Current Problems in Cancer 43 (2019) 228–235

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

The possible role of insulin-like growth factor-1 in osteosarcoma

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ARTICLE INFO

Keywords:
Osteosarcoma
Insulin-like growth factor-1
Insulin-like growth factor-1 receptor
shRNA

ABSTRACT

Osteosarcoma (OS) is a common malignant tumor of bone, of which clear understanding of molecular pathologic process is not yet possible. Insulin-like growth factor-1 (IGF-1) is a hormone that plays vital role in development and function of many tissues. Unfortunately, IGF-1 and its receptor (IGF-1R)'s over-expression have been implicated in carcinogenesis, and indicated to constitute a risk factor for the development of multiple human cancers, including OS. Increased levels of IGF-1 and IGF-1R have been reported in OS, leading to cancer progression through transformation, proliferation, pro-metastasis, and decreased susceptibility to apoptosis. Over-expression of IGF-1/IGF-1R signaling also contributes to tumor cell survival, metastasis, and resistance to chemotherapeutic drugs. IGF-1 has been included as an OS marker recently, and targeting IGF-1 is an interesting and promising approach in OS therapeutics. However more investigations with clinical trials are necessary to validate the use of drugs against IGF-1 that may provide a basis for new therapeutic approaches to treat this devastating disease. This review

☆ This work was supported by the National Natural Science Foundation of China (nos. 81874030, 81401838 and 81402224), the Provincial Science Foundation of Hunan (nos. 2015JJ3139 and 2017JJ3499), the Health and Family Planning Commission of Hunan Province (B2014-12), the Administration of Traditional Chinese Medicine of Hunan Province (no. 2015116), the Clinical and Rehabilitation Research Foundation of Xiangya Hospital and Weiming of Peking University (xywm2015II04, xywm2015II07).
Conflicts of interest: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.1016/j.currproblcancer.2018.08.008

article focused on the role of IGF-1/IGF-1R in OS progression and therapeutic aspects of OS targeting IGF-1.

Contents

Introduction

Osteosarcoma (OS) is the most common malignant bone cancer in children and adolescents, characterized by spindle cells of mesenchymal origin depositing immature osteoid matrix and fibrillary stroma. OS commonly develops at the terminus of the long bones of the body including the distal femur, followed by the proximal tibia and proximal humerus. The typical presentation of OS includes onset of pain and swelling in the affected bone.[1-3] According to the National Cancer Institute SEER (Surveillance, Epidemiology, and End Results) program, the frequency of OS has been increasing by 0.3% per year over the last decade. OS occurs more often in males than in females.[4,5] The etiology of OS remains unclear and controversial. A number of factors are associated with the risk of progression of OS, including age, sex, race, genetic, and other familial factors. There is an increased incidence of primary OS associated with several genetic syndromes such as Li-Fraumeni, hereditary retinoblastoma, Bloom syndrome, Werner syndrome, Diamond Blackfan anemia, and Rothmund Thomson.[6-8] The current possible treatment of OS combines surgical and multiagent chemotherapeutic regimens like cisplatin, carboplatin, etoposide, ifosfamide, doxorubicin, and high-dose methotrexate.[9] Despite great advances in treatments, comprising neoadjuvant chemotherapy and surgical technology, a number of patients with OS have a high risk of local relapse or metastasis after chemotherapy. So, there is a clear need for newer effective agents for patients with OS. Better understanding the molecular pathologic mechanisms of OS and identification of a specific molecular target may help to develop novel effective therapeutic approaches for the treatment of OS.[10,11]

The insulin-like growth factor-1 (IGF-1) is a hormone similar in molecular structure to insulin. It plays a significant role in the development and function of many tissues. IGF-1 system includes IGF-1, IGF-binding proteins (IGFBPs), and the IGF-1receptor (IGF-1R).[12,13] IGF-1 is produced in the liver under the stimulus of growth hormone, and therefore, it has a strong impact on cell proliferation, differentiation, and apoptosis inhibition.[14] IGF-1 and IGF-1R over-expression have been implicated in carcinogenesis and indicated to constitute a risk factor for the development of multiple human cancers. The IGF-1/IGF-1R signaling has been extensively studied in cancer that has been implicated in many aspects of angiogenesis and metastasis.[15-17] In this review, we provide an overview on the function and regulation of IGF-1 as well as the role it plays in the pathogenesis of OS.

IGF-1: Structure and function

IGF-1, also called somatomedin C, is a protein that in humans is encoded by the *IGF-1* gene. It consists of 70 amino acid polypeptide with a weight of 7.6 kDa. IGF-1 is mainly produced in the liver but is also produced locally in different tissues in the body.[12,18] IGF-1 system con-

sists of 3 ligands (IGF-1, IGF-2, and insulin), their cell membrane receptors (IGF-1R, IGF-2R, and IR), and a group of IGF-binding proteins (IGFBPs). There are 6 members in IGFBP super family (IGFBP-1 to 6) that modulate the effects of IGF-1 by preventing their action on the receptors. IGF-1R is a hetero-tetrameric ($\alpha 2\beta 2$) transmembrane glycoprotein with tyrosine kinase activity which is ubiquitously expressed in various human cell types and tissues.[19,20] It plays an important role in growth and various physiological functions, including development, differentiation, apoptosis, and metabolism by binding of the IGF-1 ligands. Once IGF-1R binds to IGF-1, it has been shown to preferentially favor IGF-1 mediated signaling. Upon activation by its ligands, IGF-1R first binds to intracellular adaptor proteins-predominantly insulin receptor substrate1, which are necessary for IGF-1R to transmit signals downstream in the cell through the phosphatidylinositol-3 kinase-AKT1-mammalian target of rapamycin pathway and through the mitogen activated protein kinase pathway, leading to cell cycle progression, cell proliferation, and cell survival. High circulating levels of IGF-1as well as over-activation of the mitogenic, antiapoptotic, and pro-motility signaling cascades induced by IGF-1R have been implicated in multiple human cancers.[21-24]

IGF-1 pathophysiology in OS

A simplified schematic presentation (Fig 1) shows the relationship between IGF-1 and OS. Local expression of IGF-1 has been linked to OS due to the overlapping of the highest levels of IGF-1and the peak incidence of OS. Increased levels of IGF-1and IGF-1R have been detected in OS, leading to tumor progression through transformation, proliferation, decreased susceptibility to apoptosis, and pro-metastasis (motility, invasion, and angiogenesis).Over-expression of IGF-1/IGF-1R signaling also contributes to tumor cell survival, metastasis, and resistance to chemotherapeutic drugs.[25-27] Several studies suggested that supplementation of OS cell lines with IGF-1 increases their growth.[28,29] Raile et al found that IGF-1 treatment stimulated cell growth and proliferation exceeded cell death.[30] Wang et al reported that IGF-1 signaling pathway is aberrantly activated in OS and can promote proliferation and chemotherapy resistance by activating Akt signaling pathway.[29] Jentzschet al investigated the expression of IGF-1 in surgical primary tumor resection tissue specimens of patients with OS using a tissue microarray. Their study suggested that local IGF-1 expression is associated with more aggressive tumor types and survival time.[26] Maniscalco et al investigated the levels of IGF-1R mRNA and protein expression in canine OS tissues and cell lines. Their study demonstrated that the over-expression of IGF-1R was closely associated with surgical stage and distant metastasis in canine appendicular OS model.[31] In humans, IGF-1 signaling pathway also contributes to the malignant phenotype in canine OS, as reported by MacEwen et al,[32] where they showed that IGF-1R expression is correlated with a poor prognosis of OS.

Targeting IGF-1 in OS

OS is 1 of the major threats in human health and the most common primary malignancy of bone. Despite the modern multimodality chemotherapeutic success, the treatment for OS is still unsatisfactory for the risk of metastasis and local relapse. The understanding of detailed pathogenic mechanism is essential to develop the potential treatment strategies that might target both metastatic progressions and reduce the risk of recurrence in the treatment of OS.[33-35] Recently, targeting IGF-1 and IGF-1R in the treatment of OS has gained significant interests among the researchers.[36,37] The important strategies to target IGF-1 are pointed in Table 1, and Table 2 summarizes the potential chemotherapeutic strategies of OS by targeting IGF-1. Mansky et al have developed a novel and long-acting somatostatin analogue, named OncoLAR that could suppress the serum level of IGF-1 with more convenient dosing (once monthly) and a more favorable toxicity profile.[38] Khanna et al initiated a trial of OncoLAR plus chemotherapy

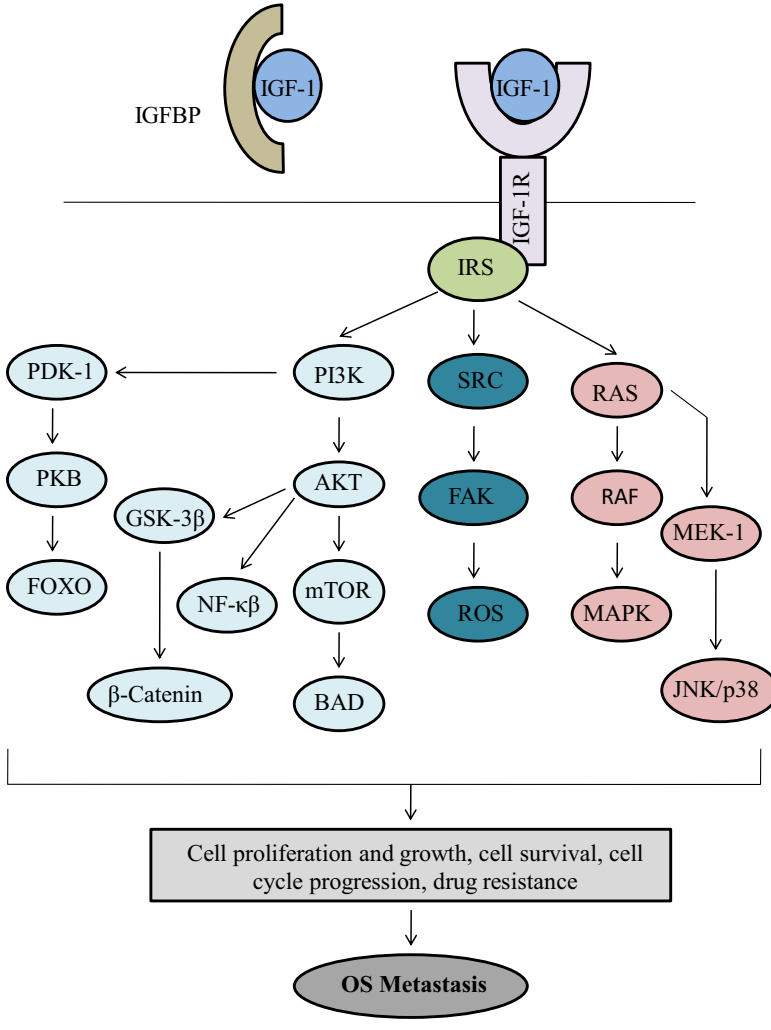

Fig. 1. Schematic representation of the IGF-1 system in OS progression. IGF-1 is regulated by binding to insulin growth factor binding protein (IGFBP). Free IGF-1 can bind to IGF-1R, and activate downstream signaling through the insulin receptor substrate (IRS) to trigger both PI3K/AKT/mTOR and MAPK signaling pathways, leading to OS metastasis.[22,23,25] BAD, Bcl-2-associated death promoter; FAK, focal adhesion kinase; FOXO, forkhead box O; GSK-3β, glycogen synthase kinase 3 beta; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; MAPK, mitogen activated protein kinase; MEK-1, mitogen activated kinase-1; mTOR, mammalian target of rapamycin; NF-$\kappa\beta$, nuclear factor kappa-light-chain-enhancer of activated B cells; PDK-1, phosphatidylinositol trisphosphate dependent kinase-1; PI3K, phosphatidyl inositol 3 kinase; PKB, protein kinase B; ROS, reactive oxygen species.

Table 1
Major strategies to target insulin-like growth factor-1 (IGF-1).[36,37]

1. Blockage of IGF-1 by small RNA technologies
2. Disruption of IGF-1 regulatory proteins
3. Development of IGF-1 specific chemotherapeutic drugs
4. Suppression of serum IGF-1 through inhibition of growth hormone
5. Inactivation of IGF-1 by applying antibodies that compete with IGF-1 receptor
6. Epigenetic modification of *IGF-1* gene to silence its expression

Table 2
The potential chemotherapeutic strategies of OS by targeting IGF-1.

Therapeutic agents	Effects	Ref
OncoLAR	Suppressed the serum level of IGF-1	38
OncoLAR plus chemotherapy	Induced antitumor activity	39
Trastuzumab	Inhibited tumor growth	40
miR-26a	Inhibited tumor growth	41
miR-133a	Inhibited cell proliferation and invasion	43
miR-503	Inhibited cell proliferation and invasion	44
miR-100	Inhibited cell proliferation, migration and invasion	45
Lentivirus-mediated shRNA)	Suppressed cell growth and invasiveness, and induced apoptosis	46
Lentivirus-mediated shRNA with chemotherapy (CDDP or DTX	Suppressed cell growth and induced apoptosis	47
Cisplatin	Enhanced antitumor activity	48
Chimaphilin	Increased sensitivity to chemotherapeutic drugs	49
6-fluoro-(3-fluorophenyl)-4-(3-methoxyanilino) quinazoline (LJJ-10)	Inhibited migration and invasion	50
Cyclolignan picropodophyllin (PPP)	Inhibited cell proliferation and promoted apoptosis	51

compared with chemotherapy alone in pet dogs with naturally occurring OS and they suggested that the antitumor activity of chemotherapy would be enhanced by the inhibition of IGF-1.[39] Blockage of the IGF-1Rwith trastuzumab inhibits tumor growth of several human OS cell lines.[40] Hong et al developed an experimental approach based on the liver-specific IGF-1-deficient (LID) mouse model, in which, LID mice (B6 background) were backcrossed to balb/c mice to allow for growth of K7M2 OS cells. K7M2 murine OS cells were then injected orthotopically into the backcrossed LID mice leading to have 75% reduction in serum IGF-1 in newly derived balb/c LID mice compared to litter-mate controls.[25] It has been investigated that miR-26a is significantly down-regulated in OS and miR-26a has a suppressor role in OS tumorigenesis. IGF-1 is a target of miR-26a, and miR-26a exerted its tumor-suppressor function by inhibiting IGF-1 expression.[41] IGF-1R participates in tumorigenesis through activating the downstream signaling pathway. IGF-1R has been suggested to be a therapeutic target for OS.[42] Recently, miR-133a is reported to inhibit OS cell proliferation and invasion via targeting IGF-1R.[43] Another study identified IGF-1R as a novel target gene of miR-503 inhibited U2OS cell proliferation and invasion via directly targeting IGF-1R.[44] IGF-1R is inversely correlated with miR-100 in OS tissues. Over-expression of miR-100 decreased the expression of IGF-1R and inhibited cell proliferation, migration, and invasion abilities of OS cells, U-2OS, and MG-63 through the inhibition of phosphatidyl-inositol-3 kinase/AKT and mitogen activated protein kinase/ERK signaling.[45]

IGF-1R antibody treatment or receptor level reduction by siRNA results in decreased invasiveness and slows growth of OS xenografts.[28] In a study, Wang et al lentivirus-mediated siRNA was employed to down-regulate endogenous IGF-1R expression in OS cells. Down-regulation of IGF-1R expression in OS cells could induce potent antitumor activity and radio-sensitizing activity by suppressing cell growth and invasiveness as well as inducing apoptosis correlated with the activation of Caspase-3.[46] In another study, Wang et al reported lentivirus-mediated RNAi targeting IGF-1R as an attractive anticancer strategy to chemo-sensitization of OS cell. They combined lentivirus-mediated shRNA targeting IGF-1R with chemotherapy (CDDP or DTX) that could lead to growth suppression, enhanced Caspase-3-mediated apoptosis of OS cells through the down-regulation of Bcl-2 and up-regulation of Bax.[47] Inhibitors of IGF-1R and its downstream pathways have shown promise in preclinical models of OS. Multiple IGF-1R inhibitors have been developed as potential therapeutics for OS. IGF-1R inhibition by using cisplatin reduced the accumulation of p53 and increased p53s apoptotic function through the inactivation of IGF-1R/AKT/mTORC1 pathway.[48] Chimaphilin (an active compound separated from pyrola) possesses highly efficient antitumor activities. Chimaphilin can inhibit the receptor tyrosine ki-

nase activity of IGF-1R and can increase the sensitivity of doxorubicin in doxorubicin-resistant OS cell lines.[49] 6-fluoro-(3-fluorophenyl)-4-(3-methoxyanilino) quinazoline (LJJ-10) possesses potential anticancer activity in U-2 OS cells. Molecular targeting of IGF-1R signaling leads to the inhibition of matrix metalloproteinase-2 (MMP-2) and MMP-9 enzyme activities, migration and invasion levels in LJJ-10-treated U-2 OS cells.[50] Cyclolignan-picropodo-phyllin is a member of the cyclolignan family that selectively inhibits the receptor tyrosine kinase activity of IGF-1R in OS cell lines. Picropodo-phyllin significantly inhibits IGF-1R expression and this inhibition of the IGF-1R correlates with suppression of proliferation of OS cell lines and with apoptosis induction.[51]

Conclusion

OS remains a life-threatening disease and its treatment is a major challenge in oncology due to the risk of aggression and recurrence. The greater understanding regarding the pathogenic mechanisms of OS is necessary for the development of novel and effective therapeutic strategies. Development of modern molecular medication scheme has led to the discovery of several possible tumor markers. Recent studies have taken attempt to use IGF-1 as a diagnostic marker for OS. Novel agents targeting the local IGF-1 pathway may increase the possibility of therapeutic success. R1507, an IGF-1R inhibitor has recently been used in a cohort study to treat participants of 2 years of age and older with recurrent or refractory osteosarcoma (https://clinicaltrials.gov/ct2/show/study/NCT00642941), of which result is yet to come out. More clinical trials are necessary to validate the use of drugs against IGF-1/IGF-1R that may provide a basis for new therapeutic approaches to treat this devastating disease.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2018.08.008.

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