The research progress of Monopolar Spindle 1 Kinase (Mps1) in the treatment of tumor and osteosarcoma

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Abstract

The spindle assembly checkpoint (SAC) is an indispensable guardian machinery for cell mitotic progression, which ensures the successful alignment of chromosomes on the metaphase plate before metaphase/anaphase transition. This checkpoint anomaly is closely related to tumor-ogenesis. Monopolar spindle kinase 1 (Mps1) is a conserved bispecific protein kinase whose main function is central replication and activation of SAC, both of which contribute to the prevention of mitosis and prevent tumor occur. Recent studies have found that Mps1 expression level is associated with malignant degree of breast cancer. More it is worth noting that the inhibition of Mps1 kinase activity or by siRNA knockout Mps1 disorders can lead to the obstacle of cell division process, this may lead to tumor cell death and will not affect the normal cell activity. The cell cycle imbalance is closely related to the invasive biological behavior of malignant tumors, which is a basic marker of tumor progression. The cell cycle is mainly regulated by a number of checkpoint regulators, which are specifically out of tumor cells Has the potential to be a potential target for designing selective treatment of tumor cells. This paper reviews how Mps1 regulates spindle test points and its latest advances in anti-tumor and osteosarcoma applications.

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Introduction

Any cell is closely monitored and regulated in the value-added process and must follow certain rules. For example, DNA replication will not begin until the preparation is completed; Only after DNA replication has been completed can cell division be carried out. In the process of cell proliferation, once some key steps appear to violate the above rules and related monitoring and control points fail to play a role, there will be many serious consequences of cell death, clearance by the body’s immune system and canceration. In eukaryotes, cells divide the sister chromatid into their progeny cells by mitosis, whereas cells in the process of division may encounter physical, chemical, and biological external stimuli that, if they occur in cell-specific Stage and failed to be repaired in time, some genetic diseases, tumors and so on may occur. In the evolving process of eukaryotic cells, in order to deal with these damages, many regulatory structures have been evolved during cell division. Through the monitoring and regulation of these regulatory structures, errors in mitosis can be promptly repaired. The beginning of the last stage of mitosis is very important throughout the regulatory process and is monitored and controlled by the Spindle assembly checkpoint (SAC). The roles of SAC is to ensure that all chromatids are properly arranged on the equatorial plate before metaphase mitosis to the late transformation, and the absence of this effect will result in incorrect transmission of sister chromatids in mitosis or failure to be effective, the result is the formation of Chromosomal instability (CIN) or aneuploidy in progeny cells, the literature suggests that the formation of aneuploid cell line is the common feature of the development of tumor cells [1]. Mps1 is a exist in the upstream of SAC regulation pathways, conservative eukaryotic gene product, is the necessary structure of SAC, and it regulates and controls SAC, and in the process of the whole mechanism is still unclear. The basic characteristics of Mps1 and its relationship with tumor, osteosarcoma and the research progress were reviewed in the article.

Mitotic checkpoint signal transmission form

The process of eukaryotic cell mitosis is divided into two stages of intercellular and dividing stages, of which the dividing stage can be divided into G1, S, G2 three different stages. Cell cycle monitoring system - Mitotic checkpoint (SAC) is mainly in the mid-cell division, and many of the cell structure with monitoring function, SAC is also composed of many proteins, and Mps1 is one of the most important proteins that make up SAC. Liu Dan and other studies have shown that composed of the above structure CENP-E, Dynein, Mps1 and other motor proteins and EB1, APC, Clip170, Clasp1 and other microtubule-binding proteins coordinate microtubule capture and chromosome movement to complete the chromosome arrangement [2]. SAC controls SAC by regulating the onset of the late mitotic period to ensure that all sister chro-
matids establish precise contact with the bipolar spindle and that any incorrect connection activates SAC [3, 4]. If the spindle assembly is incomplete, or the moving particles cannot be fully captured by the microtubule, the cell cannot start to enter the signal molecule behind [5]. Only when the mitotic chromosomes are precisely taken up by the spindle and arranged on the equatorial plate will the SAC signal be eliminated and the elimination is mainly due to the dissociation of the MCC complex and the inhibition of the new MCC complex formation. After the dissociation of MCC complex, Cdc20 binds to APC / C and is activated to promote the degradation of Securin and CyclinB, and then the sister chromatid segregates under the guidance of the spindle and initiates the progression towards the later stage of cell division [6-13].

Various factors such as X-ray, chemicals, germ invasion and so on in internal and external environment may cause different degrees of damage to mitochondrial DNA during mitosis, and the corresponding checkpoints prevent cell DNA damaged from entering the next stage of cell cycle and apoptosis. If the checkpoint goes wrong, cannot be detected in time damaged DNA and repair, then the DNA error will produce genetic signal instability or aneuploidy, then the possibility of tumor will be significantly increased.

**The roles of Mps1 in SAC**

The Mps1 gene was originally a differential DNA found in the cDNA library of Breast cancer cells treated with TGF-β1 using a differential hybridization method. The concentrations of mRNA detected by these factors were significantly increased. Mps1 phosphorylates a variety of amino acids with both anti-phosphorylation and autophosphorylation [14, 15]. In SAC, the relevant monitoring signals can be amplified step by step by a cascaded amplification system to finally work. Mps1 has many important functions in cell cycle. The most prominent one is inhibition of the new MCC complex formation. After the dissociation of MCC complex, Mps1 plays an important role in ensuring that all chromosomes are correctly captured by the spindle until the late stage of mitosis. Mps1 is also involved in the function of other cellular processes, such as the arrangement of metaphase chromosomes, cytokinesis, centrosome duplication, DNA damage and other functions [16, 17]. The DNA damage checkpoint, Mps1 activates the effector protein checkpoint kinase 2, which is linked to the corresponding protein through CHK2, and the signal of DNA damage is amplified step by step. In a series of cascade phosphorylation and dephosphorylation reactions after affecting the intracellular response [18]. Mps1 protein concentration in the mitotic G0 phase cells was extremely low, G2 phase cells significantly increased, and reached the highest concentration before the mitotic peak; further to the late stage, Mps1 protein levels gradually decreased, and then the concentration level of...
stability period [19, 20]. Another important function of cell cycle checkpoint is to effectively trigger the course of the reaction (eg, apoptosis, mitotic catastrophes, and aging) to prevent severely damaged cells from propagating high-risk cells and eventually forming tumor cells. The normal cell cycle consists of five stages: G0, G1, S, G2 and M-period. The first four phases are collectively called the middle phase. At M stage, chromosomes and cytoplasm are divided into two daughter cells (cell division). Several checkpoint mechanisms have been established in the cell cycle [21]. The G1/S checkpoint limits the DNA of cell damage from entering the S phase until the high risk of injury is removed or triggers cell death or aging. The G2/M checkpoint prevents cells from prematurely entering mitosis, which minimizes the chance of erroneous chromosome segregation. SAC is a major cell cycle control mechanism in mitosis and is responsible for ensuring the isolation of high fidelity chromatids from daughter cells. The key role of Mps1 in SAC lies in convening other checkpoint components to reach the kinetochores, including Mad1, Mad2, Bub1, BubR1, Bub3 and inhibiting APC/C ubiquitination [17, 22, 23], mitotic checkpoints preventing abnormalities. Cells enter the next process of mitosis. All of these checkpoint mechanisms are effective in reducing the cell cycle genome instability. Cell cycle aberration is the key to tumor cell formation, development and metastasis. Autonomic regulation of tumor cell cycle plays a crucial role in tumor cells. The imbalance of the cell cycle is also closely related to the aggressive biological behavior of malignant tumors, becoming a basic marker of tumor progression. In Violeta Morin, Susana Prieto's study showed that Mps1 overexpression is conducive to the tumor, but not for the survival of cancer patients, Mps1 high expression of the median survival of the population in 487-913 days, 95% confidence interval in the 751-1075. The 2-year survival rate was 35%. The median survival of Mps1 population was 858-1183 days, 95% confidence interval was 1177-1189, and the 2-year survival rate was 56%. Mps1 inhibitor Mps1-IN-3 combined with vincristine can make malignant glioma cell mitosis abnormalities [19, 20], with CCT271850 inhibitor treated tumor cells may present an abnormal number of chromosomes, and because of mitotic checkpoint error, causes abnormal cell division, followed by cell death. Experiments have demonstrated that CCT271850 inhibitors have a moderate level of single agent effect in human colorectal cancer xenograft models [24]. Can be seen, Mps1 is a tumor chemotherapy drug target, can be related to the inhibition of kinase inhibitors. Other experiments show that Mps1 is highly expressed in human soft tissue tumors [25]. According to Wang and Ling, an siRNA (abbreviated as siMps1) was synthesized by targeting the 5’end of Mps1 gene. Western blotting was used to detect the interference effect of siMps1 and the effect on the proliferative
tion and mitosis of tumor cells after the interference, to construct a cell line SW480-YFPsiRNA stably expressing siMps1 and to detect whether the overexpression of exogenous Mps1 can restore the phenotype of its endogenous gene deletion. Thus, transfection of siMps1 can reduce the level of Mps1 protein in cells and result in mitosis Index decreased, chromosomal midrange arranged abnormally. Meanwhile, vertebrate Mps1 participates in centrosome replication and plays a role in cytoplasmic fractionation. Cells in hMps1-siRNA-transfected cells can not complete cytosolic separation and result in the formation of multinucleated cells [16, 26]. Related experiments showed that blocking the degradation of Mps1 can promote the centrosome replication of human cervical cancer cells, whether RPE1 telomerase or RPE1 transfected human embryonic kidney cells, overexpression of GFP-Mps1 is not enough resulting in the replication of these cell centrosomes [27]. The results of gene expression analysis showed that the expression of Mps1 mRNA in malignant tumors was significantly higher than its corresponding normal cells and tissues and was a tumor-related gene. Meanwhile, protein analysis and immunohistochemistry showed that the expression of Mps1 at the protein level was also significantly Tumor-related [28-30]. This correlation is also associated with the malignancy of the tumor and its expression is significantly increased in malignant cells [31].1 At present, although the application of high-dose non-targeted chemotherapy drugs in cancer therapy has achieved good results, the serious side effects and drug resistance caused by the treatment often result in the failure of treatment. Gene-targeted therapy based on Mps1 has been previously reported in foreign countries. Its main theoretical basis is to reduce the expression of Mps1 in tumor cells by siRNA, resulting in the wrong accumulation of mitosis of tumor cells without affecting the normal cells Activity [32]. However, the cell cycle is mainly regulated by a number of checkpoint regulatory pathways. These checkpoints are specifically dysregulated in tumor cells and have the potential to be potential targets for the design of selective treatment of tumor cells [33-35], Mps1 inhibitors BAY1161909 and BAY1217389 combined with paclitaxel, low doses of Mps1 inhibitors can arrest mitosis by reducing the amount of paclitaxel used by reducing SAC activity [34].

**The research for the treatment of osteosarcoma with Mps1**

Osteosarcoma from the interosseous leaf tissue, is a primary malignant bone tumor, the proliferation of bone tumor cells to form immature bone or bone-like tissue, the incidence of about 0.3/million, accounting for 15% of primary bone tumors, Hematogenous metastasis occurs early and the incidence is high, rapid progress, the lungs are the most common, the earliest involvement of metastatic organs [36]. Typical osteosarcoma occurs mainly in young men and women aged 8-25 years old; limb long bones, such as the distal femur, proximal tibia, proxi-
mal humerus osteosarcoma is the best site. Before the 1970s, osteosarcoma was mainly treated by surgical amputation. However, most patients had metastases at the time of diagnosis. The average time from surgical intervention to pulmonary metastasis was 8 months. The overall five-year survival rate was low, with high mortality within 1 year after diagnosis [21]. In recent years, with the application of anti-tumor chemotherapy drugs, surgical techniques, bone reconstruction and other treatment ideas, the limb salvage therapy has gradually replaced amputation treatment, limb salvage surgery has become the preferred treatment of patients. The overall annual survival rate has increased from 20% to 55% -75% [22]. The latest research shows that in the recent decade, the five-year overall survival rate of our patients with osteosarcoma averaged 64%. The five-year disease-free survival rate was 56% on average [23]. However, Mps1 plays a crucial role in the late stage of mitosis in eukaryotes, and it has been confirmed that it is highly expressed in tumor cells such as breast cancer, cervical cancer and gastric cancer, and has statistical significance compared with normal cells [34].

The relevant literature shows that Mps1 checkpoint mechanism in the study of osteosarcoma is still less. Numerous treatments in recent years have suggested strategies for targeting the cell cycle in osteosarcoma. However, the existing drugs are not specifically targeted and have the cytotoxicity of non-malignant cells while being treated. Therefore, the next generation of anti-mitotic therapies for osteosarcoma will need to address not only the cell cycle, but more importantly, osteosarcoma-specific, targeted genetic traits that are specific to tumor cells in order to ameliorate the treatment of anti-mitotic oncology drugs toxic side effect. With the rapid progress of related science such as oncology and cell biology, it has laid a good foundation for the exploration and research of osteosarcoma.

Based on this study, we can further explore whether Mps1 expression in osteosarcoma typical cell lines (MG63, U2OS, KHOS, KRIB) and normal osteoblasts. Experimental data demonstrate that a non-biodegradable Mps1 allele is expressed in the U2OS osteosarcoma cell line, the U20S osteosarcoma cell line is centrosome-replicating and the inertly catalyzed Mps1 blocks centrosome replication while the wild Mps1 accelerates cellular centrosome replication of U2OS [30]. This clear difference in the expression of Mps1 in osteosarcoma cell lines can prompt us to explore the mechanism of Mps1 in the occurrence, development and metastasis of osteosarcoma.

**Conclusions and prospects**

Currently, research on osteosarcoma has shifted to molecular and genetic levels [37, 38]. Tumor invasion and metastasis is a multi-link, multi-step pathological process consisting of a combination of factors, involving a series of genetic and molecular changes in regulation, high metastatic potential of osteosarcoma cells need to find suitable for infiltration, colonization and...
cloning of proliferation through Regulatory cloning and detection of false mitotic inhibition of osteosarcoma metastasis may be more advantages in the treatment of osteosarcoma. Our previous experiments found that Mps1 in osteosarcoma tissue was significantly higher than that in normal group. Further studies showed that Mps1 was highly expressed in various osteosarcoma cell lines [34]. However, the specific mechanism of action in osteosarcoma remains unclear. Therefore, we explore the mechanism of Mps1 in the occurrence, development and metastasis of osteosarcoma on the basis of which we hope to find a new target for the treatment of osteosarcoma and the inhibition of metastasis Hope. In the future, we can use gene knockout, Mps1 inhibitors and low doses of chemotherapy drugs to target kill osteosarcoma cells and retain normal cells in order to make a breakthrough in the treatment of osteosarcoma.

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References


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