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Significance of MTA1 in the molecular characterization of osteosarcoma

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Abstract Osteosarcoma is the most common malignant bone tumor in children and characterized by aggressive biologic behavior of metastatic propensity to the lung. Change of treatment paradigm brings survival benefit; however, 5-year survival rate is still low in patients having metastastatic foci at diagnosis for a few decades. Metastasis-associated protein (MTA) family is a group of ubiquitously expressed coregulators, which influences on tumor invasiveness or metastasis. MTA1 has been investigated in various cancers including osteosarcoma, and its overexpression is associated with high-risk features of cancers. In this review, we described various molecular studies of osteosarcoma, especially associated with MTA1.

Keywords Osteosarcoma · Metastasis-associated protein · MTA1 · Chromatin modifiers · MicroRNA · Genetics · Cancer

1 Introduction

Osteosarcoma (OS) is the most common primary bone sarcoma, which tumor cells produce osteoid. It occurs most often in children and adolescents, accounting for 2.4 % of childhood cancers, making it the eighth most common malignancies in the childhood [1]. OS shows a bimodal age distribution with a peak in the second decade of life (at the age of 15–19 years) and a secondary peak in older adults age 60 to >85 years [2]. Approximately 900 new OS cases were diagnosed annually in the USA. It has a slight male predominance (male/female= 1.35:1) [3]. Although the cause of OS is uncertain, there are some preexisting conditions, such as Paget disease or radiation [4, 5]. OS is the most common radiation-induced sarcoma, and 1 % of Paget disease takes a sarcomatous transformation at the end. There are other assumed predisposing conditions, which are fibrous dysplasia, hereditary multiple exostosis, bone infarct sites, and chronic osteomyelitis [5, 6]. OS associated with predisposing conditions shows older age distribution. Some genetic predisposing conditions are also known, which are hereditary retinoblastoma, Li-Fraumeni syndrome, and Rothmund-Thomson syndrome [7, 8].

The goal of treatment is surgical removal of primary tumor and chemoprevention of metastasis. Local treatment is usually limb salvage wide resection, and chemotherapy is carried out preoperatively (neoadjuvant chemotherapy) or postoperatively (adjuvant chemotherapy). Telangiectatic OS is quitely chemosensitive [9]. Radiation therapy is used in an unresectable tumor [10]. Conventional OS shows locally aggressive growth and rapid hematogenous metastases, predominantly to the lung. The prognosis is influenced by age, sex, tumor size/volume, surgical margins, stage, and detectable metastases at diagnosis and response to preoperative chemotherapy [11–15]. Low-grade OS, including low-grade central OS, parosteal OS, and periosteal OS, reveals relatively favorable prognosis than conventional type [16, 17]. They show about 90 % overall survival at 5 years [17].

Metastasis-associated protein (MTA), a family of cancer progression-related genes, is a component of the nucleosome remodeling and histone deacetylation (NuRD) complex. It includes MTA1, MTA2, and MTA3 and functions as transcription regulation by ATP-dependent chromatin remodeling and histone deacetylation [18]. Recently, there have been some reports, which reveal other roles of MTA1 in DNA damage response, inflammation, and infectious agent-driven

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cancers [19]. MTA1 has a dual function as a transcriptional coactivator or corepressor of various oncogenes or tumor suppressor genes and influences on tumor invasion, epithelial-mesenchymal transition (EMT), and metastasis. MTA1 expression and its clinicopathologic and biologic relevance have been widely investigated in various cancers including breast cancer, gastrointestinal carcinoma, carcinoid, nonsmall cell lung carcinoma, ovarian cancer, prostatic cancer, as well as OS [20–27]. In most human cancers, overexpression of that is common and is associated with disease progression, prognosis, and metastasis.

A few decades ago, there was a change of treatment frame of OS from single surgery to combined therapy of surgery and chemotherapy [28]. Overall survival at 5 years increased to 70 % in extremity, nonmetastatic OS, and it has not been significantly changed up to days [29]. Although metastases at diagnosis are noted in 15–20 % of OS patients, overall survival at 5 years is still 37 %, and this level is not changed despite of more intensive chemotherapy protocol [29, 30]. There is a need to understand a mechanism of metastasis, which is most common cause of treatment failure. We describe here the genetic and molecular alterations of OS, especially associated with MTA1, which could be a new treatment target.

2 Genetic and molecular studies

2.1 MTA family

Molecular mechanisms of MTA1 in cancer have been demonstrated by various levels of cancer progression. Toh et al. identified a gene that is overexpressed in highly metastatic rat mammary adenocarcinoma cell lines than nonmetastatic cell lines and named mta1 [31]. Human counterpart was also cloned, and high expression of MTA1 mRNA was correlated with invasive property. In breast cancer, MTA1 could transform into more aggressive phenotype by repression of the estrogen receptor-α transactivation through chromatin deacetylation of ER-responsive gene. And, MTA1 also represses BRCA1 tumor suppressor gene in the same manner [32].

In addition to chromatin histones, MTA also deacetylates nonhistone proteins such as p53 and hypoxia-inducible factor-1α (HIF-1α). While acetylated HIF-1α is converted to deacetylated, and stable form by MTA1, which leads to angiogenesis, p53 protein is deacetylated by MTA1 or MTA2, resulting in inhibition of cell growth arrest and apoptosis [33].

MTA1 expression has been investigated in regard to angiogenesis in various cancers such as breast cancer, early-stage nonsmall lung cancer, prostate cancer, esophageal squamous cell cancer, and histologically node-negative gastric cancer [34–38]. Overexpression of MTA1 is usually correlated with intratumoral microvessel density. Kai et al. revealed that MTA1-expressing tumors secreted higher levels of vascular endothelial growth factor (VEGF) and silencing MTA1 suppressed the angiogenic activity *in vivo* [36].

Park et al. reported that MTA1 is strongly expressed in high-grade OS tissue and metastatic lesion but not in low grade, and mRNA of MTA1 and MTA2 is increased in high-grade OS cell lines. MTA might be involved in the progression of high-grade OS, especially in metastasis of OS [27]. Other study using OS of the jaw revealed similar results that the high-grade tumors show higher positive rate of MTA expression [39].

2.2 Angiogenesis

Blood supply is required for delivery of oxygen and nutrients and removal of waste products via blood vessels in normal and neoplastic tissue. Cancer cells can induce neovascularization for the sustained growth and a way to systemic vasculature. Neovascularization is controlled by the balance between angiogenic factors and angiogenesis inhibitors. Angiogenic switch is induced when angiogenic factors are increased or angiogenesis inhibitors are decreased. Both intrinsic factors such as tumor cells themselves (oncogene activation or tumor suppressor gene inactivation) and tumor stromal cells and extrinsic factors like hypoxia, acidosis, and inflammation could lead to angiogenesis [40–42]. As tumor angiogenesis is a condition, which proangiogenic stimuli overwhelmed antiangiogenic factor, there could also be antiangiogenic factors such as angiostatin, endostatin, and thrombospondin as a counterpart [43–45]. There have been many reports, which show correlation between proangiogenic or antiangiogenic factors and clinicopathologic parameters [46–48].

HIF-1α is induced by tissue hypoxia, which is known to be associated with resistance to anticancer therapy, aggressive phenotype, and poor survival [49, 50]. It stimulates VEGF and acts as a potent proangiogenic factor. Some authors documented that MTA1 increases the stability and transcriptional activity of HIF-1α [51, 52]. It also enhances the expression of VEGF, which is a downstream target of HIF-1α. Recently, high expression of HIF-1α is associated with poor prognosis in various cancers such as ovarian cancer, breast cancer, and pancreatic cancer [53–55]. It is also highly expressed in OS cell lines than nonneoplastic osteoblasts in both normoxia and hypoxia conditions and functions as a protector of apoptosis [56]. High expression of HIF-1α is associated with significantly shorter overall survival and disease-free survival [50]. HIF-1α expression using prechemotherapy samples could be a good predictor of pathologic response of tumor cells (tumor necrosis) [57].

VEGF is one of the most important growth factors, which are involved in physiologic angiogenesis and tumor angiogenesis. It also interacts with various growth factors and signaling pathway, thereby enhancing angiogenesis or cell

proliferation. Factors, which could upregulate VEGF, are transforming growth factor-α (TGF-α), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), fibroblast growth factor 2 (FGF-2), TGF-β, and hepatocyte growth factor (HGF) [58, 59]. Lammli et al. presented that VEGF expression or level significantly increased in OS serum or tissues. They also showed that high expression of VEGF is associated with advanced clinical parameters such as frequent recurrence or metastasis [47]. However, prognostic value of VEGF is controversial [60, 61]. Recent study revealed that MTA1 is more potent angiogenesis inducer than VEGF in nonneoplastic and neoplastic lesions and upregulates VEGF and its receptor Flt-1 gene. VEGF also induces phosphorylation of endogenous MTA1, and this cross talk between them regulates angiogenesis and metastasis of tumor cells [62].

The Notch signaling pathway is known to be involved in physiologic angiogenesis, tumor angiogenesis, and tumor metastasis [63]. In physiologic angiogenesis, Notch interacts with VEGF, thereby blocking excessive sprout formation. However, aberrant activation of Notch signaling has been associated with tumor progression or metastasis. Hughes demonstrated that high expression of Notch 1, Notch 2, Notch ligand DLL1, and Notch target gene Hes1 is observed in metastatic OS cell lines compared to normal human osteoblasts or nonmetastatic OS cell lines. In murine model of OS with pulmonary metastasis, inhibition of Hes1 and Notch signaling eliminated tumor spread from the primary tumor. Hes1 expression is inversely correlated with survival in OS tumor tissues [64]. In other study using murine OS cell lines, similar results are found that Notch gene and Notch downstream targets Hes1 and Stat3 are upregulated in metastatic cell line [65]. Won et al. suggested that microRNA-199b-5p is upregulated in OS cell lines and is associated with Notch signaling pathway. Under the microRNA-199b-5p inhibitor, components of Notch pathway expression were altered [66].

2.3 Invasion of extracellular matrix

Matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases, primarily act on the extracellular matrix (ECM) and basement membrane components and degrade them. They take part in various physiologic and pathologic processes that require ECM or basement membrane remodeling such as morphogenesis, wound healing, tissue repair, tumor migration, invasion, and metastasis [67, 68]. In general, high expression of MMPs is associated with tumor progression such as invasion and metastasis or prognosis [69, 70]. MMP-9 is reported as a downstream target of MTA1 in esophageal squamous cell carcinoma and breast cancer cell lines MDA-MB-231 and MCF-7 [71, 72]. Forced downregulation of MTA1 reduces protein levels of MMP-9 and influences on the invasiveness. In OS, high-level expression of MMP-2 and MMP-9 is associated with increased risk of mortality and shorter overall survival, respectively [73, 74]. Jin J. et al. demonstrated that miR-218 is downregulated in OS tissues and cell line and functions as tumor suppressor gene by negatively regulating MMP-2 and MMP-9 [75]. MMP-1, a kind of collagenases, is overexpressed in OS cell line, especially which is highly metastatic. Forced downregulation of MMP-1 reduced an anchorage-independent growth *in vitro* and showed smaller primary tumors and decreased foci of lung metastases *in vivo* [76]. Recently, there have been a few reports that MMP-8 could be associated with antitumoral effect and protective function in breast and murine skin cancers [77, 78]. In OS, MMP-8 is expressed in primary tumors but not in metastatic foci. However, its expression could not predict patients' survival [79].

The Wnt proteins, a family of secreted cysteine-rich glycoproteins, activate intracellular signaling cascades by binding to Frizzleds and LRP-5/6 on target cells. Both the canonical and noncanonical Wnt pathways are involved in various biologic processes, especially embryogenic development and oncogenesis [80]. MTA1 and MTA1s could play a role on cell proliferation, invasion, and epithelial-mesenchymal transition by stimulation of Wnt/β-catenin pathway [81–83]. In OS, expression of Wnt components is widely investigated, and overexpression of Wnt ligands and Frizzled and LRP receptors is commonly observed. Guo et al. showed that E-cadherin expression is upregulated in Saos-2 cells with a dominant-negative, soluble LRP-5 [84]. They also demonstrated that LRP-5 promotes tumor invasion and metastasis via expression of Slug and Twist, transcriptional repressor, and MMP-2 and MMP-14 [85]. Ma et al. presented that β-catenin is overexpressed in OS cell line Saos-2 cells and its expression level is correlated with invasiveness of OS. Pharmacologic inhibition of Wnt/β-catenin and Notch pathway increased the chemosensitivity of Saos-2 cells [86].

The Snail family, zinc finger-containing transcription factor, includes Snail1 and Snail2 (also known as Slug) and functions as transcriptional repressors. Snail/Slug is also involved in EMT by downregulating E-cadherin, which causes migration, invasion, and metastasis of tumor cells [87]. Cagatay et al. reported that MTA1 enhances the expression of Snail1 and Slug, and silencing of MTA1 results in decreased recruitment of Snail and Slug to the promoter of E-cadherin. They showed that overexpression of MTA1 in colorectal cancer cells enhances proliferation, migration, invasion, and anchorage-independent growth [88]. Yang et al. reported that overexpression of Snail1 is associated with OS invasion and metastasis through suppression of E-cadherin expression [89]. Snail2 expression was investigated in long bone OS and was significantly correlated with tumor grade [90]. Same group revealed that overexpression of Snail2 increase cell motility, remodeling of the actin cytoskeleton, cellular protrusions, and expression of promigratory noncanonical Wnt pathway components [91]. E-cadherin, which is a

well-known adhesion molecule and a downstream target of Snail, has been investigated in association with MTA1. Downregulation of E-cadherin using small interfering RNA led to overexpression of MTA1, decreased cohesiveness, and enhanced motility and invasion in prostate adenocarcinoma cell lines [92]. Wang et al. showed that silencing of MTA1 using siRNA results in the upregulation of E-cadherin [93]. Contrary to MTA1, MTA3 functions as repressor of EMT by regulating Snail. Upregulation of MTA1 could repress MTA 3 expression, resulting in promotion of EMT.

Twist, a member of the basic helix-loop-helix transcription factor family, is involved in embryogenic skeletal development and remodeling as well as cancer biology, especially EMT [87, 94]. There are various signaling pathways associated with Twist in both upstream and downstream directions [94]. In OS, there are few reports that reveal association between Twist and other signaling pathways such as endothelin-1/endothelin A receptor and β-catenin signaling [95, 96]. Both pathways were associated with OS cell survival against cisplatin, which was decreased by Twist. Recent study also demonstrated that miR-33a promotes OS cell resistance to cisplatin by downregulating Twist [97]. Yin et al. showed that positive Twist expression has significantly poor overall survival and disease-free survival and independent prognostic factor in OS [98].

Src, a member of the Src family of kinases, is a nonreceptor tyrosine kinase encoded by the c-Src proto-oncogene. Src kinase activity is regulated by various tyrosine receptor kinases including epidermal growth factor receptor kinase, PDGF tyrosine kinase, and integrin receptor [99–101]. Src activation also affects downstream signaling pathways such as transcription factor STAT-3 and focal adhesion kinase (FAK) [102, 103]. Hingorani et al. revealed that dasatinib, a dual Src-Abl kinase inhibitor, effectively inhibits the adhesion and migration of OS cells. However, it does not inhibit the growth of primary tumor and pulmonary metastases even though Src activation is blocked *in vivo*. Although Src is involved in tumor progression such as invasion and metastasis, Src kinase activation is not a primary pathway for pulmonary metastasis [104].

2.4 Anoikis resistance

When cells lose contact with the adjacent cells or ECM, they undergo a specific cellular apoptosis termed anoikis. Although anoikis plays a role in regulating cell homeostasis during development or tissue remodeling, many transformed cells and tumor cell lines reveal anoikis resistance [105]. Tumor cells, entering into the circulation, should acquire the resistance to anoikis to survive and metastasize. Anoikis could be induced by transfection with Src oncogene or epidermal growth factor receptor (EGFR) activation [106–108], and inhibitors of Src and EGFR have been investigated [109]. Mahoney et al. reported that forced expression of MTA1 increases survival in forced suspension culture of immortalized keratinocytes, collaborating with EGFR [110]. Molecules or molecular pathways involved in anoikis resistance in OS are Src, PI3K/Akt signaling pathway, caveolin-1, c-met, and ezrin/β4 integrin interaction [111–113].

Integrin is a family of cell adhesion receptors, which are involved in important biologic processes such as adhesion, signaling, proliferation, and metastasis. Among them, β4 integrin is often upregulated in malignant tumors, and high expression level of that is sometimes associated with poor prognosis. β4 integrin is also highly expressed in OS cell lines and OS patient samples. Wan et al. presented that anchorage-independent growth is significantly decreased in β4 integrin shRNA cell line, and lung metastases are also markedly decreased in mice injected with β4 integrin-shRNA cells compared to the control-shRNA group. They also revealed that β4 integrin associates with ezrin, which is required for the maintenance of its expression at RNA and protein levels [113].

Caveolin-1 (Cav-1) is major protein of caveolae, which involves signaling pathway. Cav-1 functions as a tumor suppressor gene or an oncogene depending on the cell type. Its expression is decreased in met-transformed osteoblasts and OS tissues. Forced overexpression of Cav-1 inhibited anchorage-independent growth, migration, and invasion in OS cell lines by inhibiting c-Src activity and met signaling. *In vivo*, Cav-1 overexpression reduced the metastasis in experimental conditions [112]. Diaz-Montero et al. demonstrated that Src-dependent activation of the PI3K/Akt pathway is observed in anoikis-resistant SAOS-2 cells and pharmacologic inhibition of Src or PI3K/Akt activity recovers sensitivity to anoikis [111].

2.5 Homing of tumor cells, extravasation, and attachment

The lung is a preferential site for OS metastasis, which comprises more than 80 % [114]. This site-specific metastasis could be explained by chemokine axis such as C-X-C motif chemokine receptor 4 (CXCR4) and its ligand C-X-C-motif chemokine ligand 12 (CXCL12) [115–117]. CXCL12 is abundantly expressed in the lung and bone marrow and a potent chemoattractant for CXCR4 and CXCR7 expressing cells [118]. CXCR4 is highly expressed in malignant cells including prostatic cancer, breast cancer, and OS cells as a result of high expression of HIF-1α or VEGF [119, 120]. In OS, high mRNA expression of CXCR4 is adversely correlated to overall survival, event-free survival, and metastasis-free survival [115]. As interactions of CXCR4 or CXCR7 and CXCL12 make tumor cells to adhere and extravasate in pulmonary metastasis, CXCR4 and CXCR7 are considered as a target of an anticancer therapy [121]. Brennecke et al. presented CXCR4 antibody inhibits lung micrometastases in mice with intratibial human OS xenografts [122].

Ezrin, a cytoskeleton linker membrane protein, mediates interaction of cells and surrounding microenvironment and facilitates signal transduction [123]. Khanna et al. presented that significantly diminished metastases could be induced by blocking ezrin with antisense ezrin or a dominant-negative inhibitor in murine OS models [124]. They also found that ezrin suppression results in decreased activity of Akt and MAPK. Akt signaling pathway is involved in OS metastasis through MMPs. High ezrin expression is associated with aggressiveness and a worse survival in OS patients [125–127]. MiR-183, markedly downregulated in OS cell lines and tissues, is inversely correlated with ezrin [128]. Combined miR-183 downregulation and ezrin upregulation were significantly associated with high tumor grade, poor response to chemotherapy, recurrence, and overall survival [129].

2.6 Inactivation of tumor suppressor genes

TP53 functions as a blocker of neoplastic transformation in various cancers. When DNA damage occurs, it binds to DNA and induces and maintains cell cycle arrest until DNA is repaired. Unless DNA is recovered, TP53 activates programmed cell death (apoptosis). MTA1 is also known as a DNA damage-responsive protein; it could control p53 stability by destabilizing constitutive photomorphogenic protein 1 (COP1) and mouse double minute 2 (MDM2), thereby regulating p53-dependent transcription of p53R2, a gene for supplying nucleotides for DNA repair [130]. It also transcriptionally suppresses $p21^{WAF1}$, consequently leads to PCNA-dependent DNA repair in p53-independent mode [131]. Since MTA1 promoter has two p53 response elements, poly(ADP-ribosyl)ation of p53 could induce transcriptional repression of MTA1 [132]. TP53 mutation is a common genetic alteration in OS, and it is found in up to 50 % of OS patients [133–135]. Germline TP53 mutation is observed in Li-Fraumeni syndrome, which is known as a predisposing condition for OS, and shows higher incidence for OS. Some authors revealed that TP53 mutation is not a prognostic marker for chemotherapy response [136]. Recently, systematic review articles demonstrated that TP53 mutation is associated with poor overall survival and prognostically significant [137, 138]. TP53 function can be blocked by other mechanisms such as MDM2. MDM2 is frequently amplified, which is known as a major inhibitor of TP53 [139, 140]. It induces a degradation of TP53, and similar functional results as mutation. Amplification of MDM2 is commonly observed in low-grade OS, which usually does not have TP53 mutation [141].

RB1 gene is located on human chromosome 13q14, which is known as a common loss area by cytogenetics in OS tissue. Inactivation of RB1 gene is one of the most common genetic alterations in OS, which is found in up to 70 % of OS patients [142]. Patients with bilateral retinoblastoma have higher risk of subsequent OS [143], and both of them are associated with RB1 gene. RB1 gene is an important regulator of cell cycle, especially G1/S cell cycle transition. When there is a mitogenic signaling, RB1 is phosphorylated by cyclin D/CDK4, cylin D/CDK6, and cyclin E/CDK2 complexes, and it releases E2F transcription factors. Chromatin-remodeling proteins, such as histone deacetylases and histone methyltransferase, which are recruited at hypophosphylated RB state are also released, and promoters become more sensitive [144]. Functional loss of RB1 gene causes persistent transcriptional activation and tumorigenic effect. However, prognostic value of loss of heterozygosity at the RB gene is uncertain [145, 146]. P16 is cyclin-dependent kinase inhibitor and activator of RB dephosphorylation. Deletion of p16 was detected in 7~16 % OS patients, and loss of p16 expression is correlated with decreased survival [147, 148]. Recently, Borys et al. demonstrated that p16 expression could be used as a predictor of chemotherapy response [149]. Cyclin-dependent kinase 4 (CDK4) and cyclin D1 are negative regulators of p16 [150]. CDK4 and MDM2 are coamplified or overexpressed in low-grade OS including parosteal OS and dedifferentiated type of high-grade OS [151, 152].

RECQL4 gene, a member of RecQ family DNA helicases, mutation is found in Rothmund-Thomson syndrome, which has a higher incidence in OS [8]. Deficiencies of RecQ family helicases result in increased levels of recombination and chromosomal aberrations [153]. However, RECQL4 gene mutation is not common in sporadic OS, and its prognostic value is also limited [154]. Some cytogenetic studies revealed recurrent deletion or loss of heterozygosity at 3q13 in OS, which contains LSAMP gene [155, 156]. Kresse SH et al. presented that low expression of LSAMP gene is associated with poor survival [157].

2.7 Activation of protooncogene

Activator protein-1 (AP-1) is a transcription factor complex containing c-jun, c-fos, and activating transcription factor family. Increased activity of AP-1 is observed in more aggressive OS cell line. Inhibition of AP-1 activity by TAM67, dominant-negative mutant of c-jun, suppresses the migration, invasion, and pulmonary metastasis in experimental murine OS [158]. c-jun and Fra-1, components of AP-1, regulate tumor invasion by controlling the matrix metalloproteinase (MMP)-1 in 143B OS cells [159]. c-fos also induce podoplanin and thereby control cell migration in OS cell lines [160].

Human epidermal growth factor receptor 2, also known as ErbB2/Her2/neu, is overexpressed in various tumors, including breast cancer [161]. In OS, there have been conflicting results of HER-2 status [162–164]. Recent papers suggested that HER2 amplification or overexpression is rarely observed in OS, and differences in the results between studies are due to interpretation of immunohistochemical results based on the poor methodology [165].

RUNX2, a member of transcription factor Runx family, is associated with osteoblast differentiation, and its expression is oscillates during the cell cycle [166, 167]. Although there are some reports of RUNX2 function, which is associated with RB, p53-MDM pathway, and cell cycle regulators, the role of that in OS is uncertain [168–170]. However, its level is elevated in OS cell lines and tissues, and increased expression is associated with metastases, poor response to chemotherapy, and poor prognosis [171, 172].

2.8 MicroRNAs in tumorigenesis

MicroRNAs, small noncoding RNAs, regulate gene expression posttranscriptionally. They function as a tumor suppressor or oncogene [173, 174]. There are several microRNA expression profiling studies, which compared nonneoplastic osteoblast and OS cells [175, 176]. Differentially expressed microRNAs could be involved in OS tumorigenesis and be therapeutic targets. Liu et al. reported that miR-125b is downregulated in OS cell lines and its upstream regulator is STAT3 [177]. MTA1 is known to be another upstream regulator of miR-125b, and it promotes the migration and invasion of nonsmall cell lung cancer cells. miR-199a-3p, miR-143, and miR-145 are also downregulated in OS cell lines and function as tumor suppressor [178–181]. miR-21 is overexpressed in OS tissues and negatively regulates RECK gene [182]. miR-199b-5p plays a role in Notch signaling in OS [66].

3 Conclusion

Despite of chemotherapeutic advance, survival rate of OS has stagnated for a few decades. New treatment strategies using molecular targets are required to patients who are unresponsive to current therapy. The aforementioned diverse molecular studies have advanced knowledge of OS pathogenesis and roles of MTA1 in OS. Since MTA1 influences on not only various levels of tumorigenesis or tumor progression, but also DNA damage repair, it could be a possible therapeutic target in high grade or metastatic OS. More comprehensive research and investigations are needed to refine and definitize MTA roles in OS pathogenesis.

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