Abstract. MicroRNAs (miRNAs/miRs), non-coding single-stranded RNAs of length 18-24 nucleotides, can modulate gene expression through post-transcriptional control. As such, they can influence tumor proliferation, apoptosis, invasion, metastasis as well as chemotherapy resistance by regulating certain downstream genes. In this context, miR-200b-3p, one particular member of the miR-200 family, possesses the ability to suppress tumor progression. However, many studies have suggested that, in certain cases, this miRNA may also promote the development of some tumors due to differences in the microenvironments and molecular backgrounds of different cancers. This review summarizes previous studies on the involvement of miR-200b-3p in tumors, including the underlying mechanism.

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1. Introduction
Cancer has become a global public concern and according to data available in CA: A Cancer Journal for Clinicians, the number of new cancer cases around the world for the year 2020 reached 19.3 million while the number of deaths related to this condition was 10 million (1). It is a well-established fact that the human genome possesses oncogenes that promote tumor formation as well as tumor-suppressor genes that, instead, inhibit tumor development. However, in addition to these, the potential role of non-coding RNAs (ncRNAs) in tumor occurrence and development has also been reported. ncRNAs represent one type of RNAs that do not code for proteins; and although they make up 90% of all RNAs in the human body, their role has only been appreciated during the past decade (2).

MicroRNAs (miRNAs/miRs) are a class of ncRNAs, encoded by endogenous genes, that typically consist of 18-24 nucleotides. The process of miRNA synthesis starts when the microprocessor complex, composed of Drosha and DGCRI8, first recognize and splice the miRNA's primary transcripts (pri-miRNAs) to produce precursor miRNAs (pre-miRNAs) which are basically hairpin-like RNAs of about 70 bp (3). Exportin 5 then transports these pre-miRNAs into the cytoplasm where they undergo cleavage by Dicer ribonuclease to produce mature miRNAs (3), with the latter subsequently binding to Argonaute (Ago) proteins to yield the RNA-induced silencing complex (RISC). Eventually, on binding to the miRNA response elements (MREs), this RISC complex silences target mRNAs. miRNAs influence various biological processes of cells and hence, they influence a number of cancer-related processes such as tumor growth, cell death, metastasis, stemness, angiogenesis and chemotherapy resistance.

One type of microRNA is the miR-200b family which includes miR-200a, miR-200b, miR-200c, miR-429, and miR-141. Given that this family affects many malignant phenotypes of tumors, this review provides a summary of the functions of miR-200b-3p in different types of tumors, including its regulatory mechanism.

In PubMed, Web of Science and other relative databases, we searched the literature studies of 10 years (2012-2022) with ‘miR-200b-3p’ as the key word. We selected the articles that were related to tumors and identified the finding concerning
the mechanism of miR-200b-3p and tumor development and the tumor microenvironment.

2. Mechanism of action of miR-200b-3p in cancer

miR-200b-3p, along with other members of the miR-200 family, are generally considered to be part of the tumor-suppressor gene group due to their suppressive effects on most tumors, especially in inhibiting their metastasis. Although metastatic inhibition can take place through several mechanisms, miR-200b-3p is best known to exert this effect by inhibiting epithelial-mesenchymal transition (EMT) through zinc finger E-box-binding homeobox 1/2 (ZEB1/2). In addition, further studies have suggested that this miRNA can also act on other genes such as microfibril-associated glycoprotein 2 (MAGP2), mothers against decapentaplegic homolog 2 (SMAD2) and high mobility group box 3 (HMGB3) to silence their mRNAs, thereby inhibiting tumor proliferation, apoptosis, invasion as well as migration.

However, even though members of the miR-200b family are known as a group of tumor-suppressor genes, some researchers have pointed out that miR-200b-3p may even have oncogenic functions. Indeed, miR-200b-3p can actually promote tumor progression by downregulating a number of tumor suppressor genes, including ATP binding cassette subfamily A member 1 (ABCA1), large tumor suppressor kinase 2 (LATS2) and transcriptional intermediary factor 1 γ (TIFF1).

In addition, miR-200b-3p can also improve cancer treatment by influencing tumor resistance to chemotherapy. Unlike the case for tumor progression, most reports suggest that miR-200b-3p can reduce tumor resistance to chemotherapy by inhibiting the expression of downstream targets such as tubulin β 3 class III (TUBB3), AKT serine/threonine kinase 2 (AKT2), and fibronectin-1 (FN1).

3. miR-200b-3p function is dependent on cancer type

miR-200b-3p can exert different functions depending on the type of tumor. For instance, in most cases, it exhibits tumor-suppressive effects and is therefore downregulated, with examples of such tumors being colorectal cancer (CRC) (4-7), hepatocellular carcinoma (HCC) (8-12), pancreatic cancer (13,14), gastrointestinal stromal tumors (15), breast cancer (16-18), melanoma (19), glioblastoma (20), glioma (21), thyroid carcinoma (22), cemento-ossifying fibroma (23), esophageal cancer (24,25), oral squamous cell carcinoma (26), prostate cancer (27,28), renal cell carcinoma (29), bladder cancer (30), and malignant mesothelioma (31). However, as already noted, this microRNA can also be oncogenic in various types of cancers, with examples of such tumors being prostate cancer (32,33), lung cancer (34-38), oral squamous cell carcinoma (39), esophageal squamous cell carcinoma (40), breast cancer (41), colorectal cancer (42,43), neck cancer (44), cholangiocarcinoma (45), and hepatocellular carcinoma (46). Table I and Fig. 1 summarize the effects of miR-200b-3p dysregulation.

miR-200b-3p and its functions in hepatocellular carcinoma. For HCC, microRNAs can display tumor-suppressive effects, with its most important mechanism of action being the inhibition of epithelial-mesenchymal transition (EMT) by acting on ZEB1/2. Indeed, ZEB1, as an important regulator in tumors (47), promotes EMT by downregulating or upregulating E-cadherin (48) and vimentin (49) respectively and it has been shown that, by acting on both ZEB1 and ZEB2, miR-200b-3p can silence their mRNAs to downregulate their expression, thus suppressing EMT as well as reducing metastasis in HCC (10,12,50). Interestingly, similar mechanisms have also been reported for CRC (7), pancreatic cancer (14), breast carcinoma (17), and bladder cancer (30). In addition, Notch1, an oncogene which regulates biological processes in most cancers, is also targeted by miR-200b-3p (9). In this case, the Notch signaling pathway can be activated when miR-200b-3p is expressed at low levels and this can lead to both tumor growth and metastasis in HCC. In fact, since miR-200b-3p can also inhibit the expression of the endothelial erythroblast transformation-specific (ETS)-related gene (ERG), its downregulation and subsequent low expression can further promote tumor progression by inducing angiogenesis in HCC (8).

miR-200b-3p and its effects in colorectal carcinoma. Regarding CRC, in addition to ZEB1/2, the c-Myc/miR-200b-3p/peroxiredoxin-2 (PRDX2) regulatory pathway is also targeted by miR-200b-3p to inhibit cancer progression, with this regulatory mechanism controlling the activation of c-Myc through the WNT/β-catenin pathway (6). However, in CRC, reduced expression of miR-200b-3p can disrupt this regulatory loop, resulting in the activation of c-Myc and subsequent tumor metastasis (6), with miR-200b-3p even able to influence the expression of Wnt1 within this pathway (4). Low expression levels of the miRNA can, in fact, further lead to the overexpression of microfibril-associated glycoprotein 2 (MAGP2) which forms part of the extracellular matrix and this process can be associated with local lymphatic metastasis in CRC.

Finally, miR-200b-3p can cause CRC to become more resistant to chemotherapeutic agents. In this context, Lv et al suggested that disruptions to the abovementioned c-Myc/miR-200b-3p/PRDX2 regulatory pathway due to reduced miR-200b-3p expression can cause colorectal cancer to develop greater resistance to oxaliplatin (6). Moreover, as an additional target of miR-200b-3p, tubulin β 3 class III (TUBB3) can also be involved in oxaliplatin resistance (51) and in this case, the downregulation of miR-200b-3p can ultimately result in enhanced oxaliplatin resistance by reducing the presence of TUBB3 in CRC (51).

miR-200b-3p and its involvement in breast cancer. For this type of cancer, in addition to ZEB1/2, miR-200b-3p can also influence the expression of the LIM domain kinase 1 (LIMK1) gene. More specifically, low levels of the miRNA tend to reduce inhibition of the LIMK1/phosphorylation of cofilin 1 (CFL1) pathway, thereby promoting the proliferation and metastasis of breast cancer (16). Furthermore, in triple-negative breast cancer, miR-200b-3p can target the Rho GDP-dissociation inhibitor (RHOGDI) signaling pathway to being about increased CDH1 expression as well as EMT suppression (18). In terms of treatment, miR-200b-3p can also be helpful for inhibiting the transforming growth factor (TGF)-β signaling pathway which lead to enhanced tumor sensitivity to tamoxifen (17), and in this case, research has shown that upregulation of miR-200b-3p can lead to improved pathologic responses to
Table I. Functions and mechanism of miR-200b-3p in various types of cancer.

| Types of cancer               | Expression | Target gene | Pathway                        | Activity                                      | (Refs.) |
|-------------------------------|------------|-------------|--------------------------------|-----------------------------------------------|---------|
| Anaplastic thyroid carcinoma  | Down       | ASH1L       | /                              | Inhibition of proliferation                   | (22)    |
| Bladder cancer                | Down       | ZEB1        | miR-200/ZEB axis               | Inhibition of invasion and migration          | (30)    |
| Breast cancer                 | Down       | TGF-β2 and ZEB1 | TGF-β2/ZEB1 signaling axis    | Inhibition of invasion and migration; enhancement of chemotherapy resistance | (17)    |
| Colorectal cancer             | Down       | TUBB3       | /                              | Enhancement of chemotherapy resistance       | (51)    |
| Gastrointestinal cancer       | Down       | ETV1 and EGFR | /                             | Inhibition of invasion and migration          | (30)    |
| Glioma                        | Down       | HMGB3       | MAPK signaling pathway         | Inhibition of proliferation, invasion and migration | (20)    |
| Hepatocellular carcinoma      | Down       | ERG         | /                              | Inhibition of proliferation, invasion and migration | (9)     |
| Lung cancer                   | Up         | ABCA1       | /                              | Promote proliferation, invasion and migration  | (34)    |
| Melanoma                      | Down       | SMAD2       | TGF-β signaling pathway        | Inhibition of invasion and migration          | (19)    |
| Osteosarcoma                  | Down       | AKT2        | PI3K/Akt pathway               | Enhancement of chemotherapy resistance        | (56)    |
| Pancreatic cancer             | Down       | Notch       | Notch signaling               | Inhibition of proliferation                   | (13)    |
| Prostate cancer               | Down       | PRKAR2B     | /                              | Inhibition of proliferation                   | (53)    |

(Refs.) denotes the references for each entry.
Table 1. Continued.

| Expression | Activity | Pathway | Target gene | Promote proliferation, invasion and migration |
|------------|----------|---------|-------------|-----------------------------------------------|
| DNMT3A/3B  | Up       | PPARG2/AKAP12 axis | TIMP4 | Inhibition of proliferation (27) |
|            |          |         |             | Promote proliferation, invasion and migration |

Role of miR-200b-3p in prostate cancer. For prostate cancer, the functions of miR-200b-3p are less understood due to contrasting effects. Indeed, in some instances, it has been shown to regulate tumor progression by targeting the regulatory subunit RIIβ (PRKAR2B) and DNA methyltransferase 3A/3B (DNMT3A/3B). The former, as an oncogene (53), is not only involved in adipogenesis but is also significantly upregulated in metastatic lesions compared with primary tumors in prostate cancer (53). In contrast, the protein products of DNMT3A/3B are both enzymes that act on DNA sequences to catalyze the methylation of CpG and by targeting DNMT3A/3B, miR-200b-3p facilitates interactions between peroxisome proliferator-activated receptor γ 2 (PPARG2) and demethylated A-kinase anchoring protein 12 (AKAP12) gene promoter to suppress the growth of prostate cancer (27).

However, Janiak et al found that, in prostate cancer, miR-200b-3p could even regulate the level of tissue inhibitor of metalloproteinase 4 (TIMP4) expression (33), with this regulation being mediated by ZEB1 and ETS proto-oncogene 1 (ETSI) which represent two targets of miR-200b-3p (33). In addition, Samli et al reported that, compared with parental cells, prostate cancer cells that were resistant to paclitaxel displayed a significantly higher expression of miR-200b-3p. Yet, even though the results of that study indicated that miR-200b-3p could be involved in the paclitaxel resistance of prostate cancer (54), the specific mechanism behind this process remains unknown (54).

miR-200b-3p and its functions in lung cancer. In the case of lung cancer, miR-200b-3p mainly acts as an oncogene by regulating the expression of the ATP-binding cassette transporter A member 1 (ABCA1) (34), the transcriptional intermediary factor 1 γ (TIF1γ) (35), the large tumor suppressor kinase 2 (LATS2) as well as the suppressor of cytokine signaling 6 (SOCS6) (36), all of which are involved in tumor progression. Among these, the tumor-suppressor gene ABCA1 encodes a transmembrane protein that transports cholesterol to the outside of the cell and a study by Liu et al demonstrated that, by acting on this gene, miR-200b-3p could encourage non-small-cell lung cancer to grow and metastasize (34). Similarly, TIF1γ, also known as tripartite motif-containing 33 (TRIM33), inhibits tumorigenesis and proliferation by degrading β-catenin, a key component of the Wnt pathway but when miR-200b-3p targets this gene, TGF-β-induced EMT is promoted along with tumor invasion (35). Finally, even though both LATS2 and SOCS6 act as tumor suppressors in various tumors, the upstream miR-200b-3p can regulate their expression to promote the proliferation of lung cancer as well as metastasis (36).

Even though miR-200b-3p is known for its tumor-suppressive effects in most studies, its ability to act as an oncogene in lung cancer could actually be attributed to differences in the molecular backgrounds of different tumors. For example, according to The Cancer Genome Atlas (TCGA) database, TIF1γ expression levels in lung cancer are higher than those in HCC or CRC, and therefore, its inhibition under the influence of miR-200b-3p may result in greater effects.
miR-200b-3p and its functions in esophageal cancer. Regarding esophageal cancer, tumor progression is regulated when miR-200b-3p act on both fibronectin-1 (FN1) (24) as well as the solute carrier family 2 member 3 (SLC2A3) (25). FN1 has been shown to enhance tumor growth by activating the mTOR signaling pathway while metastasis can be induced through the overexpression of genes such as MMP2 that encode matrix metalloproteinases. Similarly, SLC2A3, also referred to as glucose transporter 3 (GLUT3), is not only associated with proliferation and EMT but it can even act as immune signatures in various cancer. In esophageal cancer, the down-regulation of miR-200b-3p causes both FN1 and SLC2A3 to be overexpressed, thereby promoting tumor proliferation and metastasis (24,25).

Role of miR-200b-3p in glioma. The hypoxic environment present in tumors causes a key transcription factor known as the hypoxia-inducible factor-1 (HIF-1) to be produced. This allows interactions between HIF1-α, vascular endothelial growth factor (VEGF) and matrix metallopeptidase 9 (MMP9) which largely contribute to tumor growth and metastasis (55); but by inhibiting such interactions, miR-200b-3p suppresses both tumorigenesis and invasion in glioblastoma multiforme (55). Moreover, miR-200b-3p also targets the high mobility group box 3 (HMGB3) which regulates the MAPK signaling pathway as well as the extracellular-regulated protein kinase 5 (ERK5) which forms part of the mitogen activated protein kinase (MAPK) family. For the first gene, miR-200b-3p acts by regulating glioblastoma multiforme progression (20) while in the latter case, both the growth of tumors and the EMT process is inhibited when miR-200b-3p suppresses ERK3 expression (21).

miR-200b-3p and its functions in other cancers. The signal transducer SMAD family member 2 (SMAD2) mediates a number of signaling pathways (19) and in melanoma, it is involved in the nuclear enriched abundant transcript 1 (NEAT1)/miR-200b-3p/SMAD2 axis that promotes the progression of tumors through EMT activation (19). On the other hand, in the case of gastrointestinal stromal tumors (GISTs), Gyvyte et al (15) pointed out that cell viability and migration was reduced when miR-200b-3p downregulated the expression of ETV1 and EGFR. Finally, in cancers such as anaplastic thyroid carcinoma (ATC), miR-200b-3p can inhibit the growth of tumors by silencing the ASH1L/CCAT1 axis (22) while for osteosarcoma, the downregulation of miR-200b-3p mediates doxorubicin resistance through its effects on AKT2, a member of the AKT family, as well as on FN1 (56,57).

In summary, although miR-200b-3p acts as a tumor suppressors in most cancers, it may also act as an oncogene in some of them, depending on the tumor microenvironment. However, by understanding its role and mode of action in different tumors, miR-200b-3p can prove to be a useful biomarker for diagnostic purposes or even for applications in targeted therapy.

4. Mechanism of miR-200b-3p regulation

Being an miRNA, regulation of miR-200b-3p is achieved by various mechanisms, of which the most important include the competing endogenous RNA (ceRNA) mechanism, regulation at transcription factor levels as well as epigenetic modifications (Fig. 2).

Mechanism of ceRNA regulation. In our summary, IncRNA XIST is the most mentioned ceRNA-based regulation of miR-200b-3p, and it can induce HCC as well as CRC.
progression by inhibiting miR-200b-3p (7,10,11). ZEB1-AS1 can also act as a ceRNA to inhibit miR-200b-3p as reported by Liu et al (50), with similar inhibitory effects on the miRNA observed in other cancers. For instance, H19 participates in the metastasis of HCC by reducing miR-200b-3p levels (12). Similarly, in osteosarcoma, both IncRNA MEG3 (56) and OIP5-AS1 (57) act upstream of miR-200b-3p to promote tumor development, while in the case of esophageal cancer, tumor progression occurs as LINC00667 (25) and LNC-ABCA12-3 (24) act on the miRNA. Finally, for melanoma as well as breast cancer, miR-200b-3p is respectively targeted by NEAT1 and LINC00894-002 that inhibit its functions, thereby promoting tumor progression (17,19).

In addition to the above IncRNA, circRNAs can also be an important part of the ceRNA-based mechanisms, with studies showing that circPTK2 (35), circ_103820 (36) as well as circKDM4C (30) can exert inhibitory effects on miR-200b-3p, resulting in the development of breast and bladder cancer.

Transcription factor-based regulation. The ZEB/miR-200 feedback loop is the most common transcription factor that regulates miR-200b-3p, and this mutual inhibitory relationship can enhance EMT progression in various cancers (48). P53, being a well-known tumor-suppressor gene, can also upregulate all genes from the microRNA-200 family (58) while, c-Myc, as part of the c-Myc/miR-200b-3p/PRDX2 regulatory loop as
mentioned earlier, can reduce miR-200b-3p levels (6). Finally, for androgen-independent prostate cancer (AIPC), it has been reported that p73 is positively correlated with miR-200b-3p (28).

Epigenetic modification. Methylation is the most common epigenetic modification regulating miR-200b-3p, and it has been reported that the methylation of its adenosine at the N6-position can interfere with its inhibitory effects on downstream targets by preventing the miRNA/3UTR/mRNA duplex from being generated (58,59). In addition, studies have shown that high methylation of CpG islands in DNA can promote EMT by silencing genes belonging to the miR-200 family (60).

5. Conclusion

In summary, miR-200b-3p is an miRNA closely related to human tumors. By inhibiting the expression of downstream mRNAs, miR-200b-3p participates in regulating various tumor processes. Among them, the most noteworthy mechanism is that miR-200b-3p inhibits the tumor EMT process through ZEB1/2 interaction. ZEB1/2 is an important factor in the EMT process, and it can affect the tumor EMT process by influencing downstream molecules such as E-cadherin and vimentin. miR-200b-3p and ZEB1/2 can inhibit the expression of each other, respectively. The disruption of this delicate balance may play a key role in the EMT process, which is helpful to our understanding of the mechanism of EMT. In addition, miR-200b-3p can also regulate tumor proliferation, apoptosis, invasion, migration and chemotherapy resistance through the WNT/β-catenin pathway, MAPK signaling pathway, PI3K/Akt pathway and others.

In most cancers, miR-200b-3p always shows tumor inhibition, but due to the difference in the tumor microenvironment, miR-200b-3p shows differential functions in different tumors. Especially in lung cancer, in the statistics of this review, several reports have pointed out that miR-200b-3p can promote the occurrence and development of lung cancer. However, we summarized some studies and found that even in the same tumor, miR-200b-3p may show different dysregulations and functions. This may be because they belong to different tumor stages or subtypes, and therefore have different microenvironments and molecular backgrounds.

In addition to the function of miR-200b-3p in tumors, we also summarized the regulatory mechanism of miR-200b-3p expression. miR-200b-3p is mainly regulated by the ceRNA mechanism, transcription factor-involved regulation and epigenetic modification, while the most important one is the ceRNA mechanism.

However, the specific mechanism by which miR-200b-3p plays a role in tumor, as well as its own regulatory mechanism, is not well understood. Many questions remain to be answered before it can be applied clinically. For example, we need to use different analytic strategies for different tumors because of the different regulatory patterns of miR-200b-3p in various tumors.

By further studying its mechanism, miR-200b-3p may play a valuable role in the diagnosis and treatment of tumors. The expression of miR-200b-3p can help us determine the type and malignancy of the tumor. In the future, with the development of targeted therapy, miR-200b-3p can also be used as a potential therapeutic target to provide effective treatment of tumors.

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Authors' contributions

SC and YT were the guarantors and designed the study. HY and ZS participated in the acquisition, analysis, and interpretation of the data. YG and WG drafted the initial manuscript after interpretation of the literature data. ST revised the article critically for important intellectual content in light of the literature findings. This manuscript is a review of the literature and thus no novel data were collected.

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Competing interests

The authors declare that they have no competing interests.

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