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The role of noncoding RNAs and sirtuins in cancer drug resistance

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ABSTRACT

Cancer is a rising and major health issue around the world. The acquisition of resistance to chemotherapeutic drugs is a great obstacle for the effective treatment of nearly all cancers. Drug resistance is regulated by multiple factors and mechanisms including genetic mutations, abnormal expression of some cellular transporters such as multidrug resistance (MDR) transporters, changes in apoptotic pathways, cancer stem cells, tumor microenvironment, and noncoding RNAs (ncRNAs). Evidence clearly indicates a key role for sirtuins in several characteristics of cancer drug resistance. Recent studies demonstrated the crucial impact of some ncRNAs on sirtuins expression leading to modulation of chemotherapy resistance in cancers. In this review, we will focus on the current findings about the impacts of ncRNAs on the sirtuins pathway and their role in drug resistance of cancer.

1. Introduction

Cancer is considered a complex disease associated with some genetic mutations, deletions, epigenetic alterations and chromosomal translocations that are involved in cancer initiation, promotion, metastasis and drug resistance (Bach and Lee, 2018). Chemotherapy is one of the most widely used therapies for the treatment of cancer and improves the lifespan of patients. However, prolonged utilization of chemotherapeutic drugs. may lead to drug resistance which is a major issue in cancer treatment (Szakacs et al., 2006). Based on statistical reports, over than 90% of deaths in patients with different types of cancer are associated with chemotherapeutic drug resistance (Li et al., 2008; Longley and Johnston, 2005). Cancer cells apply many different mechanisms to impede drug treatment, including the genetic mutations, cell cycle alterations, apoptosis induction, drug metabolism, efflux alterations and DNA methylation (Balch et al., 2004; Gillet and Gottesman, 2010; Xia and Hui, 2014). NcRNAs have been reported to play an essential role in determining drug sensitivity or restoring drug sensitivity in resistant cells in many cancers. (Kapranov et al., 2010).

NcRNAs are RNA molecules that do not code any protein. However, they exert an important impact on the expression of more than 60% of human genes. They are classified into two main groups including the most studied microRNAs (miRNAs) and the long non-coding RNAs (lncRNA) (Kapranov et al., 2010). MiRNAs are single-stranded RNAs, 19-23bp in length and account for approximately 30% of gene expression regulation. MiRNAs can bind to the 3′ untranslated regions (UTRs) of their target mRNAs and regulate gene expression. The most important function of miRNAs is the suppression of gene expression (Omidkhoda et al., 2019; Szulwach et al., 2010).

lncRNAs are transcripts with 200 nt to ~100 kb in length. They do not have any significant open reading frames. lncRNAs are poly-adenylated and located within the cell nucleus or cytosol. They can regulate the expression of genes by *cis*-acting or *trans*-acting regulation. *Cis*-acting lncRNAs affect the expression of neighboring genes by acting at the site of transcription, while *trans*-acting lncRNAs affect the expression of genes by acting away from the site of synthesis (Barangi et al., 2019; Batista and Chang, 2013).

Many reports demonstrated that the dysregulation of specific ncRNAs lead to cancer drug resistance via different mechanisms including overexpression of multidrug resistance (MDR) genes, changes in apoptotic pathways, alterations in drug targets, hindering the components of DNA repair pathway, regulating genes related to autophagy and drug-metabolizing enzymes (e.g. the cytochrome P450) and Epigenetic alterations (Liao et al., 2018; Ye et al., 2018). Their potential role in cancer drug resistance has been studied in many types of cancers such as colorectal, hepatocellular, prostate, ovarian, lung, and breast cancers as well as some leukemias and lymphomas (Bach et al., 2017; Sameiyan et al., 2019).

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Sirtuin (silent mating type information regulation 2, *S. cerevisiae*, homolog) 1 are class III NAD-dependent histone deacetylases (HDACs). Sirtuins are present in many living organisms from yeast to mammals (Guarente, 2013). Studies on humans revealed that sirtuins are involved in the development of many diseases such as cancers. Sirtuins have a variety of functions in cellular processes such as differentiation, cell adhesion, cell–cell communication, inflammation, cancer progression, and metastasis (Chalkiadaki and Guarente, 2012). Sirtuin family consists of seven forms of sirtuin genes, *SIRT1-7*. They have a conserved NAD + domain that is catalytic and binding domain. However, they are different in cellular localization and function. It has been documented that, all mammalian sirtuins except SIRT5 are involved in tumorigenesis. SIRT1 has been extensively studied in the field of cancer drug resistance. SIRT1 is expressed ubiquitously and is preliminarily located in the nucleus. However, it can switch between the nucleus and cytoplasm utilizing its two nuclear localization signals (NLS) and two nuclear export signals (NES) (Rifai et al., 2018). The overexpression of SIRT1 has been reported to be associated with cancer progression and drug resistance in several types of cancers (Chu et al., 2005; Karbasforooshan et al., 2018; Lim, 2007; Mostoslavsky et al., 2006; Wang et al., 2008).

SIRT1 adjusts target gene expression by removing the acetyl group from the ε-amino group of lysine residues in histones proteins as well as non-histone proteins (Zhang et al., 2009). SIRT1 promotes drug resistance in tamoxifen-resistant breast cancer cells, and also liver and prostate cancers (Chen et al., 2011; Choi et al., 2013; Wang et al., 2011; Yuan et al., 2013). The fundamental role of SIRT1 in the progression and drug resistance of chronic myelogenous leukemia (CML) has also been observed (Wang et al., 2013). According to some recent experiments, SIRT1 could inhibit cancer progression. Recent studies show a dual role for SIRT1 in cancer promotion and suppression (Bosch-Presegue and Vaquero, 2011). Based on these studies, overexpression of SIRT1 lead to suppression of breast cancer development in mesenchymal stem cells, while downregulation of SIRT1 leads to increased metastasis by Smad4 deacetylation in breast cancer cells.

Therefore, whether SIRT1 acts as an oncogene or a tumor suppressor gene remains controversial (Simic et al., 2013; Yu et al., 2016). Here, we aim to review the impact of different ncRNAs on the sirtuin pathway and their role in drug resistance of cancers (Table 1).

2. Noncoding RNAs and sirtuins function in cancer drug resistance

2.1. Breast cancer

According to the GLOBOCAN 2018 database, breast cancer is the most common cancer around the world, contributing 12.3% of the total number of newly diagnosed cases in 2018 (World Health Organization). While targeted chemotherapy can eliminate the mortality of breast cancer, drug resistance remained a challenge in the treatment of this disease (Davuluri et al., 2014; Kirsh et al., 2011).

Several studies reported that miR-34a is involved in chemosensitivity through inhibition of SIRT1, Bcl2, CD44, Rac1, Fra1, various cyclins and CDKs, MYC and MYCN expression. The miR-34a can act as a tumor suppressor and inhibits cell proliferation, migration, and invasion. It also causes cell cycle arrest, senescence, and triggers apoptotic pathways (Ghawanmeh et al., 2011; Heinemann et al., 2012; Hermeking, 2010; Liu et al., 2011; Sotillo et al., 2011; Sun et al., 2008; Yamakuchi et al., 2008; Zauli et al., 2011).

Downregulation of miR-34a expression in a wide range of cancer tissues and cell lines have been studied (He et al., 2009). In various types of cancers miR-34a plays an effective inhibitory role and directly suppresses the expression of SIRT1 and Bcl2. In an experiment conducted by Li et al., miR-34a was shown to be frequently downregulated in MDA-MB-231 and MDA-MB-435 breast cancer cell lines. They also found that miR-34a upregulation can sensitize the tumor cells to 5-fluorouracil (5-FU) treatment through downregulating Bcl2 and SIRT1 expression, thus suppressing cell proliferation and inducing apoptosis (Li et al., 2013).

A study by Ma et al. suggested that miR-34a upregulation or SIRT1 downregulation prevents the proliferation and colony formation of the MCF-7 breast cancer cell lines, as well as breast cancer stem cells. In an experiment on nude mice xenografts, SIRT1 downregulation was shown to be positively correlated with reduced expression of breast cancer stem cell markers and decreased cancer development (Ma et al., 2015).

Zou et al. revealed that miR-22 could negatively regulate SIRT1 in the MCF-7 cell line (Zou et al., 2017). Another *in vitro* study by Zhang et al. demonstrated that miR-22 overexpression blocks cancer cell proliferation and enhances the sensitivity of breast cancer cells to radiotherapy through targeting SIRT1. The authors claimed that SIRT1 knockdown triggers apoptosis by downregulating Bcl2 and enhances the sensitivity of breast cancer cells to radiotherapy by suppressing DNA damage repair (Zhang et al., 2017c).

Tormo et al. investigated that miRNA-449a is overexpressed in patients with triple-negative breast cancer (TNBC). SIRT1 is one of the miR-449a targets. In sensitive breast cancer cells, treatment with doxorubicin lead to miR-449a upregulation as well as DNA-damage responder factors (*E2F1* and *E2F3*), while their expression does not change in resistant ones. Overexpression of miR-449 results in the downregulation of genes including *CDK2, E2F1*, and *E2F3* and promotion of apoptosis in doxorubicin-resistant cells leading to increased doxorubicin sensitivity. Hence, miR-449a could have clinical application for the treatment of chemoresistant breast cancers (Tormo et al., 2019).

Emerging evidence indicates that some lncRNAs may serve as competing endogenous RNA (ceRNA) and inhibit the miRNA expression and biological functions (Tano and Akimitsu, 2012). Liang et al. found that lncRNA-PRLB knockdown results in inhibition of cell migration, overexpression of epithelial markers (E-cadherin), downregulation of mesenchymal markers (N-cadherin, vimentin, and fibronectin) and enhanced the 5-FU-induced cell apoptosis via caspase-8 and caspase-3. lncRNA-PRLB overexpression leads to miR-4766-5p downregulation and enhanced expression of SIRT1. Collectively, lncRNA-PRLB promotes breast cancer cell proliferation and drug resistance through miR-4766-5p mediated regulation of SIRT1 signaling (Liang et al., 2018).

2.2. Colorectal cancer

Nowadays, colorectal cancer is the third common cancer in the world with 1.8 million new cases in 2018. 5-FU is frequently used drug for metastatic colorectal cancer therapy (Kurkjian and Kummar, 2009). Recently, more effective chemotherapeutic agents such as oxaliplatin and the monoclonal antibodies panitumumab and cetuximab have been applied in clinical practice (Jemal et al., 2011). Radiotherapy is another approach to colorectal cancer therapy. Thus far, drug resistance is the most serious challenge in the treatment of colorectal cancer (Kurkjian and Kummar, 2009).

Downregulation miR-34a is associated with resistance to 5-FU in human colorectal cancer. Therefore, chemoresistance to 5-FU could be attenuated by miR-34a overexpressing, which in turn downregulated the expression of SIRT1 and E2F3 (a critical component of the apoptotic process). Anti-apoptotic pathways such as PI3K may contribute to drug resistance. Inactivation of PI3K/AKT signaling significantly results in the upregulation of miR-34a and growth impediment (Akao et al., 2011).

SIRT1 has an inhibitory effect on p53 by its deacetylation. Inhibition of SIRT1 by miR-34a contribute to increased levels of acetylated p53 and expression of p21 and PUMA. Thus, triggering apoptosis in 5-FU resistant cancer cells. Conclusively, miR-34a could be applied in the treatment of 5-FU resistance in human colorectal cancers (Yamakuchi et al., 2008).

It has been confirmed that downregulation of miR-29b was associated with drug resistance. The miR-29b targets SIRT1 and reverses colorectal cancer cells oxaliplatin resistance through ROS/JNK

Table 1
NcRNAs involved in cancer drug resistance via alteration of sirtuin pathway.

ncRNA	Cancer type	Corresponding drug	Mechanism of action	Ref.
miR-34a	Breast cancer	5-FU	Inhibits the expression of SIRT1, Bcl2, CD44, Rac1, Fra-1, various cyclins, *CDKs*, and the proto-oncoproteins *MYC* and *MYCN*	Li et al. (2013)
miR-22	Breast cancer	Radiosensitivity	SIRT1 downregulation thus, preventing tumorigenesis and triggering apoptosis	Zhang et al. (2017c)
miR-449	Breast cancer	Doxorubicin	Downregulation of CDK2, E2F1, and E2F3 genes and promotion of apoptosis	Tormo et al. (2019)
PRBL/miR-4766-5p	Breast cancer	5-FU	Inhibits the expression of E-cadherin, N-cadherin, vimentin, and fibronectin and downregulation of SIRT1 and induced cell apoptosis via caspase-8 and caspase-3	Liang et al. (2018)
miR-34a	Colorectal cancer	5-FU	SIRT1 downregulation and P53 induced apoptosis	(Akao et al., 2011; Yamakuchi et al., 2008)
miR-29b	Colorectal cancer	5-FU	Downregulation of SIRT1/ROS pathway	Liu and Cheng (2018)
H19/miR-149-5p	Colorectal cancer	5-FU	Triggering autophagy following the downregulation of SIRT1	Wang et al. (2018)
UCA1/miR-204	Prostate cancer	Docetaxel	Activation of caspase-3 and cell apoptosis following the downregulation of SIRT1	Wang et al. (2016)
miR-34a	Prostate cancer	Paclitaxel	Downregulation of SIRT1, E2F1, Bcl2, E2F3, Cyclin D1, CDK6 and triggering apoptosis	Fujita et al. (2008)
miR-34a	Prostate cancer	Comptothecin	Downregulation of *BCL2* and SIRT1 and triggering apoptosis	Kojima et al. (2010)
miR-494	pancreatic cancer	5-FU	SIRT1 downregulation, G1 phase arrest, apoptosis induction, and senescence through upregulation of BAX and p21	Liu et al. (2015)
HULC/miR-6825-5p, miR-6886-3p and miR-6845-5p	Hepatocellular carcinoma	Oxaliplatin 5-FU THP	SIRT1 downregulation and inhibition of SIRT1-induced autophagy	Xiong et al. (2017)
miR-132	Gastric cancer	Cisplatin	Downregulation of SIRT1, increases the level of acetylated CREB, and increases the ABCG2 signaling pathway	Zhang et al. (2017b)
miR-34a	Bladder cancer	Cisplatin	Inhibition of CDK6 and SIRT-1 and inducing senescence	Vinall et al. (2012)
miR-106a/b	HepG2/Hela cells	Cisplatin	Inhibition of SIRT1, decreases the expression of ABC transporter p-glycoprotein and MDR1 through deacetylating FOXO1	Raji et al. (2017)
miR-34a	Multiple myeloma	Dexamethasone	Activation of p53/miR-34a/SIRT1 signaling pathway	Murray et al. (2013)
miR-125b	Multiple myeloma	Dexamethasone	Activation of p53/miR-34a/SIRT1 signaling pathway	Murray et al. (2013)
miR-761	Synovial Sarcoma	Pazopanib	Overexpression of thyroid hormone receptor interactor 6 (TRIP6), lamin A/C (LMNA), and SIRT3 and triggering apoptosis via SIRT3/GSTP1/JNK	Shiozawa et al. (2018)
MEG3	Glioma	Cisplatin	Increased cell apoptosis via increased SIRT7 expression and decreased the phosphorylated levels of PI3K/AKT/mTOR	Xu et al. (2018)

pathway. An important way to obtain the acquired drug resistance in cancer cells is inactivation of reactive oxygen species (ROS) (Goldberg et al., 2004). SIRT1 inhibits reactive oxygen species formation in cells via increasing the expression of cellular antioxidants such as superoxide dismutase (Cheng et al., 2014). Studies showed that the JNK pathway is a molecular linkage between oxidative stress and apoptotic pathways. JNK activation upregulates the expression of pro-apoptotic proteins and blocks the function of Bcl2 which is an important anti-apoptotic protein (Dhanasekaran and Reddy, 2008). Therefore, overexpression of miR-29b may inhibit SIRT1 expression, promotes reactive oxygen species generation and JNK mediated cell apoptosis leading to increased oxaliplatin-sensitivity (Liu and Cheng, 2018).

Under metabolic and therapeutic stress such as chemotherapy, autophagy helps the tumor cells to survive via sequestering proteins and organelles in autophagic vesicles and delivering these vesicles to lysosomes for degradation. Therefore, autophagy inhibitors can enhance the efficacy of chemotherapy for many cancers (Zhang et al., 2017a). H19 is a lncRNA that is upregulated in colorectal cancer and increased the 5-FU resistance through triggering autophagy. H19 promotes autophagy via SIRT1 upregulation and miR-194-5p down-regulation. H19 has a sequence that can directly attach to miR-194-5p, suggesting that the suppression of H19 via miR-194-5p may result in diminished autophagy and increased 5-FU sensitivity (Wang et al., 2018).

2.3. Prostate cancer

Prostate cancer is a common cancer among men and is a major contributing factor of cancer-related mortality (Tian et al., 2018). Recent investigations have illustrated that miR-221 and miR-222 are upregulated in some cancers, such as prostate cancer, resulted in the downregulation of SIRT1 and inhibition of autophagy and angiogenesis. Thus, miR-221 and miR-222 may have therapeutic effects for the treatment of prostate cancer (Karbasforooshan et al., 2018; Yang et al., 2014).

Urothelial carcinoma-associated 1 (UCA1) is a lncRNA, up-regulated in many cancers such as prostate cancer. UCA1 downregulation leads to increased miR-204 expression and suppresses SIRT1 expression. Therefore, UCA1/miR-204/SIRT1 axis activate the docetaxel-induced caspase-3 activation and triggers apoptosis in 22RV1/DR cells (Wang et al., 2016).

Fujita et al. suggested that miR-34a could suppress cell growth and stop cell cycle at the G1 phase in PC3 prostate cancer cells. Their investigation also revealed that miR-34a expression is decreased in p53-null PC3 and p53-mutated DU145 cells compared with normal cancer cells. An increase in miR-34a expression results in downregulation of SIRT1 and E2F1 as well as Bcl2, E2F3, Cyclin D1, and CDK6. Thus, inhibiting cell growth and enhancing apoptosis leading to camptothecin sensitivity in resistant cells (Fujita et al., 2008).

Kojima et al. reported that miR-34a performs on the 3'-UTR of *BCL2* and *SIRT1* mRNAs directly and indirectly and downregulates their expression resulting in increased apoptosis in paclitaxel resistant PC3 cells and sensitize them to chemotherapy (Kojima et al., 2010). Fig. 1 shows a schematic representation of ncRNAs impact on sirtuins that lead to chemosensitivity in different cancers.

2.4. Ovarian cancer

Ovarian cancer with a 5-year survival rate is an aggressive gynecological cancer. Because of being diagnosed at late stages, high risk of recurrence and resistance to the current chemotherapeutic drugs. (Norouzi-Barough et al., 2018).

Recently, Shuang et al. found that the upregulation of SIRT1 expression results in poor prognosis and drug resistance in epithelial ovarian cancer (Shuang et al., 2015). Besides, Mvunta et al. illustrated that SIRT1 can promote invasion in ovarian cancer cells (Mvunta et al., 2017). It has been found that miR-142-3p plays an important role in several common cancers as a tumor suppressor (Colamaio et al., 2015; Ghanbari et al., 2015). Gao et al. showed that miR-142-3p promotes apoptosis and enhances the cisplatin sensitivity of SKOV3/DDP cells via downregulation of SIRT1. Conclusively, miR-142-3p could be a suitable choice for the treatment of ovarian cancer (Gao et al., 2018).

2.5. Pancreatic cancer

Among all malignant cancers, pancreatic cancer is placed in the fourth rank worldwide, because of high mortality, invasiveness, early metastasis and lack of specific symptoms. The average survival time is only 3–6 months (Chitkara et al., 2015; Duguang et al., 2017). Several number of ncRNAs are related to biological behavior and signaling pathways in pancreatic cancer (Fu et al., 2017). Chemotherapy is an essential treatment strategy in most pancreatic cancers. However, drug resistance is a big challenge that leads to treatment failure (Lv and Huang, 2019). The upregulation of miR-494 negatively regulates c-MYC and SIRT1 expression directly by binding to the 3′-UTR of *c-MYC* and *SIRT1* and inhibits drug-resistant pancreatic cancer cell proliferation *in vitro* and *in vivo*. Therefore miR-494 bears therapeutic potential in the treatment of 5-FU and Gemcitabine resistance in pancreatic cancer (Liu et al., 2015).

2.6. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the most widespread cancers in the world, placed as the second leading cause of cancer-related death because of its high invasiveness and metastatic risk. Several ncRNAs are associated with HCC progression and drug resistance (Carter, 2014; Wei et al., 2019; Wu et al., 2015).

Highly upregulated in Liver Cancer (HULC) is a type of lncRNAs that has a key role in the carcinogenesis and promotion of HCC and acts as an oncogenic lncRNA. Through overexpressing the SIRT1 protein, HULC can cause autophagy in HCC cells. SIRT1 induced autophagy through suppressing the acetylation of the autophagy-related proteins including ATG5 and ATG7. HULC reduces miR-6886-3p, miR-6845-5p and miR-6825-5p expressions and contribute to USP22 and SIRT1 upregulation. As mentioned before, autophagy has an important role in tumor chemoresistance. Therefore, downregulation of HULC by miR-6886-3p, miR-6845-5p and miR-6825-5p contribute to the downregulation of SIRT1 and make HCC cells sensitive to the chemotherapeutic agents such as Tetrahydropalmatine (THP), oxaliplatin and 5-FU (Xiong et al., 2017).

2.7. Gastric cancer

Gastric cancer is one of common malignancies in East Asian counties (Wang et al., 2012; Yin et al., 2012). Resistance to cisplatin has been a major problem in the treatment of gastric cancer for a long time. Cancer stem cell-like cells (CSCs) are responsible for many features of tumors such as drug resistance. CSCs possess many stem cells characteristics which distinguish them from the other tumor cells. CSCs are very tumorigenic and resistant to chemotherapy and could be accountable for post-therapy tumor relapse. An experiment on CSCs demonstrated that miR-132 is upregulated in Lgr5+ CSCs. The expression of miR-132 leads to the downregulation of SIRT1 expression. ABCG2 which is a member of ABC transporter family genes is involved in the chemoresistance of gastric cancer. Downregulation of SIRT1 leads to increase in the level of acetylated CREB which in turn raise the ABCG2 signaling pathway (Zhang et al., 2017b).

2.8. Bladder cancer

The miR-34a has been shown to target CDK6 and SIRT1 in TCC bladder cancer cell lines and sensitizes cells to cisplatin treatment. MiR-34a can simultaneously targetmultiple components of p53-Rb signaling

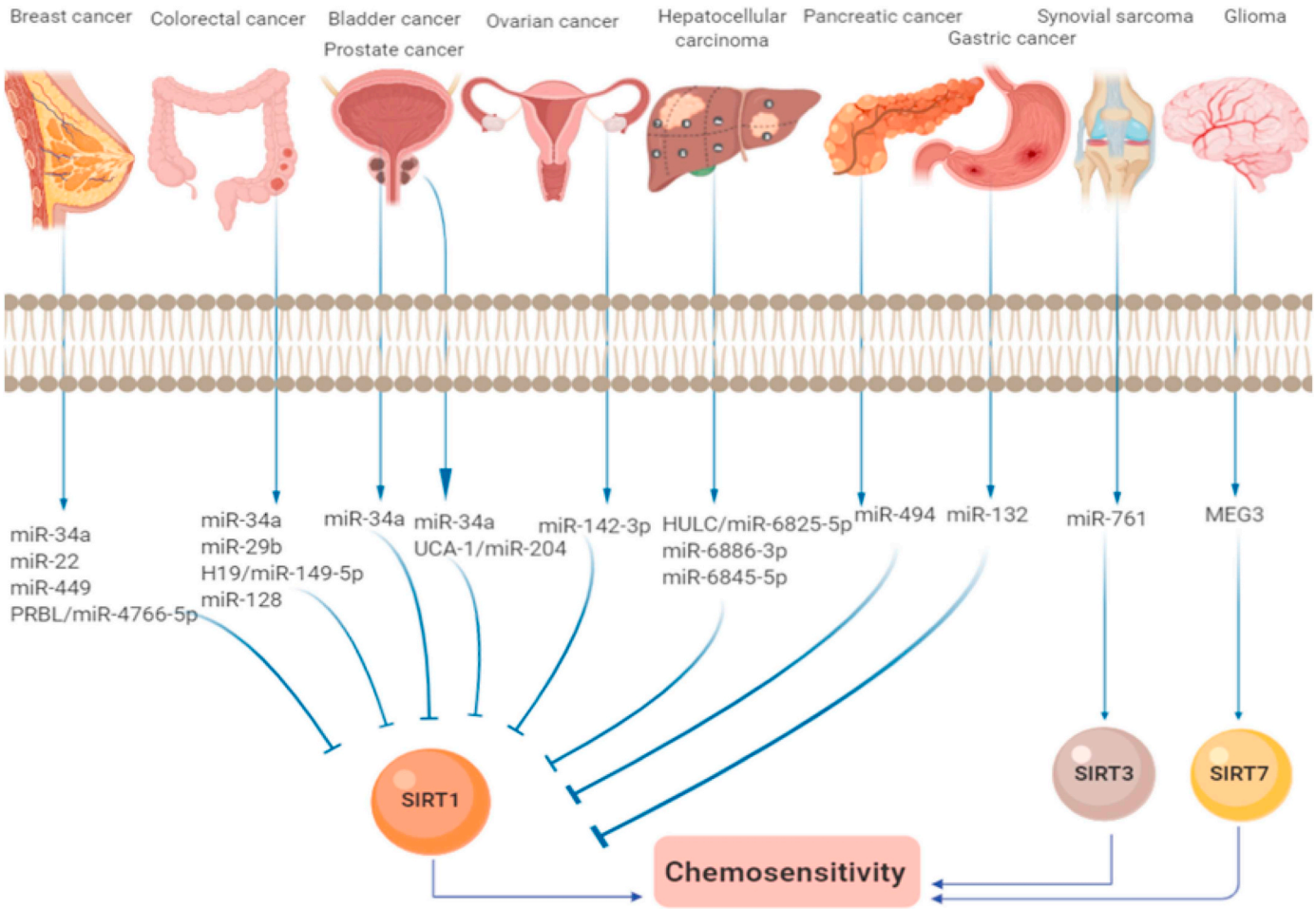

Fig. 1. Schematic of ncRNAs impact on sirtuins leading to chemosensitivity in different cancers.

axis. Cdk6, in complex with Cdk4 and cyclin D1, is a key regulator of Rb activity and thereby G1/S transition. There is a positive correlation between senescence and increased chemo-sensitivity (in both clinical and *in vitro* studies). Thus, targeting of CDK6 by miR-34a is directly responsible for G1/S arrest and induction of senescence. This finding indicates that manipulation of miR-34a expression could have therapeutic potential for patients with bladder cancer (Vinall et al., 2012).

Recent studies have illustrated that horizontal transfer of genetic components could be a way for communication between heterogeneous tumor cell populations. Therefore, this phenomenon alters the susceptibility of cancer cells to chemotherapeutic drugs. Raji et al. found that cisplatin-resistant HepG2 cells can make HeLa cells resistant to cisplatin by horizontal transfer of miR-106a/b via exosomes. They found that miR-106a/b overexpression can decrease SIRT1 protein expression. Inhibition of SIRT1 decreases the expression of MDR1 and ABC transporter p-glycoprotein via FOXO1 deacetylation resulting in enhanced sensitivity to cisplatin (Raji et al., 2017).

2.9. Multiple myeloma

Dexamethasone has a key role in the chemotherapy of multiple myeloma. However, when used as monotherapy, it does not cause significant cytotoxicity. Dexamethasone induces the miR-34a overexpression. The miR-34 can downregulate SIRT1 and activation of p53. Therefore, p53/miR-34a/SIRT1 signaling pathway is responsible for dexamethasone sensitivity in cancer cells via induction of apoptosis. The miR-125b can enhance the miR-34a levels. Using dexamethasone combined with miR-125b-mRNAs could increase cancer cell apoptosis via activation p53/miR-34a/SIRT1 signaling pathway. These findings help us to put more emphasis on miR-125b to manipulate B-cell apoptosis to improve the treatment of multiple myeloma (Murray et al., 2013).

2.10. Osteosarcoma

Osteosarcoma is a common type of bone malignancy, usually located at the end of long bones and arises from epithelial-mesenchymal transition. SIRT1 upregulation significantly promotes the doxorubicin-resistance phenotype and increases the expression of multidrug resistance molecule P-glycoprotein in osteosarcoma cells. The miR-204 was found to have an inhibitory effect on Saso-2 osteosarcoma cells by downregulating SIRT1 expression thus, sensitizing cells to chemotherapy (Li et al., 2009; Shi et al., 2015).

2.11. Synovial sarcoma

Synovial sarcoma is a type of soft tissue sarcoma that has few known effective therapies. Pazopanib is a commonly prescribed drug for patients with synovial sarcoma. However, its efficacy is mostly restricted by the emergence of chemoresistance (de Necochea-Campion et al., 2017; Hosaka et al., 2012; Rajendra et al., 2013). Shiozawa et al. revealed that miR-761 overexpression in extracellular vesicles of synovial sarcoma cells is associated with pazopanib-resistance *in vitro*. Changes in miR-761 expression regulates the response to pazopanib by targeting lamin A/C (LMNA), thyroid hormone receptor interactor 6 (TRIP6), and SIRT3 (Shiozawa et al., 2018). They demonstrated that TRIP6 knockdown could increase drug resistance via up-regulating the phosphorylated cyclin-dependent kinase inhibitor 1B (CDKN1B also known as

p27Kip1) (Miao et al., 2016). Another study demonstrated that LMNA knockdown increased aggressiveness-related genes and molecules resulting in enhanced invasion and drug resistance in cells (Maresca et al., 2012). Moreover, SIRT3 downregulation increased drug resistance, while overexpression of SIRT3 enhanced chemosensitivity by promoting chemotherapeutic-induced apoptosis via SIRT3/GSTP1/JNK pathway. Overexpression of Glutathione S-transferase pi 1 (GSTP1) has been reported in many cancers, such as breast, colon, kidney, lung, and ovarian cancers (Depeille et al., 2005). GSTP1 overexpression negatively regulated the sensitivity of cancer cells toward chemotherapeutic agents, including cisplatin, doxorubicin, and epirubicin via sequestering the JNK kinase in a complex, thus preventing apoptosis (Di Pietro et al., 2010; Kalinina et al., 2012). SIRT3 expression leads to GSTP1 downregulation and induces apoptosis in chemoresistant cancer cells (Tao et al., 2016).

2.12. Glioma

Zhao et al. revealed that downregulation of MEG3 lncRNA expression is associated with a poor prognosis in patients with glioma. MEG3 can inhibit autophagy and increase apoptosis (via Bax and cleaved caspase-3/-9 overexpression). It also inhibits cell proliferation and migration through increased SIRT7 expression and diminished the phosphorylated levels of PI3K/AKT/mTOR in the glioma cells (Xu et al., 2018). Following cisplatin treatment in a glioblastoma cell line, MEG3 expression enhances cisplatin-induced apoptosis and suppresses autophagy leading to increased chemosensitivity (Wu et al., 2018).

3. Future prospective and conclusion

One of the major complications in the field of cancer therapy is drug resistance. NcRNAs including microRNAs and lncRNAs are rapidly being accepted as fundamental regulators of gene expression in cancer. Dysregulation of particular ncRNAs is correlated with the progression of cancer drug resistance. The diversity and complexity of ncRNAs is an indicator of their important regulatory role in the cell. NcRNAs are involved in cancer drug resistance by targeting various molecules within different signaling pathways related to cell proliferation and apoptosis. It is now clear that sirtuins are strongly related to cancer by several mechanisms, including those involved in cancer cell proliferation, apoptosis, genome stability and metabolism. Many ncRNAs for activation or repression of sirtuins have been identified. Such molecules could have the potential to enter clinical trials to overcome the challenge of drug resistance in cancer. Although the delivery of ncRNAs is considered as a challenge and should be studied more intensively before clinical using of miRNA therapeutics. In conclusion, further studies are required to find more ncRNA targets and to reach a better knowledge of the principal mechanisms of drug resistance in different types of cancers.

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