs are involved in this efficient way of drug resistance. For instance, miR-381 could directly suppress expression of multidrug resistance 1 (MDR1, also known as p-glycoprotein) in breast cancer cells. MDR1 knock-down in turn sensitized MCF-7 and MDA-MB-231 cancer cells to cisplatin, while MDR1 overexpression was able to increase resistance. Therefore, miR-381 overexpression could revert the resistance of breast cancer to cisplatin by directly targeting the drug transporter MDR1 [23]. In liver cancer MDR1 has been demonstrated to be indirectly a target for miR-122. Overexpression of miR-122 increased the sensitivity of HCC cells to oxaliplatin and promoted apoptosis in *in vitro* and *in vivo* assays. MiR-122 directly targets and inhibits Wnt/β-catenin signalling pathway resulting in downregulating β-catenin that in turn decrease MDR1 expression. Thus, targeting miR-122 has been suggested as potential therapeutic strategy to enhance chemosensitivity to oxaliplatin [24]. Furthermore, miRNAs can positively regulate MDR through other mechanisms like by controlling autophagy. MiR-495-3p overexpression was able to reverse MDR to four common drugs *in vitro* and also inhibit the tumour growth *in vivo* in GC cells. Enhanced expression of miR-495-3p caused down modulation of its target GRP78, a critical component in regulation of misfolded proteins caused by endoplasmic reticulum stress, resulted in anti-autophagy effects through activation of mTOR and its substrates 4E-BP1 and S6K. Therefore, balanced levels of autophagy might be essential in cancer for conservation of MDR and miRNAs can restore sensitivity to chemotherapeutics by disrupting this balance [25•]. Another report showed similar effects in GC where overexpression of miR-874 reversed drug resistance (5-fluorouracil, vincristine and cisplatin*) in vitro* and in relative mice model through downregulation of autophagy-related 16-like1 (ATG16-L1) [26]. While upregulation and silencing experiments of another miRNA in GC (miR-195-5p) resulted in regulation of transcription factor ZNF139. Up-modulation and down-modulation of miR-195-5p was also able to enhance or restore, respectively, chemosensitivity to 5-fluoruracil and oxaliplatin through disruption of protein expression of MDR1, BCL-2 and MRP [27]. Nevertheless, it is worth to point out that since MDR1 has not proved to be the direct transporter of the aforementioned drugs other important drug efflux pumps (e.g., BCRP and MRPs) which are also modulated by miRNAs have been studied and might mediate and contribute to more complex drug resistance mechanisms observed for these drugs [28–30].

MiRNAs and pathways in drug resistance

Several reports have added new insights on multiple pathways deregulated directly or indirectly by miRNAs, in mediating resistance or enhancing sensitivity, depending on their roles in oncogenic or tumour suppressive mechanisms, to a number of standard regimens drugs in various cancers. For instance, overexpression of miR-421 in lung cancer is controlled by the Wnt/β-catenin pathway. In turn miR-421 overexpression was shown to regulate KEAP1 expression, a regulator of Reactive Oxygen Species (ROS), whose levels mediate several biological and cancer processes such as survival, metastasis and proliferation. This miR-421-mediated mechanism was able to enhance paclitaxel resistance in NSCLC, thus showing a novel β-catenin/miR-421/KEAP1 signalling

pathway that can regulate antioxidant mechanisms in drug resistance [31]. On the contrary, in ovarian cancer, miR-137 was found as mediator of response in ROS increase and regulation of cisplatin resistance. In cisplatin-resistant ovarian cancer cells, elevated ROS was directly responsible for enhanced expression of c-Myc, which in turn was triggering miR-137 suppression and thus restoring expression of its direct target EZH2. Higher EZH2 then was promoting cisplatin resistance by activating pro survival pathways [32]. MiRNA-mediated mechanisms in cisplatin resistance/sensitivity hve been shown in other new reports [33–39], supporting further the evidence of their important involvement in controlling drug response of a common used drug in standard therapy regimens, acting in different pathways and targets but in particular affecting PI3K/PTEN pathway [40–42,43••]. MiRNAs dysregulation has been also observed as mechanism of resistance to targeted drugs so that its restoration has been suggested as a new approach to overcome resistance. MiR-200c down regulation in ovarian cancer cells resulted in olaparib resistance [44], whereas in melanoma miR-126-3p down regulation was shown to be involved in acquired resistance to dabrafenib and regulation of its targets VEGF-A and ADAM9 [45]. Moreover, in ER-alpha positive breast cancers loss of miR-135a, due to genomic deletion, has been demonstrated to disrupt an oestrogen receptor-induced negative feedback loop, maintaining disease progression and

Table 1

miRNAs expression status and relative drugs' effect impaired in different types of cancers

Drug	miRNA	Expression	Target	Cancer type	Refs
Cisplatin	miR-1208	Down	TBCK	RCC	[11]
Oxaliplatin	miR-338-3p	Down	WNTB2	OC	[12]
	miR-142-5p	Down	XIIAP/BIRC3/BCL2	OC	[13]
	miR-210-3p	Down	E2F3	OC	[17]
	miR-381	Down	ID1	NSCLC	[22]
	miR-381	Down	MDR1	BC	[23]
	miR-122	Down	Wnt/b-cat	HCC	[24]
	miR-137	Down	EZH2	OC	[32]
	miR-362-5p	Down	SUZ12	GC	[33]
	miR-200c	Up	ERCC3/ERCC4	GC	[34]
	miR-608	Down	TEAD2	NSCLC	[35]
	miR-149-5p	Down	TGFb2	OSCC	[36]
	miR-372	Up	ZBTB7A	OSCC	[37]
	miR-31-5p	Up	LATS2	CRC	[38]
	miR-509-3p	Down	GOLPH3/WLS	OC	[39]
	miR-1269b	Up	PTEN	NSCLC	[40]
	miR-181	Down	–	NSCLC	[41]
	miR-130b	Up	PTEN	LC	[42]
	miR-125b	Up	EVA1A	HCC	[54]
5FU/Oxaliplatin	miR-195-5p	Down	ZNF139	GC	[27]
	miR-567	Down	PIK3AP1	GC	[43••]
Adriamycin/Cisplatin/5FU/Vincristine	miR-495-3p	Up	GRP78	GC	[25•]
5FU/Cisplatin/Vincristine	miR-874	Down	ATG16L1	GC	[26]
Olaparib	miR-200c	Down	NRP1	OC	[44]
Dabrafenib	miR-126-3p	Down	VEGF-A/ADAM9	M	[45]
Tamoxifen	miR-135a	Down	ESR1/ESRRA/NCOA1	BC	[46]
Erlotinib	miR-499a	Down	SHBP1	OS	[51]
Cetuximab	miR-302a	Down	CD44/NFIB	CRC	[55••]
Sorafenib	miR-494	Up	P27/PTEN/PUMA	HCC	[21•]
	miR-221	Up	CASP3	HCC	[15]
Imatinib	miR-153-3p	Down	BLC2	CML	[14]
Doxorubicin	miR-222	Up	BIM	BC	[16]
	miR-451a	Down	c-MYC	LC	[18]
	miR-7-5p	Down	PARP1	SCLC	[41]
Doxorubicin/Vinblastin	miR-210-3p	Down	ABCC1	RCC	[30]
Paclitaxel	miR-421	Up	KEAP1	LC	[31]
	miR-5195-3p	Down	EIF4AZ	BC	[48]
Temozolomide	miR-9	Down	TOPO2	G	[19]
	miR-29b	Down	STAT3	G	[20]
	miR-1268a	Down	ABCC1	GBM	[29]

miRNA = microRNA; Down = down regulated; Up = up regulated; 5FU = 5-Fluorouracil; RCC = Renal cell adenocarcinoma; OC = epithelial ovarian carcinoma; NSCLC = non-small cell lung adenocarcinoma; BC = breast adenocarcinoma; HCC = hepatocellular adenocarcinoma; GC = gastric adenocarcinoma; OSCC = oral squamous cell carcinoma; CRC = colorectal adenocarcinoma; LC = lung adenocarcinoma; CML = chronic myeloid leukaemia; SCLC = small cell lung adenocarcinoma; M = Malignant melanoma; G = Glioma; GBM = Glioblastoma Multiforme.

resistance to tamoxifen therapy [46]. Whereas in small cell lung cancer miR-7-5p targets PARP1, and by this exerting its suppressive effects on homologous recombination repair and doxorubicin sensitivity [41]. These evidences show that alteration of miR-7-5p expression might be used as a strategy for overcoming doxorubicin-resistance in small cell lung cancer therapy and further elucidate and support the clinical potential of restoring miRNAs essential functions in order to revert drug resistance and enhance back the sensitivity to therapy treatments [47]. On the contrary, up regulation of miR-5195-3p was shown to enhance the sensitivity of paclitaxel resistant breast cancer cells. Eukaryotic translation initiation factor 4α2 (EIF4A2) an ATP-dependent RNA helicase, was proved as target of miR-5195-3p mediated effect [48]. All these evidences clearly pinpoint how different miRNAs are responsible both directly and indirectly for mediating regulation of many different pathways, from membrane kinase signalling to transcriptional regulation, that translates in acquisition of resistance to common therapeutic agents and targeted drugs.

Other mechanisms of resistance: EMT and cancer stem cells

Other mechanisms that drive drug resistance effects in which miRNAs involvement is emerging, are related to EMT and the presence of cancer stem cells within tumours. EMT process and cancer stem cells have been widely acknowledged as reason of drug resistance [49,50] but also recently supported by new observations as in osteosarcoma cancer. A recent report showed that TGFβ-induced EMT in CD166+ cells, resulted in a reduced expression of miR-499a directly under transcriptional control of Snail1 and Zeb1 and restored expression of its target SHKBP1, an EGFR regulator. This mechanism in turn triggered PI3K/AKT pathway independently of EGFR and mediated erlotinib resistance [51]. Further important regulators of PI3K/AKT and TFG-β pathways which affect EMT are miR-216a, miR-217 and miR-125b [52,53]. In particular miR-125b has been shown to regulate oxaliplatin resistance in HCC through down modulation of EVA1A-mediated autophagy and EMT markers [54].

Another report showed that CD44 is a functional target of miR-302a in modulation of cetuximab resistance in CRC. CD44 silencing was able to sensitise CRC cells to cetuximab (monoclonal antibody against EGFR) whereas its overexpression restored target drug resistance, but the effect could be reversed by the re-expression of miR-302a [55••].

Conclusions and future perspectives

MiRNAs are short RNA transcripts involved in fine modulation of all essential cellular mechanisms including apoptosis, differentiation, inflammation, cell-cycle regulation, EMT and survival. As shown by the above summary, it is evident that miRNAs can act effectively in control of drug resistance mechanisms with either a positive or a negative effect in virtually all cancers type. Therefore, the knowledge of this dual aspect can be exploited for diagnostic, prognostic or predictive use in clinic for patients' stratification. Furthermore, creation of new-generation of therapeutics, in order to limit or restore miRNA expression is a current and intense focus of research [56,57]. Several lines of research are analysing the use of miRNA antagonists (e.g., anti-miRs, locked-nucleic acids) for silencing miRNAs with oncogenic potentials [58], but also for the re-expression of miRNAs whose reduced expression — due to transcriptional, genomic or epigenetic mechanisms — have impaired sensitivity to drugs [59••]. Various delivery systems are being explored for these purposes with advantages and limitations [60–62]. However, overcoming resistance to chemotherapy in cancer still remains an open challenge. Nonetheless, miRNAs have demonstrated to be ideal candidates and useful tools to tackle this foremost challenge, and might be used in parallel to traditional approaches as new therapeutic targets likely implementing currently available treatments (Table 1).

Conflict of interest statement

Nicola Valeri received honoraria for lectures from Merck Serono, Pfizer, Bayer and Eli-Lilly. All other authors declare no conflict of interest.

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