



# miRNAs and lncRNAs as Predictive Biomarkers of Response to FOLFOX Therapy in Colorectal Cancer

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### Specialty section:

This article was submitted to  
Pharmacogenetics and  
Pharmacogenomics,  
a section of the journal  
Frontiers in Pharmacology

**Received:** 01 June 2018

**Accepted:** 13 July 2018

**Published:** 06 August 2018

### Citation:

Hon KW, Abu N, Ab Mutalib N-S and  
Jamal R (2018) miRNAs and lncRNAs  
as Predictive Biomarkers of Response  
to FOLFOX Therapy in Colorectal  
Cancer. *Front. Pharmacol.* 9:846.  
doi: 10.3389/fphar.2018.00846

Chemotherapy is one of the options for cancer treatment. FOLFOX is one of the widely used chemotherapeutic regimens used to treat primarily colorectal cancer and other cancers as well. However, the emergence of chemo-resistance clones during cancer treatment has become a critical challenge in the clinical setting. It is crucial to identify the potential biomarkers and therapeutics targets which could lead to an improvement in the success rate of the proposed therapies. Since non-coding RNAs have been known to be important players in the cellular system, the interest in their functional roles has intensified. Non-coding RNAs (ncRNAs) as regulators at the post-transcriptional level could be very promising to provide insights in overcoming chemo-resistance to FOLFOX. Hence, this mini review attempts to summarize the potential of ncRNAs correlating with chemo-sensitivity/resistance to FOLFOX.

**Keywords:** FOLFOX, chemo-resistance, biomarkers, non-coding RNAs, molecular target

## INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer mortality worldwide (Torre et al., 2015). CRC begins with the appearance of benign adenomatous polyps on the inner wall of colon and rectum in large intestine, which progressively develops into advanced adenoma, invasive carcinoma and eventually distant metastases (Flor et al., 2013; Yee et al., 2013; US Preventive Services Task Force et al., 2016; Veetil et al., 2016). Despite the advancement in clinical oncology, multidrug resistance (MDR) remains a major obstacle for treatment of CRC patients especially those at the advanced stage of the disease (Hammond et al., 2016). Several mechanisms have been proposed to modulate MDR in CRC, mainly via limitation of drug transport, dysregulation of cellular processes, alteration of drug sensitivity via epigenetic modifications such as disturbance of miRNA levels and others (Holohan et al., 2013; Panczyk, 2014; Hu et al., 2016; Zhang and Wang, 2017). Over-expression of ATP-dependent transporters on plasma membrane of cancer cells could be responsible for suppressing the influx of drug into cancer cells, and simultaneously increasing the efflux of drug out of the cancers cells to reduce overall drug accumulation (Liu et al., 2010; Wilson et al., 2011; Nies et al., 2015). Dysregulation of cellular processes including apoptosis, drug metabolism, DNA damage repair and regulation of cell cycle checkpoints may also modulate MDR in CRC (Bouwman and Jonkers, 2012; Xu et al., 2012, 2013; Czabotar et al., 2014). Epigenetic modification in cancer cells such as, selective expression of miRNAs, DNA methylation and histone modification have been postulated to alter drug sensitivity in certain cancers including CRC (Brown et al., 2014; Shen et al., 2017; Zhang and Wang, 2017). There are various mechanisms that lead to drug resistance in CRC, but nevertheless, this issue still remains widely unresolved.

One of the CRC chemotherapeutic regimens being widely used today is FOLFOX, which is the combination of folinic acid (FOL), 5-fluorouracil (F) and oxaliplatin (OX) (André et al., 2004). 5-fluorouracil (5-FU) as the main component in FOLFOX, is a type of fluoropyrimidine that incorporates into the DNA molecule to inhibit thymidylate synthase (TS) (Longley et al., 2003). This subsequently hinders the synthesis of pyrimidine thymidine required for DNA replication so that actively dividing cancerous cells will undergo apoptosis due to the thymine-less condition (Noordhuis et al., 2004). 5-FU has been used to treat multiple types of cancer including esophageal cancer, gastric cancer, pancreatic cancer, breast cancer, and cervical cancer (Peters et al., 2000; Ling et al., 2012; Carter et al., 2013; Kim et al., 2016; Lee and Park, 2016). Oxaliplatin (trans-/diaminocyclohexane oxalatoplatinum; L-OHP) on the other hand, is a platinum-based antineoplastic agent that inhibits DNA replication and transcription by forming cross linkages within the double strands of DNA (Bleiberg, 1998; Woynarowski et al., 2000; Kelland, 2007). The combination of 5-FU and oxaliplatin provide a synergistic effect in anti-proliferative activity, especially among patients with metastatic colorectal cancer (mCRC) (Gustavsson et al., 2015). Folinic acid, also known as leucovorin or calcium folinate, stabilizes the 5-FU-TS complex with better cytotoxicity, and it acts by reducing the side effects of 5-FU with lower dosage required to complete the cycles of treatment (Morgan, 1989; Van Der Wilt et al., 1992). Leucovorin and oxaliplatin also exhibit antitumor properties against metastatic colorectal cancer, esophageal cancer, gastric cancer and hepatocellular carcinoma, and are either used individually or in combination with other chemotherapeutics (Lin et al., 2013b; Skinner et al., 2014; Wu et al., 2014a; Hironaka et al., 2016; Liu et al., 2016b). Currently, FOLFOX is widely administered through injection into the veins to treat mostly stage II and III CRC patients after surgical resection (André et al., 2015). Although FOLFOX is among the preferred chemotherapeutic regimen for CRC patients, the response rate to this systemic treatment is only estimated at around 50%. Studies have reported that almost half of the patients receiving FOLFOX develop chemo-resistance at a later stage of treatment, resulting in high incidence rate of cancer recurrence and metastasis to other organs (De Gramont et al., 2000; André et al., 2004, 2015; Howlader et al., 2016).

Non-coding RNAs (ncRNAs) represent a group of functional RNA molecules originally transcribed from DNA but not translated into proteins (Chen and Xue, 2016). ncRNAs can be classified into two major groups: infrastructural and regulatory ncRNAs (Kaikkonen et al., 2011). Infrastructural ncRNAs such as transfer RNAs (tRNAs), ribosomal RNAs (rRNAs) and small nuclear RNAs (snRNAs) are abundantly expressed in all eukaryotic cells and play housekeeping roles in splicing and translation of mRNAs into proteins (Mattick and Makunin, 2006). Regulatory ncRNAs include microRNA (miRNA), short interfering RNAs (siRNA), piwi-interacting RNAs (piRNA), and long ncRNAs (lncRNAs). They are involved in the epigenetic modification of other RNAs (Fu, 2014). These regulatory ncRNAs regulate gene expression at the transcriptional and post-transcriptional level, via several mechanisms namely heterochromatin formation,

histone modification, DNA methylation, and gene silencing (Meister and Tuschl, 2004; Volpe and Martienssen, 2011; Nohata et al., 2013; Matzke and Mosher, 2014). Other classes of RNAs have been discovered in recent decade, such as enhancer RNAs (eRNAs), circular RNAs (circRNAs) and promoter-associated RNAs (PARs), but the limited understanding on these minor classes of RNAs requires more studies to validate their functions in gene regulation (Han et al., 2007; Yan and Ma, 2012; Kim et al., 2015; Salzman, 2016). MicroRNAs (miRNAs) are a class of small, single stranded endogenous ncRNAs with 21–25 nucleotides (Ul-Hussain, 2012). MiRNAs bind partially or completely with complementary sequences of the target mRNAs and can silence the mRNA through regulatory mechanisms such as cleavage of the mRNA strand and destabilization of the mRNA through shortening of its poly(A) tail (Bartel, 2009). MiRNAs play important roles in a variety of biological processes, namely cellular development, proliferation, differentiation, metabolism, apoptosis and tumorigenesis (Ul-Hussain, 2012). Long non-coding RNAs (lncRNA) constitute a large family of ncRNAs with a length of 200 nucleotides and longer (Geisler and Coller, 2013). LncRNAs mostly interact with DNA, RNA and proteins on the secondary and tertiary structures to form multiple kinds of complexes that could be key regulators in modulating gene expression (Mercer et al., 2009). Aberrant expression of lncRNAs has been discovered in many diseases including cancers (Fang and Fullwood, 2016). Emerging literature has revealed the importance of lncRNAs as oncogenes or tumor suppressors to regulate several key steps in the process of carcinogenesis, such as tumor proliferation, apoptosis, metastasis and chemo-resistance by interfering with target gene expression (Gupta et al., 2010; Yang et al., 2012; Majidinia and Yousefi, 2016; Pan et al., 2016). Concurrently, lncRNA may also serve as therapeutic targets or biomarkers of disease pathogenesis and pathophysiology (Lavorgna et al., 2016). Recent discoveries from transcriptomic and bioinformatics studies have reported increasing number of miRNAs and lncRNAs which modulate epigenetic regulation of cancer chemo-resistance. Emerging evidence has also demonstrated that interactions between miRNAs and lncRNAs with other biomolecules such as proteins are equally important to modulate the molecular mechanism underlying cancer chemo-resistance. This review provides insight into promising miRNAs and lncRNAs as potential biomarkers or therapeutic targets related to FOLFOX-responsiveness in colorectal cancer.

## miRNAs and Folfox Chemo-Resistance

Chen et al. reported that the upregulation of serum miR-19a is significantly associated with FOLFOX-resistance in advanced CRC (Chen et al., 2013b). In this study, serum miR-19a was reported to have a sensitivity of 66.7% and specificity of 63.9% to differentiate FOLFOX-resistant patients from FOLFOX-responsive patients. This implicates the potential of miR-19a as a biomarker in advanced CRC to predict innate resistance before FOLFOX therapy as well as to monitor the acquired resistance of FOLFOX during the treatment (Chen et al., 2013b). MiR-19a is an integral component of the oncomiRs—miR-17-92 family (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and

miR-92-1) (Olive et al., 2009; Matsumura et al., 2015). The aberrant expression of this oncogenic cluster has been observed in different cancers, such as myeloma, acute myeloid leukemia, lung cancer, bladder cancer and CRC (Zhang et al., 2012; Collins et al., 2013; Lepore et al., 2013; Lin et al., 2013a; Feng et al., 2014; Wu et al., 2014b; Yamamoto et al., 2015; Liu et al., 2017). MiR-19a was also detected in CRC-derived exosomes and has been suggested as a possible prognostic biomarker for recurrence in CRC patients (Matsumura et al., 2015). Exosomes are microvesicles released by most of the living cells as natural carriers of molecular information such as DNA and RNA (Milane et al., 2015). Furthermore, miR-19a was also associated with other types of drug resistance, including gefitinib resistance in non-small cell lung cancer (Cao et al., 2017) and epirubicin plus paclitaxel in breast cancer (Li et al., 2014). In breast cancer, miR-19a was involved in resistance by regulating the PTEN protein (Li et al., 2014). Meanwhile, in non-small cell lung cancer, miR-19a was reported to be involved in acquired gefitinib resistance via the c-met pathway (Cao et al., 2017). This is interesting, as this shows that the method of resistance to different drugs is dependent on the type of drug. Different drugs may induce different types of resistance, even though the same miRNA is involved.

Another member of the miR-17-92 cluster, is the miR-17-5p, which has been reported to also be significantly upregulated among FOLFOX-resistant CRC patients (Fang et al., 2014). Elevated expression of miR-17-5p was associated with poor prognosis, distant metastases and advanced clinical presentation (Fang et al., 2014). miR-17-5p could serve as a biomarker to predict chemotherapy response in CRC as well as a potential target for the study of CRC tumorigenesis. Additionally, the role of miR-17-5p in relation to drug resistance was also reported in other types of cancer. For instance, miR-17-5p was involved in erlotinib resistance in non-small cell lung cancer cells (Zhang et al., 2017), paclitaxel resistance in lung cancer (Chatterjee et al., 2014) and cisplatin resistance in gastric cancer (Wang and Wang, 2018). In gastric cancer, the resistance mediated by miR-17-5p was achieved by modulating the p21 protein. In ovarian cancer, miR-17-5p was reported to contribute to drug resistance by regulating the AKT pathway through PTEN, and also other EMT players (Fang et al., 2015). Similarly, in colorectal cancer, the PTEN protein was also found to be involved in miR-17-5p-acquired drug resistance (Fang et al., 2014). Interestingly, it was reported that miR-17-5p affected paclitaxel resistance by binding to the 3'UTR of the beclin-1 gene (Chatterjee et al., 2014). The same observation was seen in erlotinib resistance, where miR-17-5p was reported to bind to the EZH1 gene instead (Zhang et al., 2017). From these reports, it can be postulated that PTEN is a major player in drug resistance, and can be used as a targeted therapy. Additionally, miR-17-5p was found to mediate drug resistance by becoming a competitive inhibitor for different types of genes.

Kjersem et al. also identified the upregulation of three other miRNAs (miR-106a, miR-130b, and miR-484) that could emerge as predictive biomarkers of intrinsic resistance among metastatic CRC patients toward FOLFOX (Kjersem et al., 2014). miR-130b was found to be involved in breast cancer resistance to

adriamycin via the PI3K/AKT signaling pathway (Miao et al., 2017). miR-484 was also reported to contribute to gemcitabine resistance in breast cancer and sunitinib resistance in renal cell carcinoma (Merhautova et al., 2015; Ye et al., 2015). In breast cancer, miR484 was found to contribute to resistance by targeting the cell-cycle related protein, CDA (Ye et al., 2015). Additionally, a comprehensive analysis conducted via real time-PCR based profiling of 742 different miRNAs using 26 CRC tissues with or without response to first-line capecitabine and oxaliplatin (XELOX)/FOLFOX treatment reported that the overexpression of miR-27b, miR-181b, and miR-625-3p was significantly associated with poor response to XELOX/FOLFOX (Rasmussen et al., 2013). The same study further validated these candidate miRNAs in primary tumor tissues of 94 metastatic CRC patients, which confirmed that high expression of miR-625-3p to be significantly associated with deprived response to XELOX/FOLFOX as first-line treatment. It was further investigated that this miRNA regulated chemoresistance by targeting MAP2K6 of the MAPK pathway (Lyskjær et al., 2016). Zhang et al screened for differentially expressed miRNAs in the serum of 20 responders and 20 non-responders to FOLFOX (Zhang et al., 2014). They reported that 14 miRNAs were differentially expressed, and the findings were further validated in a larger cohort of patients consisting of 93 responders and 80 non-responders. The validation resulted in the further stratification of potential miRNAs down to five miRNAs. The five serum miRNAs (miR-20a, miR-130, miR-145, miR-216, and miR-372) were further statistically tested whether they can be used to differentiate between the responders and non-responders. The AUC using all five miRNAs were 0.841 in the training set (40 CRC patients) and 0.918 (173 CRC patients), whereas when using CEA and CA19-9, the AUC values were 0.689 and 0.746 respectively. This indicates that the panel of five miRNAs was more accurate at determining the responsiveness toward chemotherapy than CEA and CA19-9 (Zhang et al., 2014).

Dong et al. discovered the upregulation of miR-429 in both serum and primary tissues from chemo-resistant CRC patients who received 5-FU based adjuvant chemotherapy including FOLFOX (Dong et al., 2016). Overexpression of miR-429 was positively correlated with tumor size, lymph node involvement, distant metastases and TNM staging, resulting in poor prognosis and lower survival rate for CRC patients. Furthermore, miR-429 was also implicated in cisplatin-resistance in epithelial ovarian cancer (Zou et al., 2017). It was further discovered that the method of cisplatin-resistance was achieved by targeting the ZEB1 protein. This pathway of resistance may be similar to FOLFOX resistance, as both oxaliplatin and cisplatin are platinum-based drugs. Furthermore, Takahashi et al. reported that the expression of miR-148a was lower in non-responder CRC than responders (Takahashi et al., 2012). The lower expression of miR-148a was also associated with lower progression-free survival and significantly poorer overall survival (Takahashi et al., 2012). At the molecular level, the downregulation of miR-148a in primary tissues was correlated with the development of high-grade adenoma and poor clinical outcome in stage III CRC patients (Hibino et al., 2015). All these findings suggest that miR-148a could serve as a predictive biomarker for FOLFOX.

For drug resistance, miR-148a was reported to be involved in tamoxifen resistance in breast cancer as well (Chen et al., 2017). In breast cancer, the resistance toward tamoxifen by miR-148a was achieved by targeting the ALCAM protein (Chen et al., 2017).

Liu et al. reported that the reduced expression of serum exosomal miR-4772-3p was significantly associated with a higher risk of tumor recurrence in stage II and stage III CRC patients who received FOLFOX therapy (Liu et al., 2016a). However, no study has been conducted in relation to the levels of miR-4772-3p and FOLFOX-responsiveness. In another study which involved a 3-year follow up that focused on the dynamic monitoring of serum miRNA levels (miR-155, miR-200c, and

miR-210) with adjuvant FOLFOX therapy plus cetuximab in 15 CRC patients, the researchers suggested that re-elevation of serum miR-155 levels after surgery and chemotherapy may help to predict chemo-resistance (Chen et al., 2013a). MiR-155 is one of the most multi-functional and conserved miRNA ever reported (Yu et al., 2015; Bayraktar and Van Roosbroeck, 2018). In fact, miR-155 is well known to be associated with resistance of treatment in multiple types of cancer such as breast cancer (Yu et al., 2015), lung cancer (Van Roosbroeck et al., 2017), prostate cancer (Li et al., 2017a) cervical cancer (Lei et al., 2012) and renal cell carcinoma (Merhautova et al., 2015). Though the studies reported different mechanisms on how miR-155 regulate resistance, we can still have a basic view

**TABLE 1** | Summary of ncRNAs associated with resistance to FOLFOX.

Name	Source	Cancer model	Expression	Effect on FOLFOX-resistance	Possible significance	Reference
<b>miRNAs</b>						
miR-19a	Serum	CRC	Upregulation	Enhancement	To predict innate resistance to FOLFOX	Chen et al., 2013b
miR-4772-3p	Serum exosomes	CRC	Downregulation	Enhancement	High risk of tumor recurrence	Liu et al., 2016a
miR-17-5p	Tissue	CRC	Upregulation	Enhancement	Prognostic factor for overall survival	Fang et al., 2014
miR-106a	Cell lines		Overexpression	Enhancement	–	
miR-130b	Plasma	CRC	Upregulation	Enhancement	To predict innate resistance to FOLFOX	Kjersem et al., 2014
miR-484						
miR-27b	Tissue	CRC	Upregulation	Enhancement	Poor prognosis	Rasmussen et al., 2013
miR-181b						
miR-625-3p						
miR-20a	Serum	CRC	Upregulation	Enhancement	Predictor for chemo-sensitivity	Zhang et al., 2014
miR-130						
miR-145						
miR-216						
miR-372						
miR-429	Tissue Serum	CRC	Upregulation	Enhancement	Poor prognosis	Dong et al., 2016
miR-425-5p	Cell line	CRC	Upregulation	Enhancement	-	Zhang et al., 2016
miR-148a	Tissue	CRC	Downregulation	Enhancement	Poor prognosis	Takahashi et al., 2012
miR-155	Serum	CRC	Upregulation	Enhancement	Predictor for chemo-resistance	Chen et al., 2013a
miR-320e	Tissue	CRC	Upregulation	Enhancement	Poor prognosis	Perez-Carbonell et al., 2015
miR-139-5p	Tissue Serum	CRC	Upregulation	Enhancement	To predict cancer recurrence and distant metastasis	Miyoshi et al., 2017
miR-92b-3p, miR-3156-5p, miR-10a-5p, and miR-125a-5p	Tissue	CRC	Upregulation	Enhancement	Predictor for chemo-resistance	Kiss et al., 2017
<b>lncRNAs</b>						
MALAT1	Tissue	CRC	Upregulation	Enhancement	Downregulate miR-218	Li et al., 2017b
	Cell line				–	
HOTAIR	Tissue	CRC	Upregulation	Enhancement	Downregulate miR-218	Li et al., 2017c

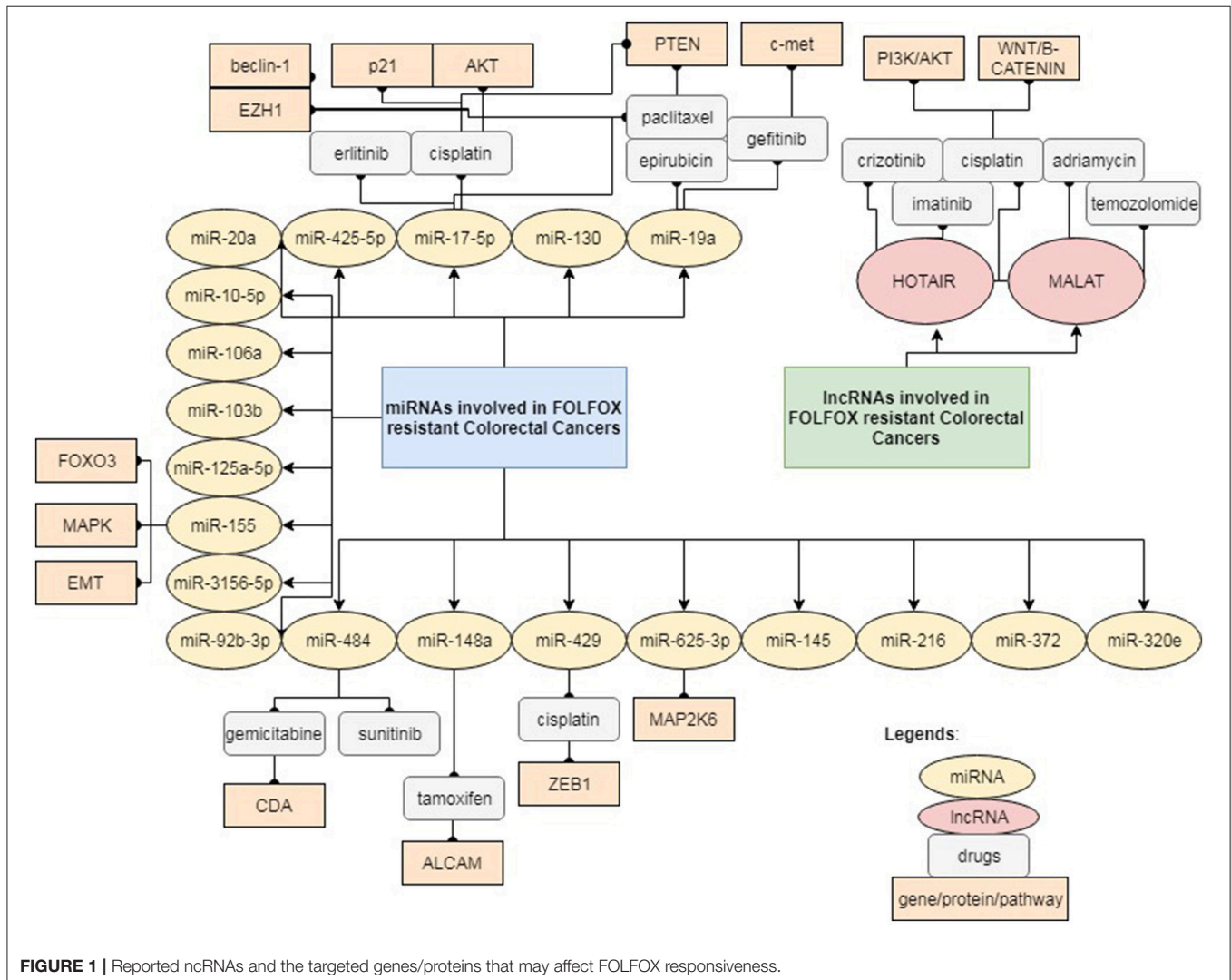
on how miR-155 operates and apply it to further understand its role. MiR-155 is one of the major oncogenic miRNAs that is known to be involved in drug resistance and is well-studied. In breast cancer, miR-155 was found to modulate resistance by targeting the FOXO3 pathway, MAPK pathway and EMT-related proteins (Bayraktar and Van Roosbroeck, 2018). Another study reported the prognostic value of miR-320e as a novel biomarker in CRC and has been validated in two different cohorts of patients treated with FOLFOX (Perez-Carbonell et al., 2015). The expression level of miR-320e in primary CRC tissues showed a positive correlation with recurrence, advanced clinical presentation, poor prognosis among stage II and III CRC patients treated with FOLFOX (Perez-Carbonell et al., 2015).

Recently, a study by Kiss et al. discovered that a cohort of CRC patients treated with the combination of bevacizumab and FOLFOX, showed a distinctive profile of tissue miRNAs (Kiss et al., 2017). The study identified 67 differentially expressed miRNAs between the responders and non-responder, where

seven of the miRNAs were independently validated (Kiss et al., 2017). From there, four miRNAs (miR-92b-3p, miR-3156-5p, miR-10a-5p, and miR-125a-5p) were significantly associated with the Response Evaluation Criteria In Solid Tumors (RECIST) criteria of responsiveness (Kiss et al., 2017). Moreover, the combination of these four miRNAs had a sensitivity of 82% and specificity of 64% to differentiate between responders and non-responders, thus indicating the potential use of these miRNAs as biomarkers of chemotherapy responsiveness and progression-free survival (Kiss et al., 2017).

### Long Non-coding RNAs (lncRNAs) and Folfox-Resistance

Li et al. presented two different lncRNAs, namely MALAT1 and HOTAIR that contribute to resistance on 5-FU/oxaliplatin-based chemotherapy via similar inhibition of miR-218 (Li et al., 2017b,c). The lncRNA MALAT1, also known as nuclear-enriched transcript 2 (NEAT2), was initially discovered as a promising



**FIGURE 1 |** Reported ncRNAs and the targeted genes/proteins that may affect FOLFOX responsiveness.

biomarker for lung cancer metastasis (Gutschner et al., 2013b). Later, discovery of MALAT1 dysregulation was expanded into various cancers to become the key regulator of metastasis and cancer development (Gutschner et al., 2013a; Tripathi et al., 2013). MALAT has also been associated with other types of drug resistance. For instance, MALAT was shown to be involved in cisplatin resistance in NSCLC (Fang et al., 2018), adriamycin resistance in diffuse large-B cell lymphoma (Long et al., 2017) and temozolomide resistance in glioblastoma (Lu et al., 2017). Upregulation of MALAT1 in primary CRC tissue was highly associated with a poor survival rate and a weak response to FOLFOX in advanced CRC patients (Li et al., 2017b). The same study demonstrated that the overexpression of MALAT1 in oxaliplatin-resistant CRC cells modulate chemo-resistance via suppression of E-cadherin expression and enhancement of epithelial-mesenchymal transition (EMT) but the underlying signaling pathways have not been fully elucidated (Wang and Zhou, 2013). Correspondingly, HOTAIR overexpression in primary CRC tissue was also demonstrated to inhibit miR-218 expression in CRC, resulting in poor response to 5FU- based adjuvant chemotherapy (Li et al., 2017c). Similarly, HOTAIR was also reported to be involved in other types of drug resistance in different cancers. It was reported that HOTAIR was associated with cisplatin resistance in lung adenocarcinoma (Liu et al., 2013), crizotinib resistance in NSCLC (Yang et al., 2018) and imatinib resistance in chronic myeloid leukemia (Wang et al., 2017). In gastric cancer, HOTAIR was involved in cisplatin resistance via inhibition of the PI3K/AKT pathway and Wnt/B-catenin pathways. Both of these pathways are hallmark pathways that are involved in colorectal cancer pathogenesis. It can be assumed that FOLFOX resistance was also achieved by the same mechanism. Collectively, **Table 1** summarizes all the mentioned ncRNAs that show correlation with chemo-resistance to FOLFOX.

## CONCLUSION, CHALLENGES AND FUTURE DIRECTION

This mini-review highlights the increasing evidence and a fresh update that will help to widen our knowledge on the potential role of ncRNAs, primarily miRNAs and lncRNAs underlying FOLFOX chemo-resistance. Most of the ncRNAs reported are not only involved in FOLFOX resistance, but in resistance to other drugs as well. This reflects that the mechanisms of drug resistance are rather complex and different pathways may crosstalk with each other as illustrated in **Figure 1**. Drug resistance may also occur in a centralized manner, regardless of the type of cancer or drug being administered. Nevertheless, there are also instances, where a certain ncRNA may modulate different pathways of resistance depending on the type of

drugs. Most of the studies mentioned above were performed on analysis of clinical tissues and serum/plasma samples from retrospective patient cohorts without sufficient validation and in-depth functional analysis. Future research is necessary to validate these findings in multi-centered cohort studies as well as to elucidate the underlying signaling pathway via *in vitro* and *in vivo* functional studies. The bioinformatics analysis in studies related to FOLFOX-resistance is still insufficient to provide solid foundation for the translation of miRNAs and lncRNAs as powerful predictor of FOLFOX-resistance in the clinical setting. More intensive and comprehensive statistical analysis is essential to validate the specificity and sensitivity of each individual miRNA/lncRNA as a biomarker (Liu et al., 2012). Ultimately, all these findings may contribute toward the development of next-generation diagnostic panel comprising of miRNAs and lncRNAs, which a more powerful diagnostic tool to predict patient response toward FOLFOX. However, it is still challenging to accurately identify those clinically promising ncRNAs suitable for early diagnosis, risk assessment, prognosis prediction and drug monitoring in patients treated with FOLFOX. Furthermore, there are still considerable obstacles that limit the clinical application of miRNAs and lncRNAs for diagnostic and prognostic purposes. Lack of standardization in the extraction of ncRNAs from tissues and bodily fluids remains a major challenge, which greatly affects the stability of ncRNAs in specimens and subsequently leads to inconsistency in most findings. Due to the high abundance of ncRNAs in human serum/plasma, the liquid biopsy approach could be an ideal method to develop standardized operative procedures for ncRNAs extraction in the clinical environment (Erbes et al., 2015; Komatsu et al., 2015). Liquid biopsy is now widely accepted as a non-invasive method to retrieve circulating cancer cells or traces of nuclei acids derived from tumor (Karachaliou et al., 2015; Murtaza et al., 2015; Birkenkamp-Demtröder et al., 2016; Jamal-Hanjani et al., 2016). Discovery and characterization of new ncRNAs related to FOLFOX-resistance will benefit the researchers to explore the diverse ncRNAs as potential biomarkers and therapeutic targets to overcome drug resistance.

## AUTHOR CONTRIBUTIONS

KH and NA drafted the manuscript. NA, N-SA, and RJ were responsible for critical feedback and manuscript revision.

## FUNDING

This manuscript was funded by the Dana Impak Perdana Grant (DIP-2016-013) awarded by Universiti Kebangsaan Malaysia.

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- Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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