Long non-coding RNAs and microRNAs as regulators of stress in cancer (Review)

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Abstract. Resistance to stress is a feature of cancer cells. Cellular stress includes oxidative, metabolic and genotoxic stress conditions, which under normal conditions lead to cell death. However, in contrast to normal cells, cancer cells overcome the checkpoints that normally restrict growth, and are able to resist cellular stress and subsequent cell death through a variety of mechanisms, which include several non-coding RNAs (ncRNAs). Within this context, long ncRNAs (lncRNAs) and microRNAs (miRNAs/miRs) are the main categories of ncRNAs that have been shown in the literature to function as regulators of stress resistance pathways in cancer. miRNAs play a key role in the majority of biological pathways, as they regulate the expression of hundreds of target genes, including genes involved in stress response and cell death, oncogenes, or tumor suppressor genes, by inhibiting protein translation or promoting the degradation of mRNAs. Respectively, lncRNAs are epigenetic regulators, which are also involved in cancer progression, stress response and metabolic pathways by promoting or inhibiting the transcription, splicing, translation and modulation of protein function. Thus, the present review summarizes recent knowledge related to the role of these molecules in the cancer response to stress, highlighting the ability of these non-coding molecules to be effective drug targets and biomarkers in cancer treatment.

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Contents

1. Introduction

In cancer biology, the transition of a cell from a normal state to a neoplastic one is a process through which the cell must overcome the anti-oncogenic checkpoints. Based on these checkpoints, a list of six hallmarks of cancer has been created. These hallmarks include the possibility of unlimited cell proliferation, prolonged angiogenesis, resistance to cell death, the possibility of invasion and metastasis, evading growth inhibitors and self-sufficiency in growth signals (1). In recent years, two other hallmarks of cancer have been added to the aforementioned list, which include the deregulation of metabolism, a process that plays a key role in cellular stress responses, and the avoidance of the immune system (2).

Overcoming environmental pressures, such as hypoxia, nutrient depletion and DNA-damaging factors is one of the key abilities of cancer cells. Cellular stress is an environmental factor that affects the growth and development of cancer, and includes oxidative stress induced by reactive oxygen species (ROS), metabolic stress due to increased metabolic procedures and genotoxic stress, including DNA damage. In general, cellular stress activates the process of cell death. However, cancer cells are able to resist cellular stress by altering their

gene expression and metabolic pathways, and avoiding growth inhibition signals (3). Key factors in these altered mechanisms are non-coding RNAs (ncRNAs).

As it is known, the coding regions of the human genome constitute only 1-2% of the whole genome, while the remaining ~98% consists of non-coding regions (4). For a number of years, these non-coding parts of the genome were considered noise and were termed 'junk DNA'. However, it has been shown that the majority of these non-coding regions are transcribed into RNA molecules, ncRNAs (5). According to the literature, these molecules are involved in various cell functions and are involved in numerous diseases, including cancer (6). ncRNAs are divided into two broad categories, the small ones, which consist of <200 nucleotides, and the long ones, which consist of >200 nucleotides. The first category includes microRNAs (miRNAs/miRs), short interference RNAs (siRNAs), Piwi-interacting (piRNAs) and small nucleolar RNAs (snoRNAs), all of which participate in either the positive or negative regulation of gene expression through the epigenetic and post-transcriptional regulation of target mRNAs (7,8). The second category includes long ncRNAs (lncRNAs) that promote and inhibit gene expression through a variety of mechanisms (9). From the aforementioned categories, miRNAs and lncRNAs have been identified mainly as critical regulators of the cellular stress response, and are thus involved in the maintenance of human cancer (10). From this point of view, the present review summarizes the current evidence on the cancer-specific role and functions of these two types of ncRNAs in cellular stress (Fig. 1).

2. Role of lncRNAs in cancer-related stress

lncRNAs can be classified according to their location in the genome, their biogenesis, their structure, their protein-binding pattern (k-mers) and their mechanisms of action. lncRNAs function as epigenetic regulators, promoting or inhibiting the transcription, splicing, translation and the modulation of protein function (11). In addition, lncRNAs can function as oncogenes or tumor suppressors through a mechanism wherein a gene encoding a lncRNA has the ability to either directly promote or inhibit oncogenesis, respectively. According to the literature, lncRNAs are involved in the regulation of cancer cell stress, which includes oxidative, metabolic and genotoxic stress, as they participate in a variety of cancer-related signaling pathways (12) (Table I).

lncRNAs in cancer-related metabolic stress. A well-recognized characteristic of cancer is metabolic reprogramming. This hallmark of cancer cells was recognized by Otto Warburg in the 1920s, who observed that cancer cells exhibit higher rates of glucose uptake and lactic acid secretion, even in the presence of oxygen, compared to normal cells. These characteristics indicate that cancer cells use aerobic glycolysis for energy production, which is termed as the 'Warburg effect' (13). The result of this abnormal metabolic pathway is, on the one hand, the production of high energy levels which are required for the rapid proliferation of cancer cells, while on the other hand, an increase in stress. Cancer cells overexpress key proteins of energy production and metabolite transport pathways in order to address this increased stress, such as 5'AMP-activated protein kinase (AMPK), PKM2 and MYC, while downregulating metabolic suppressors, such as p53 (14). lncRNAs are key factors in the treatment of metabolic stress and in the metabolic reprogramming of cancer cells (15).

As previously mentioned, lncRNAs can function as oncogenes and may aid in the treatment of metabolic stress of cancer cells. One such lncRNA is MACC1-AS1, which has been detected in gastric cancer cells and induces the stabilization of MACC1 RNA and increases the post-transcriptional expression of MACC1 (16). Subsequently, MACC1, through the AMPL/Lin28 pathway, contributes to metabolic plasticity by maintaining the expression of the metabolic enzymes, GLUT1, HK2 and LDH during glucose deprivation (16). In this context, lncRNA GLCC1 appears to have a similar function to MACC1-AS1 in colorectal cancer cells where it is expressed during glucose starvation. More extensively, this lncRNA stabilizes the oncogenic transcription factor c-MYC through its direct binding to HSP90, promoting cell survival at high glycolysis and lactation rates (17). In addition, lncRNA SAMMSON is also related to metabolic stress resistance in cancer since it promotes mitochondrial stability in melanoma (18). The aforementioned process is carried out by isolating a key regulator of mitochondrial homeostasis and metabolism, p32, to the cytoplasm, promoting cell proliferation (18).

On the other hand, as previously mentioned, lncRNAs may also have tumor suppressor functions. One such lncRNA is FILNC1, the expression of which is significantly reduced in renal cancer cells. The function of FILNC1 involves binding to a c-MYC mRNA binding protein, AUF1, leading to the inhibition of c-MYC protein and metabolic plasticity (19). Another lncRNA with a similar activity is IDH1-AS1. The expression of this lncRNA induces a decrease in the proliferation of cancer cells of the colon and cervix, while it is inhibited via transcription by c-MYC, thus promoting the 'Warburg effect' (20). Apart from the regulation of the expression of c-MYC protein and its functions by these two lncRNAs, the function of AMPK is regulated by lncRNA NBR2 (21). This lncRNA is reported in breast cancer cells and is induced under energy stress by the LKB1-AMPK pathway. It normally functions as a sensor of cellular energy, thus maintaining the control of metabolic pathways in the cell. However, the reduced expression of this lncRNA leads to increased cell proliferation, decreased apoptosis and the maintenance of cell function under conditions of high energy stress (21). Another tumor suppressor that promotes apoptosis due to metabolic stress is lncRNA HAND2-AS1 (22). It has been found in osteosarcoma, and its normal expression leads to the inhibition of glucose uptake and lactate production, as well as the expression of metabolic enzymes through the isolation of an inhibitory enzyme of the HIF1α metabolic gene, *FBP1*. Nevertheless, the inhibition of this lncRNA has been shown to result in a reduction of apoptosis induced in cases of metabolic stress, thus promoting the survival of cancer cells (22). Finally, in addition to the two categories mentioned above, there are also lncRNAs that have a dual function, sometimes acting as oncogenes and sometimes as tumor suppressors. One such lncRNA is H19, which, while under conditions of oxidative stress, promotes the growth of cholangiocarcinoma cells (23), whereas in the case of pituitary tumors, it acts as

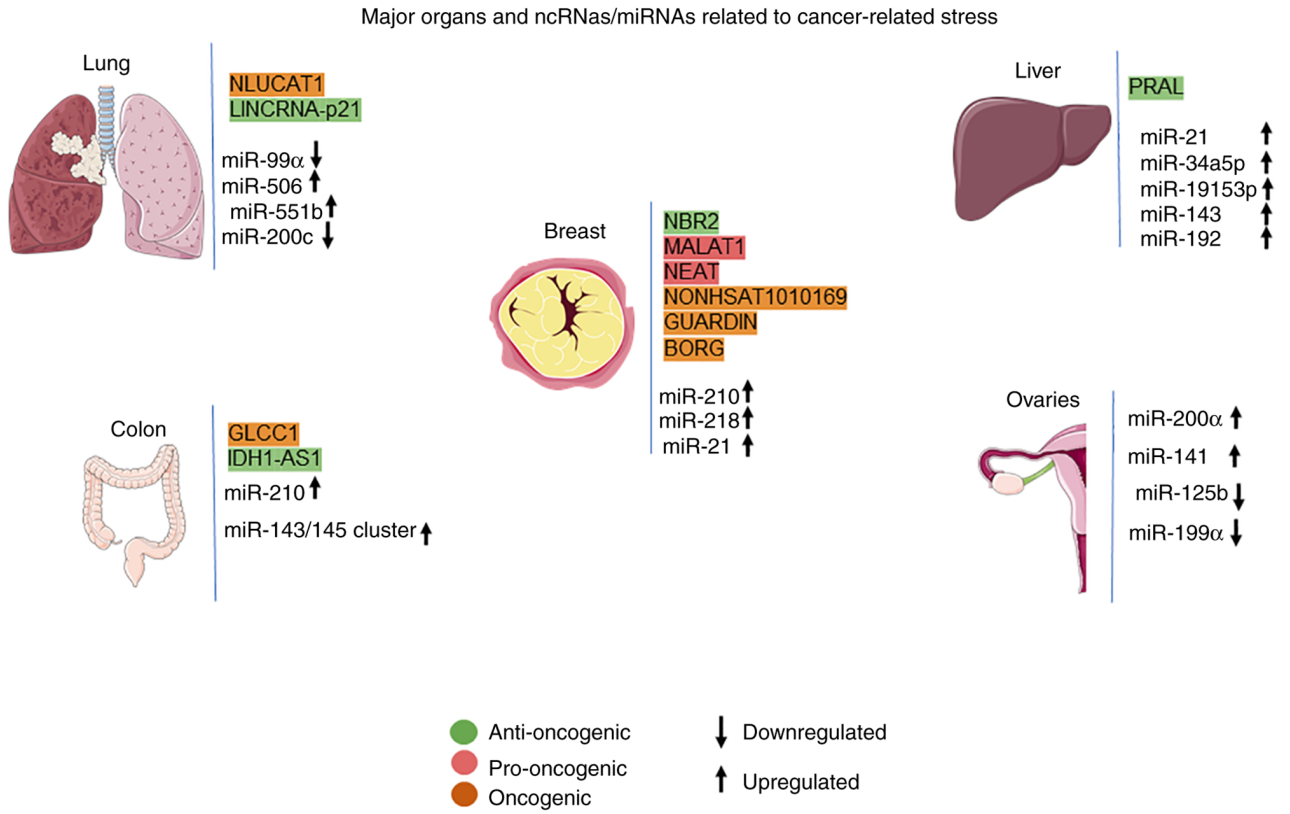

Figure 1. Major organs and lncRNAs/miRNAs related to cancer-related stress. MALAT1, metastasis-associated lung adenocarcinoma transcript 1; NEAT1, nuclear enrichment abundant transcript 1.

a suppressor by inhibiting the ability of cells to respond to metabolic stress (24).

lncRNAs in cancer-related oxidative stress. Apart from metabolic reprogramming, another characteristic of cancer cells is their hypoxic microenvironment, where high levels of reactive oxygen species (ROS), which are by-products of aerobic metabolism in the cell and are produced by mitochondria, are required for increased proliferation and metabolism. According to previous studies, lncRNAs play a crucial role in the ability of cancer cells to respond to oxidative stress. Two of these lncRNAs are H19 and HULC, which are upregulated in cholangiocarcinoma cells under conditions of oxidative stress. They regulate the expression of cytokine IL-6, which, through *in vitro* assays, has been shown to promote metastasis and cell invasion by sponging and regulating let-7a, let-7b and miR-372/miR-373 (23). Another lncRNA with a similar function is NLUCAT1, which has been detected in lung adenocarcinoma. This lncRNA upregulates the expression of the oxidative homeostasis genes, *ALDH3A1, GPX2, GLRX* and *PDK4*, increasing the resistance of cancer cells to ROS-induced apoptosis (25).

Myocardial infarction-associated transcript (MIAT) is a subnuclear lncRNA that interferes with alternative splicing and is associated with an increased risk of various heart conditions and nervous system tumors. In the study by Bountali *et al* (26), this lncRNA was found to be involved in the regulation of oxidative stress and its downstream effects in neuroblastoma and glioblastoma cell lines. In this regard, various other lncRNAs have been found to be implicated in oxidative stress and consequent hypoxia, including nuclear enrichment abundant transcript 1 (NEAT1), lincRNA-p21, urothelial cancer associated 1 (UCA1) and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) (27).

lncRNAs in cancer-related genotoxic stress. Genotoxic stress results from damage to DNA structure and genome instability due to the deregulation of key regulatory pathways in cancer cells (28). Cancer cells are capable of resisting cell death induced by genotoxic stress through a variety of mechanisms, including the inhibition of tumor suppression genes, the upregulation of cell growth factors and the omission of cell cycle control points. Notably, the basis of several chemotherapies is the induction of genotoxic stress to kill cancer cells through cell death. However, resistance to genotoxic stress also results in resistance to drugs and therapies. According to previous studies, the modified expression of lncRNAs also contributes to this process (29,30).

One such mode of function of lncRNAs in the response to genotoxic stress is through the isolation of several miRNAs. One of these lncRNAs is NONHSAT1010169 which has been studied in breast cancer cells (31). The overexpression of this ncRNA leads to resistance to treatment with the anthracycline, epirubicin, via the isolation of miR-129, which inhibits the expression of the oncogenic protein Twist1, and promotes the migration and invasion of breast cancer cells (31). From this point of view, lncRNA GUARDIN is another lncRNA that has been studied in breast cancer with a similar function. This lncRNA responds to p53, and its mechanism of action involves the isolation of miR-23a where it leads to the stabilization of

Table I. lncRNAs in cancer-related stress.

lncRNA	Cancer type	Stress	Function	(Refs.)
MACC1-AS1	Gastric	Metabolic	Pro-oncogenic	(16)
GLCC1	Colorectal	Metabolic	Pro-oncogenic	(17)
SAMMSON	Melanoma	Metabolic	Pro-oncogenic	(18)
FILNC1	Renal	Metabolic	Anti-oncogenic	(19)
IDH1-AS1	Colon/Cervical	Metabolic	Anti-oncogenic	(20)
NBR2	Breast	Metabolic	Anti-oncogenic	(21)
HAND2-AS1	Osteosarcoma	Metabolic	Anti-oncogenic	(22)
H19	Cholangiocarcinoma/pituitary, breast	Metabolic/oxidative	Pro/anti-oncogenic	(23,24)
HULC	Cholangiocarcinoma	Oxidative	Pro-oncogenic	(23)
NLUCAT1	Lung adenocarcinoma	Oxidative	Pro-oncogenic	(25)
MIAT	Neuroblastoma and glioblastoma	Oxidative	Oncogenic	(26)
MALAT1	Breast	Oxidative	Oncogenic	(27)
NEAT	Breast	Oxidative	Oncogenic	(27)
NONHSAT1010169	Breast	Genotoxic	Pro-oncogenic	(31)
GUARDIN	Breast	Genotoxic	Pro-oncogenic	(32)
NEAT1	Multiple myeloma	Genotoxic	Pro-oncogenic	(33)
BORG	Breast	Genotoxic	Pro-oncogenic	(34)
PRAL	Hepatocellular carcinoma	Genotoxic	Anti-oncogenic	(36)
LOC572558	Bladder	Genotoxic	Anti-oncogenic	(36)
LincRNA-p21	Lung/sarcoma/lymphoma	Genotoxic	Anti-oncogenic	(37)
PANDA	Bone	Genotoxic	Anti-oncogenic	(38)

TRF2 and functions as an RNA scaffold for the oncoprotein BRCA1, thus protecting cancer cells from apoptosis induced by genotoxic stress (32). In addition to those two lncRNAs, NEAT1 is a lncRNA that promotes genotoxic stress resistance in multiple myeloma cells through a different pathway. This lncRNA regulates DNA repair proteins, and its reduction leads to reduced DNA repair and sensitization of cells to therapies (33).

In several different cases, the direct induction of lncRNAs by genotoxic stress has also been recorded. lncRNA BORG is an example of this category, which is found in breast cancer cells (34); the exposure of these cells to doxorubicin induces the expression of this lncRNA. This process is driven by NF-κB. leading to chemical resistance. The aforementioned mechanism of expression of lncRNA BORG underlines the rapid and immediate synthesis of lncRNAs, rendering them the ideal study tools in cases of cellular stress (34).

By contrast, the inhibition of cancer cell resistance to genotoxic stress can be induced equally by lncRNAs. The major mechanism promoting apoptosis and the DNA-damage response pathway is the tumor suppression gene *TP53*. The p53 protein, resulting from the expression of this gene, acts as a regulator of genes involved in repairing DNA damage and apoptosis (35). One p53-associated lncRNA is PRAL (36). This lncRNA has been identified in hepatocellular carcinoma, where it induces p53 apoptosis in both *in vitro* and *in vivo* assays. lncRNA LOC572558 belongs to the same category. The overexpression of this ncRNA in bladder cancer cells enhances p53 phosphorylation, thus enhancing p53 signaling and inhibiting cancer cell proliferation (36). LincRNA-p21 is another activator of p53 in DNA damage. Its mechanism of action involves the uptake of hnRNP-K to increase the p53-dependent transcription of p21, which is a control protein of the p53 pathway (37). Finally, lncRNA PANDA is another ncRNA that stabilizes the p53 protein and protects it from proteasome degradation, although its mechanism of action is still unknown (38).

From the information presented above, the key role of lncRNAs in cancer cell resistance to genotoxic stress responses is highlighted, as well as their critical roles as biomarkers and drug targets in cancer treatment (39).

3. Role of microRNAs in cancer-related stress

The role of miRNAs has been elucidated and studied mainly in oxidative stress conditions in cancer cells. Studies have demonstrated that the expression of miRNAs can be affected under the influence of stressful conditions, such as hypoxia, through mechanisms involving a change in the function or expression of enzymes involved in the biogenesis of miRNAs (40,41). An example is the inhibition of DROSHA and DICER1 expression in cancer cells under hypoxic conditions, leading to the incomplete biogenesis of miRNAs (42).

As previously mentioned, as the microenvironment of cancer cells is hypoxic, increased ROS production is observed, inhibiting antioxidant activity in an uncontrolled state. ROS is generally considered a carcinogenic factor that promotes carcinogenesis (43). There is a significant increase in ROS levels due to the accumulation of oxidative stress, thus activating the oncogenic signaling pathway, mutagenesis and genomic

Table II. Condition and functions of oxidative stress-related microRNAs in different types of cancer.

miRNA	Cancer type	Condition in cancer	Function	(Refs.)
miR-210	Breast	Upregulated	Oncogenic	(47)
miR-28	Breast	Upregulated	Oncogenic	(48)
miR-21	Breast	Upregulated	Oncogenic	(49)
miR-143/miR-145 cluster	Colon	Downregulated	Oncogenic	(51)
miR-210	Colon	Upregulated	Oncogenic	(54)
miR-34a-5p	Hepatocellular	Upregulated	Oncogenic	(55,56)
miR-1915-3p	Hepatocellular	Upregulated	Oncogenic	(55)
miR-143	Hepatocellular	Upregulated	Oncogenic	(58)
miR-21	Hepatocellular	Upregulated	Oncogenic	(60)
miR-92	Hepatocellular	Upregulated	Oncogenic	(61)
miR-99a	Lung	Downregulated	Oncogenic	(62)
miR-506	Lung	Upregulated	Oncogenic	(64)
miR-551b	Lung	Upregulated	Oncogenic	(65)
miR-200c	Lung	Downregulated	Oncogenic	(66)
miR-200a	Ovarian	Upregulated	Oncogenic	(69)
miR-141	Ovarian	Upregulated	Oncogenic	(69)
miR-125b	Ovarian	Downregulated	Anti-oncogenic	(72)
miR-199a	Ovarian	Downregulated	Anti-oncogenic	(72)
miR-193a-5p	Prostate	Upregulated	Oncogenic	(73)
miR-21	Prostate	Upregulated	Oncogenic	(74)
miR-137	Prostate	Downregulated	Anti-oncogenic	(76)
miR-96	Prostate	Downregulated	Oncogenic	(79)
miR-494	Pancreatic	Downregulated	Anti-oncogenic	(80)
miR-155	Pancreatic	Upregulated	Oncogenic	(82)
miR-29c	Pancreatic	Downregulated	Anti-oncogenic	(83)

instability in cancer cells, promoting cancer progression (44). In this section, the miRNAs associated with oxidative stress in different types of cancer are summarized (Table II).

Breast cancer. Several miRNAs associated with oxidative stress have been identified in breast cancer. One of these is miR-500a-5p, the expression of which is induced by H_2O_2 treatment, and it leads to the targeting of oxidative stress response genes (45). In addition, the induction of oxidative stress, DNA damage and apoptosis have been observed with the simultaneous induction of miR-139-5p and radiation both *in vitro* and *in vivo* (46). miR-210 is another ncRNA that can increase ROS production and mitochondrial metabolism levels by targeting cytochrome *c* oxidase assembly protein (COX10) and transferrin receptor 1, thereby increasing carcinogenesis (47).

Another mechanism through which miRNAs affect intracellular ROS levels is through the targeting of antioxidant defense factors. One such factor is Nrf2, which causes an increase in the transcription of catalase and dismutase peroxide. This factor has been shown to inhibit miR-28, a miRNA that increases cell proliferation. The result of this inhibition is increased levels of intracellular ROS and increased oncogenesis. In addition, the increased expression of oncomiRs has been observed due to increased ROS levels in cancer cells (48). In addition, one such miRNA is miR-21. Its expression is affected by the factor NF-κB, which in conjunction with STAT3, induces miR-21 expression, thereby inhibiting the expression of PTEN and PDCD4. The aforementioned pathway results in the escape of cancer cells from apoptosis and increased metastasis in breast cancer (49).

Colorectal cancer. As with breast cancer, miRNAs associated with oxidative stress have been found in cases of colon cancer. One of these is miR-1915-3p, which targets genes that affect oxidative stress and is involved in chemotherapy-induced DNA damage, which is achieved by targeting Bcl-2 (50). The miR-143/145 complex comprises two more miRNAs that are downregulated in solid tumors. However, the overexpression of these ncRNAs induces apoptosis and reduces the proliferation of cancer cells, while rendering the cells sensitive to chemotherapy (51). In addition, due to the increased regulation of miR-143, there is an increased activation of ROS production, which indicates oxidative stress, leading to the sensitization of cancer cells to oxaliplatin (52).

In another study, the activation of ROS production and the induction of aging by four miRNAs, miR-186, miR-216b, miR-37-3p and miR-760, which target protein kinase 2, were identified, leading to the inhibition of oncogenesis (53). Another miRNA is miR-210, which increases ROS production and inhibits the iron-sulfur cluster scaffold homolog and COX10 genes, which are part of the electron transport chain (54).

Hepatocellular carcinoma. In the case of hepatocellular carcinoma, an increase in four miRNAs under conditions of oxidative stress has been identified, specifically miR-34a-5p, miR-1915-3p, miR-638 and miR-150-3p. The expression of the first two is dependent on p53, while the expression of the latter two is independent (55). The aforementioned miRNAs negatively control the oxidative stress pathway where more specifically, miR-34a-5p promotes ROS production by inhibiting mitochondrial antioxidant enzymes (56), and miR-638, which is located in the *Dnm2* gene, induces oxidative stress (57).

As oxidative stress and ROS production frequently occur in inflammatory conditions by activating NF-κB, the regulation of the expression of a number of miRNAs is affected by this signaling pathway. miR-143 is one such miRNA in hepatocellular carcinoma, the expression of which is increased by NF-κB, and its mechanism of function involves targeting the fibronectin type III domain-containing 3B (FNDC3B), thus promoting metastasis (58). miR-224 is another miRNA the expression of which is NF-κB-dependent. In this case, this factor also causes an increase in the expression of this miRNA, which is equally associated with metastasis and cell invasion (59). Another miRNA that promotes metastasis, proliferation and invasion in liver cancer is miR-21. Its expression is increased by ROS and its upregulation leads to a significant reduction in PTEN expression (60). Finally, the increased expression of miR-92 is responsible for the development of chronic liver disease into hepatocellular carcinoma (61). ROS and oxidative stress, in combination with the induction of telomerase activity, lead to DNA damage. It has also been found that miR-92 inhibits apoptosis in hepatocellular carcinoma by targeting the *Bad* and *Bax* genes (61).

Lung cancer. In the case of lung cancer, the decreased expression of miR-99a is associated with a poor prognosis, as it is associated with metastasis and increased cell proliferation. By contrast, the increased expression of this miRNA leads to the targeting of NADPH oxidase 4 (NOX4), which causes an increase in ROS levels, leading to metastasis and cell proliferation (62). Thus, the increased expression of miR-99a leads to a significant reduction in ROS levels. Otherwise, the inhibition of this miRNA and ROS production lead to the activation of the PI3K/Akt pathway, and the regulation of MMP2 and MMP9, which are the basic proteases of cell migration in this type of cancer (63). In contrast to miR-99a, miR-506 expression is increased in lung cancer. This miRNA inhibits NF-κB p65 expression, thus increasing ROS production (64).

In general, miRNAs, which inhibit enzymes involved in oxidative stress and ROS production, are responsible for carcinogenesis. One such miRNA is miR-551b, which is upregulated in apoptosis-resistant cancer cells (65). This increase causes an accumulation of ROS, which leads to the activation of the mucin-1 oncogene, resulting in increased survival and the resistance of lung cancer cells to drugs (65). miR-200c is another ncRNA whose expression can affect the level of intracellular ROS. More specifically, it functions as a regulator of the oxidative stress response genes by downregulating their expression, thus increasing the levels of ROS and p21 (66). Finally, the increased expression of miR-200c has been shown to predispose cancer cells to radiotherapy, thus setting an example of the potential of using miRNAs as an effective strategy in the treatment of lung cancer (66).

Ovarian cancer. In this type of cancer, one of the miRNAs studied is miR-29b. This miRNA functions as a tumor suppressor, as it is associated with apoptosis and the inhibition of cancer cell viability. Its mode of action involves targeting the *SIRT1* gene, which is involved in oxidative stress, cell survival and differentiation. This increased ROS production inhibits miR-29b expression (67,68). miR-200a and miR-141 are two other miRNAs that target the *P38α* gene, which is a stress-activated kinase, thus modulating oxidative stress responses (69). The result of the expression of miR-200a and miR-141 is the inhibition of this kinase, resulting in the increase of the tumor in animal models, but also in the increase of the response to chemotherapy (70). Another miRNA whose expression increases in response to increased ROS production is miR-182. The expression of this miRNA occurs due to the increase in β-catenin levels induced by ROS. The upregulation of miR-182 in this type of cancer leads to increased p53-mediated expression of p21, although miR-182 may function as an oncomiR and increase oncogenicity in the case of a mutation in p53 (71). Finally, miR-125b and miR-199a are two miRNAs that are inhibited by ROS in ovarian cancer. Their increased expression leads to the inhibition of tumor-induced angiogenesis (72).

Prostate cancer. In cell lines of this type of cancer, such as LNCap, PC3 and DU145, the increased expression of miR-193a-5p has been observed. miR-193a-5p induces cancer progression by inhibiting the *BACH2* gene and increasing heme oxygenase-1 expression, which leads to the resistance of cancer cells to apoptosis. By contrast, the inhibition of this miRNA leads to increased sensitivity to chemotherapy (73). miR-21 is another miRNA in prostate cancer, the expression of which is regulated by the NADPH oxidase enzyme, which is the main source of ROS. Increased ROS production leads to an increase in miR-21 expression via the Akt pathway (74). In contrast to the aforementioned miRNAs, miR-137 expression is decreased in prostate cancer (75). The expression of this ncRNA leads to the inhibition of oncogenesis by targeting NOX4, thereby inhibiting glycolysis and cancer cell proliferation (76).

In addition, according to a previous study, an increase in the expression of miR-708-5p has been observed by the effects of metformin (77), inducing the apoptosis of cancer cells, thus being a possible therapeutic mechanism in the treatment of prostate cancer (78). Finally, the dual function of miR-96 has been observed in hypoxic conditions in prostate cancer cells. More specifically, its increased expression inhibits mTOR protein expression, inducing autophagy; however, the overexpression of this miRNA leads to the inhibition of ATG4 and consequently, to the inhibition of autophagy (79). In general, autophagy is a condition that has been found to reduce the apoptosis of cancer cells, contributing to their survival under conditions of hypoxic stress (80).

Pancreatic cancer. c-MYC and SIRT1 have been identified as regulators of oxidative stress in pancreatic cancer and are targets of miR-494. The increase in the expression

of this miRNA inhibits cell proliferation and promotes apoptosis (81). On the other hand, miR-155 has been found to significantly increase ROS levels in cancer cells by down-regulating the basic enzymes in the defense mechanism of oxidative stress, namely catalase and superoxide dismutase 2 (82). Finally, the decreased expression of miR-29c in cancer cells leads to an enhanced invasive capacity. This miRNA targets MMP9, thus leading to the suppression of migration and invasion (83).

4. Conclusion

In conclusion, cancer cells have the ability to resist the mechanisms of cellular stress, resulting in tumor progression and resistance to treatment. These mechanisms involve a variety of ncRNAs that sometimes function beneficially, while in other instances,, they inhibit tumor progression, with the two main categories being lncRNAs and miRNAs. Further research is therefore required to clarify the roles of these molecules in cancer-stress responses in order to provide important additional information about their functions. This may aid in the utilization of these non-coding molecules in therapeutic strategies against various types of cancer.

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