MINI-REVIEW

Long Non-coding RNAs and Drug Resistance

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Abstract

Background: Long non-coding RNAs (lncRNAs) are emerging as key players in gene expression that govern cell developmental processes, and thus contributing to diseases, especially cancers. Many studies have suggested that aberrant expression of lncRNAs is responsible for drug resistance, a substantial obstacle for cancer therapy. Drug resistance not only results from individual variations in patients, but also from genetic and epigenetic differences in tumors. It is reported that drug resistance is tightly modulated by lncRNAs which change the stability and translation of mRNAs encoding factors involved in cell survival, proliferation, and drug metabolism. In this review, we summarize recent advances in research on lncRNAs associated with drug resistance and underlying molecular or cellular mechanisms, which may contribute helpful approaches for the development of new therapeutic strategies to overcome treatment failure.

Keywords: lncRNA - drug resistance - cancer

Introduction

There are only 20,000-25,000 protein-coding genes in the entire human genome (Costa FF, 2005; Djebali S, et al., 2012), only account for <2% of the whole human genome. However, the degree of complexity in human biological functions is more associated with non-coding RNAs (ncRNAs) (Frith et al., 2005; Taft et al., 2007), which have not significant open reading frame and are classified as small and long ones depend on the length of transcript size, those length >200 nt are long non-coding RNAs (lncRNAs) (Rinn et al., 2012). lncRNAs are a heterogeneous type of ncRNAs that include thousands of different species, with poorly conserved (Fatica et al., 2014). The number of lncRNAs in the genome is still debated, but it is estimated that there are >60,000 lncRNAs in the human genome (Derrien et al., 2012; Hangauer et al., 2013). Although lncRNAs are considered as transcriptional noises or experimental artifact at first (Werner et al., 2005), it has been known that lncRNAs play an essential role in biological pathways, including chromosome silencing and activation (Tian et al., 2010; Hung et al., 2011), genomic imprinting (Sleutels et al., 2002), differentiation (Kretz et al., 2013), acting as scaffolds for transcription factors and epigenetic modifiers (Brunner et al., 2012). LncRNAs themselves may also serve as precursors of microRNAs (miRNAs) encoding miRNAs, or function as miRNAs sponge and target certain miRNAs leading to RNA degradation or inhibit translation (Kallen et al., 2013). LncRNAs have been implicated in development events, therefore dysregulation of lncRNAs links with cancer and lncRNAs may be potential biological markers of tumors (Shi et al., 2013).

Chemotherapy has been widely used in cancer treatment for a long time, it usually has an effect on cancer cells by interfering with the metabolism of nucleic acid, DNA replication and mitosis, synthesis of protein. Nevertheless, drug resistance, either de novo or acquired, is still a challenge for cancer therapy since it often cause therapeutic failure. The underlying mechanism of resistance to chemotherapeutic agents are not fully elucidated. With the development of new technologies in combination of bioinformatics, more and more genes related to drug resistance are discovered or predicted (Potti et al., 2006; Raguz et al., 2008; Crijns et al., 2009; Etemadmoghadam et al., 2009). Drug resistance results from diverse factors, including individual variations in patients, genetic and epigenetic changes within tumors (Roberti et al., 2006; Tan et al., 2010) such as mutations, translocations, deletions and amplifications of coding genes or promoter regions, gene rearrangement (Fojo T, 2007), alteration of tumor microenvironment and tumor stromal cell components (Bouzin et al., 2007), self-protection of cancer stem cells (Rosen et al., 2009), epithelial-mesenchymal transition (Han et al., 2014), energy metabolism and hypoxia (Broxterman et al., 1991; Robey et al., 2009; Ruan et al., 2009). In addition, other reasons like classical drug efflux (Gottesman et al., 2006), acceleration of drug metabolism and decreasing sensitivity to induction of apoptosis (Janne et al., 2009; Coley, 2010) also result in drug resistance.

Accumulating evidences have been revealed that

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LncRNAs Modulate Gene Expression

It is uncovered that gene expression may be different dependent on the function of RNA molecules themselves as well as their interactions with DNA and/or proteins, especially emphasis long non-coding RNAs (Harries 2012; Ernst et al., 2013). Studies have revealed that lncRNAs have abilities of changing gene expression in response of various extracellular stimuli (Castelnuovo et al., 2013), which indicates that lncRNAs may adjust the timing of gene expression and there are fine-tuning steps in the regulation of gene expression at the epigenetic, transcriptional or post-transcriptional level (Wang et al., 2013). Long intergenic non-coding RNAs (lincRNAs) can interact with chromatin remodeling proteins to epigenetically silence genes in trans (Khalil et al., 2009; Tsai et al., 2010). LncRNAs such as X-inactive specific transcript (XIST) and homeobox A1 (HOXA1) have been shown to serve as molecular scaffolds for the recruitment of chromatin-modifying complexes, notably polycomb repressive complex 2 (PRC2) to alter gene expression in cis (Lee et al., 2013; Maamar et al., 2013). LncRNAs also bind specific gene clusters to prevent the binding of transcriptional activators (Chu et al., 2011). LncRNAs like enhancer RNAs (eRNAs) and lincRNA-p21 transcription may enhance expression of neighboring protein-coding genes through locally modulate chromatin structure or act as locus-restricted co-activators (Melo et al., 2013; Dimitrova et al., 2014). Similarly, transcription of lncRNAs near protein-coding loci can suppress transcription since the transcriptional machinery on lncRNA gene locus physically prevents binding to protein-coding genes (Malek et al., 2014). The post-transcriptional roles of lncRNAs including mRNA splicing, editing, transport, translation and degradation. It is reported that IncRNA HOX antisense intergenic RNA (HOXAIR) has an influence on mRNA translation and is shown to induce ubiquitin-mediated proteolysis in a way of post-transcriptional. HOXAIR associates with certain E3 ubiquitin ligases containing RNA-binding domains such as Dzip3 and Mex3b, as well as with their respective ubiquitination substrates, Ataxin-1 and Snurportin-1. HOXAIR promotes the ubiquitination of Ataxin-1 by Dzip3 and Snurportin-1 by Mex3b respectively, then accelerating their degradation (John et al., 2012). These collective results suggest that IncRNAs may regulate many genes expression through interacting with DNA/RNA or proteins at different levels.

LncRNAs and Cell Death

It is known that IncRNAs can promote or suppress cell death pathways through diverse molecular mechanisms including epigenetically silencing (Zheng et al., 2014), acting as sponge or precursors for miRNAs (Wang et al., 2014), activating or inhibiting signal molecules and interacting with proteins or nucleic acids (Wang, 2011) in various cell types. For example, recently one lncRNA named PANDAR (promoter of CDKN1A antisence DNA damage-activated RNA) is reported to interacts with the transcription factor NF-YA to limit the expression of pro-apoptotic genes in lung cancer cell lines. The results demonstrate that overexpression of PANDAR leads to a loss of NF-YA binding at the promoter of Bcl-2 thus inhibiting Bcl-2 expression and promoting apoptosis (Han, 2015). In contrast, IncRNA urothelial cancer associated 1 (UCA1) may restrain apoptosis induced by Ets-2 knockdown in bladder cancer BLZ-211 cells. Knockdown of Ets-2 reduced expression of UCA1 which cause an increase of apoptosis via inactivating of Akt in BLZ-211 cells (Wu et al., 2013). Additionally, it is also reported that reduction of UCA1 may serve a pro-apoptotic role in cardiomyocyte partly through enhancing the protein level of p27 (Liu et al., 2015).

LncRNAs Link with Drug Resistance

Numerous mechanisms can illustrate the molecular basis of drug resistance. Recent research demonstrate that there is a relationship between the drug-resistance phenotype and non-mutational regulation of gene expression. LncRNAs are the major modulators of non-mutational gene regulation. LncRNAs have been reported to be dynamically changed in response to various drugs, and could affect gene expression involved in cell cycle arrest, inhibition of apoptosis and DNA damage repair (Goldman 2003; d'Adda 2008; Lipovich et al., 2010). In this section, we will discuss current experimental findings showing molecular evidences of IncRNAs involved in the drug resistance rely on different drugs (Table 1).

Cisplatin Resistance and IncRNAs

Cisplatin is one of the most common anticancer drugs by interfering with DNA synthesis to prevent cancer cells proliferation, and often result in drug resistance during
### Effect up-/down-regulation of Different lncRNAs Expression on Sensitivity to Chemotherapy

The Table Presents the Findings Indicating a Negative Correlation between Expression of lncRNAs and Effect on Sensitivity to Chemotherapy (except AK126698, GAS5 and SnaR)

| lncRNAs | Up-/downregulation | Possible targets | Chemotherapeutic agent | Effect on sensitivity to chemotherapy |
|---------|---------------------|------------------|------------------------|---------------------------------------|
| HOTAIR | #                   | p21              | Cisplatin              | Lung adenocarcinoma                   | Liu Z (2013) |
| AK126698 | $                  | Wnt/β-catenin   | Cisplatin              | Non-small-cell lung cancer            | Yang Y (2013) |
| UCA1 | #                   | Wnt6             | Cisplatin              | Bladder cancer                        | Doyle LA (1996), Tsang WP (2007) |
| MDR-1/P95 |               |                    | Doxorubicin             | Prostate cancer, liver cancer         | Doyle LA (1996) |
| ARA    | #                   | Cyclin B1, ToPo IIα | Doxorubicin             | Breast cancer, liver cancer           | Jiang M (2014) |
| ACSL4, Bcl-xl, Bax | # |                    | Doxorubicin, etoposide | Prostate cancer, renal cell carcinoma | Tsang WP (2007) |
| CUDR   | #                   | Caspase-3         | Doxorubicin, etoposide | Squamous carcinoma                    | Tsang WP (2007) |
| PRKCI, PCGEMI | # |                    |                        | Prostate cancer                       | Lee H (2014) |
| DAPL   | #                   |                    |                        | Prostate cancer                       | Lee H (2014) |
| SnaR   | --                  | --               |                        | Colon cancer                          | Lee H (2014) |

Doxorubicin resistance and IncRNAs

Doxorubicin is a kind of broad-spectrum anthracycline anticancer drug which has strong cytotoxic effect. It is associated with cisplatin resistance in non-small-cell lung cancer cells. Expression of AK126698 is reduced in lung cancer cells with cisplatin resistance. Knockdown of AK126698 may decrease the vertebrate orthologs of naked cuticle family member NKD2 which can negatively regulate Wnt signaling pathway through binding to Dvl protein and enhance the accumulation and nuclear translocation of β-catenin, thus activating canonical Wnt/β-catenin pathway and significantly suppressing apoptosis induced by cisplatin in lung cancer cells. It is appeared that AK126698 promotes cisplatin resistance through targeting the Wnt pathway (Yang et al., 2013). However, more research are needed to elucidate whether there are other mechanisms by which AK126698 mediates within cisplatin resistance.

UCA1, a recently identified long non-coding RNA, whose expression is positively correlated with cell proliferation and migration in bladder cancer cells. It is shown that expression of UCA1 is upregulated in both cisplatin treatment patients with bladder cancer and cisplatin-resistant bladder cancer cells. UCA1 knockdown reduced the cell viability and wingless-type MMTV integration site family member 6 (Wnt6) expression levels, whereas overexpression of UCA1 strongly enhances the cell viability and expression of Wnt6 in human bladder cancer cell lines during cisplatin treatment, thus activating canonical Wnt signaling pathway. Moreover, inhibition of Wnt6 in UCA1-overexpressing cells can partially alleviate the increase of cell viability induced by UCA1 during cisplatin treatment. Expression of UCA1 and Wnt6 is also positively correlated in vivo. Therefore, UCA1 promotes cisplatin resistance by activating Wnt signaling pathway in a Wnt6-dependent manner (Fan et al., 2014), but how UCA1 intensifies Wnt6 expression will be investigated in future.

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one of the most widely employed chemotherapy agents for cancers, like breast cancer and liver cancer (Sen GS, et al., 2011). LncRNA H19 has been proved function as an oncogene. It is shown that compared with parental human breast carcinoma cells or drug-sensitive revertant cells, H19 gene is overexpressed within multidrug resistance phenotype of cells, which are characterized by overexpression of a 95-kilodalton membrane glycoprotein (p95) that correlates with lower accumulation and retention of doxorubicin. Another human lung carcinoma with p95-overexpressing multidrug-resistant cell lines, also displays high level of H19 mRNA (Doyle LA, et al., 1996). Besides, H19 gene is considered to induce P-glycoprotein expression and multidrug resistance 1 (MDR1)-associated drug resistance by mediating MDR1 promoter methylation in liver cancer cells. It is observed that expression of H19 mRNA, MDR1 gene and its protein product P-glycoprotein are all upregulated, contrast to a decrease of doxorubicin accumulation level in doxorubicin-resistant cells. H19 knockdown markedly increases the percentage of MDR1 promoter methylation, then reduces MDR1 and P-glycoprotein expression, thus enhancing the cellular doxorubicin accumulation level and sensitizes doxorubicin toxicity in both parent sensitive and resistance cells (Tsang WP, et al., 2007). It provides a new strategy (anti-H19) to improve the efficacy of cancer chemotherapy. ARA-Doxorubicin Resistance Associated-as a new specific differently expressed LncRNA is validated in doxorubicin resistant cells. Sustained doxorubicin treatment can significantly upregulate ARA expression in parenta sensitive cell lines. Knockdown of ARA can reverse drug resistance, diminish the proliferation, induce G2/M arrest and cell death through decreasing the accumulation of ToPo IIα (topoisomeraseII alpha), expression of cyclin B1 and ACSL4 (acyl-CoA synthetase 4), downregulation Bcl-xl and upregulation Bax in doxorubicin resistant cells. ARA also involves in other multiple signaling pathways that are crucial for drug resistance, including MAPK signaling pathway, metabolism pathways, cell cycle and cell adhesion-related biological pathways (Jiang et al., 2014). It suggests that ARA has important roles in doxorubicin resistance development. The long non-coding RNA novel gene cancer up-regulated drug resistant (CUDR) induces drug resistance in cells through suppressing apoptosis induced by drugs. Expression of CUDR is significantly upregulated in a doxorubicin-resistant subline of human squamous carcinoma cells, which are more resistant to drug-induced apoptosis. Overexpression of CUDR can increase resistance to doxorubicin and etoposide, decrease drug-induced apoptosis as well as expression and activity of caspase-3, promote anchorage-independent growth in squamous carcinoma cells. The present results demonstrate that CUDR may regulate the drug sensitivity through caspase 3-dependent apoptosis (Tsang et al., 2007). Whether or not CUDR will modulate other genes in drug resistance would require detailed investigation.

The P21-associated ncRNA DNA damage Activated LncRNA PANDA is an evolutionarily conserved LncRNA located between the protein-coding CDKN1A gene and lncRNA-p21. Expression of PANDA is elevated in a subset of breast cancer cells that contribute to doxorubicin resistance, a crucial component of breast cancer chemotherapy. PANDA exerts effect through physically interacting with the nuclear transcription factor NF-YA subunit to diminish p53 dependent pro-apoptotic effect. Moreover, depletion of PANDA in human fetal lung fibroblasts has been shown to increase cell death induced by doxorubicin then enhancing sensitivity to doxorubicin (Sotillo E, et al., 2011). However, more studies is needed to validate the function of PANDA in drug resistance.

**Hormone drugs and lncRNAs**

The growth arrest-specific 5 LncRNA GAS5 as a long non-coding RNA encoded through its exonic sequences, is usually accumulated in growth-arrested cells. GAS5 can resist migration and invasion as well as promote apoptosis in renal cell carcinoma (RCC) cells, a role as a tumor suppressor in RCC has also been demonstrated (Pickard et al., 2013; Qiao et al., 2013). Downregulation of GAS5 contributing to glucocorticoid resistance through alleviating sensitivity of tumor cells to apoptosis via suppressing glucocorticoid-mediated induction of several responsive genes like anti-apoptotic cellular inhibitor of apoptosis 2 (cIAP2) and serum/glucocorticoid-regulated kinase 1 (SGK1). GAS5 acting as a decoy competes with cIAP2/SGK1 glucocorticoid response elements (GREs) for binding to the DNA-binding domain of the glucocorticoid receptor (GR) to prevent cIAP2/SGK1 transcripational activation (Kino et al., 2010). Whether GAS5 interacts with other chromatin components to stimulate transcription of glucocorticoid-responsive genes need to be examined.

The LncRNA prostate noncoding RNA 1 (PRNCR1, also known as PCAT8) and prostate cancer gene expression marker 1 (PCGEM1) are both highly expressed in aggressive prostate cancer and enhance proliferation of prostate cancer cells. Hyperactive androgen receptor (AR) activity is a crucial determinant of resistance to current castration therapies. Knockdown of PRNCR1 and PCGEM1 can lessen the activity of AR and viability of castration-resistant prostate cancer cells. Moreover, PRNCR1 increases activity of AR through binding to acetylation AR C-terminus motif which is correlated with disruptor of telomeric silencing (DOT1)-like, histone H3 methyltransferase (DOT1L) and its association with DOT1L. This is required for sequential recruitment of the PCGEM1 to DOT1L-mediated methylated AR N-terminus (Yang et al., 2013; Pestell et al., 2014). Decrease of PRNCR1 may be a therapy strategy in castration-resistant prostate cancer.

**Other drugs resistance and lncRNAs**

Sorafenib is a multikinase inhibitor that exerts anti-angiogenic and anticancer effect by inhibiting multiple growth factor pathways (Wilhelm et al., 2004). LncRNA ROR is a stress-responsive lncRNA enriched within extracellular vesicles and upregulated in human hepatocellular cancers (HCC) cells, may as a modulator of chemotherapeutic response. Sorafenib raises lnc-ROR expression in tumor cells and extracellular vesicles,
whereas knockdown of linc-ROR may enhance sorafenib-induced apoptosis and cell toxicity through significantly increasing p53 activity that can decrease cell viability of HepG2 cells during doxorubicin (Takahashi et al., 2014). Hence, targeting linc-ROR may improve responses to conventional therapeutic agents that are used for treatment of HCC.

Multidrug resistance (MDR) is a common reason of chemotherapy failure in cancer treatment. The long non-coding RNA MDR-related and upregulated lncRNA (MRUL) is strongly upregulated in both doxorubicin/vincristine-resistant gastric cancer (GC) cells and GC tissues. MRUL is negatively correlated with growth inhibition rates of GC specimens treated with chemotherapy drugs in vitro and indicates a poor prognosis for GC patients. MRUL knockdown not only results in increased rates of cell death by enhancing doxorubicin accumulation and reducing the Bcl-2/Bax ratio, but also decreased ABCB1 mRNA levels via the enhancer-like role of MRUL, whereas reversal of MRUL sequence and alteration of position of MRUL inserts do not change transcriptional enhancement, indicating that MRUL might positively affect ABCB1 expression in an orientation- and position-independent way (Wang Y., et al., 2014). It indicates that MRUL depletion would be helpful in GC MDR patients.

5-Fluorouracil (5-FU) is a classical anti-metabolite drug which is widely used for cancer treatment through affecting nucleoside metabolism to cause cell death (Zhang N., et al., 2008). lncRNA SnaR is transcribed by RNA polymerase III that links with nuclear factor 90 (NF90). It is shown that SnaR is downregulated in 5-FU-resistant colon cancer cells. Loss of SnaR in 5-FU-resistant colon cancer cells leads to increase the cell viability, decrease Annexin V-positive (ANN+) apoptotic cells after 5-FU treatment, which suggests that SnaR as a negative modulator in development of 5-FU resistance in colon cancer (Lee E., et al., 2014). But it does not describe the detail genes or pathways which SnaR modulates in 5-FU resistance of colon cancer cells.

Docetaxel is the first agent approved for treating hormone refractory prostate cancer by inhibiting tubulin to prevent proliferation and divide of cancer cells. GAS5 is aberrantly expressed in breast cancer, head and neck squamous cell carcinoma (HNSCC) and glioblastoma multiforme. It is reported that overexpression of GAS5 can enhance prostate cancer cell death induced by chemotherapeutic drugs docetaxel, nutlin-3a and mitoxantrone, while cell death is attenuated by downregulation of GAS5 expression. It is indicated that cell death is strongly correlated with cellular GAS5 levels and GAS5 is sufficient to mediate this activity. Accordingly, abnormally low levels of GAS5 expression may lessen the effectiveness of chemotherapeutic agents (Pickard et al., 2013). Enhancement of GAS5 in combination with chemotherapeutic drugs may improve the efficacy of cancer therapies.

**LncRNAs and Therapy**

As discussed above, these studies have documented lncRNAs roles during drug resistance, meaning lncRNAs may be the major players in contributing to drug resistance through modulating gene expression or signal pathways. The knowledge of lncRNAs related to drug resistance would be helpful in clinical therapy. It seems that some lncRNAs can be used as tools to evaluate the effectiveness of anticancer treatment in term of the response of drugs to adjust their dosage. For example, lncRNA Xist could be used as a biomarker to predict histone deccatylases inhibitors (HDACi, abexinostat) treatment effect on the breast cancer stem cell (CSC). Compared with low-dose sensitive breast cell lines (BCLs), high-dose BCLs tend to be enriched in Xist. X chromosomes number correlates with drug response to abexinostat. Low-dose sensitive BCLs present essentially X chromosome mono- or disomy, whereas high-dose sensitive BCLs present X chromosome normo- or polyosity. Only the CSC population will be reduced by abexinostat treatment in patient-derived xenografts (PDXs) with low Xist expression and abexinostat treatment targets the CSC population in vivo is inversely correlated to Xist expression (Salvador et al., 2013).

In addition, these lncRNAs themselves may be attractive therapeutic agents, since lncRNAs are differently expressed in chemosensitive and chemoresistance tumor cells. Although the molecular mechanism of lncRNA function in drug resistance are not full elucidated, some lncRNAs with unique characteristics can be potential candidates of therapeutic intervention. For instance, HOTAIR regulates cisplatin resistance through modulation of apoptosis and cell cycle distribution by affecting p21 expression in human LAD cells. This raises the possibility that anti-HOTAIR may have potential therapeutic value for those cisplatin-resistant LAD patients (Liu Z., et al., 2013). Because of the lower expression and baseline level of CUDR in human normal tissues compared with other current cancer biomarkers (for example, CEA), the gene might be a potential biomarker for assessment of cancer therapeutic response. Nevertheless, it need more investigation to support the future use of CUDR in cancer therapy (Tsang et al., 2007). These studies provide theoretical basis for targeting lncRNAs participated in anticancer therapy.

**Conclusion**

Despite the progression of knowledge on resistance mechanisms, there is still a considerable lack of understanding of the detailed mechanisms and intracellular pathways mediated by lncRNAs. In this review, we attempt to summarize the roles of lncRNAs in drug resistance. These results demonstrated that lncRNAs are differently expressed in sensitive and resistant cells and most of them positively correlates with chemoresistance, directly or indirectly modulate drugs efficacy via regulating gene expression. One lncRNA can regulate many drugs resistance, and one drug resistance can be modulated by many lncRNAs. Studies to better understand the molecular mechanisms of lncRNAs in drug resistance offers promise for the development of more effective cancer therapies.
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