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THE ROLE OF MICRORNA-186 IN UROGENITAL TUMORS

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Abstract: MicroRNA (miR) is involved in carcinogenesis and the development of human cancers. A large number of studies have been conducted on the expression of miR-186 in various cancers, including genitourinary system tumors. The results show that miR-186 affects various aspects of tumors. This biological process can be used as a marker for the diagnosis and prognosis assessment of genitourinary system tumors. This article reviews the research progress of miR-186 in urogenital tumors.
Keywords: Genitourinary system tumors; MICRORNA-186; Tumor biology

1 EXPRESSION AND CLINICAL SIGNIFICANCE OF MIR-186 IN GENITOURINARY SYSTEM TUMORS

MicroRNA (miR) is a non-coding small RNA composed of 18 to 24 nucleotides. It recognizes and binds to the 3' UTR of the target gene mRNA, causing translation inhibition of the mRNA, thereby regulating genes at the post-transcriptional level. MiR regulates various biological networks such as target genes and protein interactions, which are intertwined to form a complex regulatory system. It plays an important role in tumor occurrence and development and is widely involved in the regulation of gene expression during tumor invasion and migration [1]. Among a large number of cancer-related miRs, miR-186 has attracted much attention recently. Human miR-186 is located on chromosome band 1q31.1, and studies have shown that miR-186 can play a tumorigenic or tumor suppressive role in genitourinary system tumors [1-2].

1.1 Expression of miR-186 in Urogenital Tumors

The expression of miR-186 in various cancers has been widely studied, including up-regulation and down-regulation patterns. Decreased expression of miR-186 has been confirmed in urogenital tumors, including renal cell carcinoma, ovarian cancer, and cervical cancer [2-5]; however, miR-186 is overexpressed in endometrial cancer (EMC) [6]. In addition, both low and overexpression of miR-186 have been reported in bladder cancer and prostate cancer [7-14].

1.2 miR-186 as a Non-Invasive Marker for Tumor Diagnosis

Circulating miR-186 is dysregulated in urogenital tumors. Serum miR-186 is significantly upregulated in patients with prostate cancer [14], and the expression levels of miR-186 in the blood and urine of patients with bladder cancer are decreased [7]. In the serum samples of EMC patients, the expression of four miRNAs including miR-186, miR-222, miR-223 and miR-204 was up-regulated [15]. Among these miRNAs, miR-186 has the highest sensitivity and specificity for distinguishing EMC patients from healthy individuals.

1.1 The Evaluation Value of miR-186 in Tumor Prognosis

The difference in expression of miR-186 in tumors may be related to survival prognosis. In patients with non-small cell lung cancer, the expression level of miR-186 in tumor tissue is negatively correlated with tumor stage and lymph node metastasis, and the downregulation of miR-186 predicts poor survival of patients [16]. There are few reports on the expression of miR-186 in patients with genitourinary system tumors. Zhu et al. [17] reported that chemotherapy-resistant ovarian cancer patients have down-regulated expression of miR-186, and high expression of miR-186 indicates that their progression-free survival is longer. long.

2 BIOLOGICAL ROLE OF MIR-186 IN GENITOURINARY SYSTEM TUMORS

2.1 Proliferation and Apoptosis

The imbalance between cell proliferation and apoptosis is a possible cause of cancer, and miR-186 affects cell proliferation and apoptosis in various urogenital tumors. In renal cell carcinoma, miR-186 inhibits cell proliferation and induces apoptosis by targeting SENP1 [2]. In bladder cancer, miR-186 inhibits bladder cancer cell proliferation by reducing MEAL expression [9]. In addition, miR-186 may also exert its anti-proliferative effect in bladder cancer through NSBP1 [8]. Studies have shown that miR-186 inhibits cell proliferation in prostate cancer through negative regulation of important oncogenes YY1 and GOLPH3 [12-13]. On the contrary, other studies have shown that miR-186 may promote prostate cancer cell proliferation by reducing AKAP12 [14]. In ovarian cancer, miR-186 acts as a tumor suppressor to inhibit cell proliferation [18]. In addition, miR-186 can also promote the apoptosis of ovarian cancer cells by inhibiting Twist1 [17]. In EMC, overexpressed miR-186 works synergistically with other miRNAs to inhibit the expression of FOXO1 and impair the apoptotic response, thereby inhibiting apoptosis [6]. In cervical cancer, miR-186 inhibits cell proliferation and promotes cell apoptosis by down-regulating Kazrin F [5].

2.2 Migration and Invasion

Metastasis, as a distinctive feature of malignant tumors, is the main cause of cancer-related death. Enhanced migration and invasion abilities facilitate the spread of primary tumor cells, leading to metastasis. Cancer cells can acquire the ability to invade and metastasize through the process of epithelial-to-mesenchymal transition (EMT). Many studies have shown that miR-186 is an inhibitor of EMT. In bladder cancer, miR-186 reverses EMT by inhibiting NSBP1 to limit cell migration and invasion [8]. In cervical cancer, miR-186 induces Kazrin F to down-regulate the expression of EMT-related molecules and inhibit cell migration and invasion [5]. miR-186 reverses EMT in ovarian cancer cells by directly targeting PIK3R3, ultimately inhibiting cell migration and invasion [3].

In addition to the EMT process, cancer metastasis also involves multiple signaling pathways. Abnormal activation of the nuclear factor κB pathway regulates the biological behavior of various tumors. As transcription factors, members of the nuclear factor κB family promote and maintain the aggressive phenotype of various tumors by regulating EMT markers [19]. In renal cell carcinoma, miR-186 targets SENP1 to inhibit the nuclear factor κB pathway, resulting in downregulation of matrix metalloproteinase 9 and inhibition of tumor invasion [2]. Regarding prostate cancer, inhibition of miR-186 significantly reduced the invasive ability of cells.

2.3 Cell Cycle

Abnormal cell cycle progression is closely related to excessive proliferation of cancer cells. Therefore, cell cycle blockade provides a new direction for cancer treatment. miR-186 may affect cell cycle progression by regulating G1-S transition. p21Clip1 and p27Kip1 are two important protein-dependent kinase inhibitors that negatively regulate G1-S transition. In prostate cancer, miR-186 upregulated the expression of p21Clip1 and p27Kip1, whereas the expression of cyclin D1 and cyclin-dependent kinase 6 and the phosphorylation of Rb protein were inhibited. Therefore, miR-186 regulates G0/G1 arrest. In addition, G1-S transition block in prostate cancer cells may be due to the inhibition of GOLPH3 by miR-186 [13]. Twist1 is a classic EMT inducer. In addition to participating in cell proliferation and EMT processes, it also promotes G1-S transition. In ovarian cancer cells, miR-186 induces Twist1 down-regulation leading to G0/G1 phase arrest [17].

In addition to its inhibitory effect, miR-186 can also act as a positive regulator of G1 -S transition. In bladder cancer, miR-186 inhibits the expression of protein phosphatase 1B, and the downregulation of protein phosphatase 1B inhibits the expression of p21Clip1 and p27Kip1, and induces the expression of cyclin D1, resulting in Rb protein phosphorylation. Finally, the phosphorylation of Rb protein promotes the G1-S transition and proliferation of bladder cancer cells [10]. In EMC, FOXO1 negatively regulates p27Kip1 and causes G0/G1 arrest. However, miR-186 cooperates with other overexpressed miRNAs to weaken the G0/G1 blocking effect regulated by FOXO1 in EMC cells [6].

2.4 Chemotherapy Resistance

Chemotherapy resistance is one of the biggest obstacles to treating cancer, and effective therapies to reverse cancer resistance are still being explored. The involvement of miR-186 in chemotherapy of genitourinary tumors has been observed in a series of studies. The EMT phenotype is associated with reduced expression of miR-186, chemotherapy resistance, and poor prognosis in ovarian cancer patients. Overexpression of miR-186 reverses the EMT phenotype and induces apoptosis, thereby enhancing the sensitivity of ovarian cancer cells to cisplatin. Specifically, the reversal of EMT and chemotherapy resistance in ovarian cancer depends on the inhibition of Twist1 by miR-186 [17]. In addition to Twist1, other signaling molecules may also be involved in the regulation of miR-186 on chemotherapy resistance in ovarian cancer. The research results of Sun et al. [20] showed that miR-186 may re-sensitize ovarian cancer cells to cisplatin and paclitaxel by inducing apoptosis. MiR-186 directly targets ABCB1 and GST-π to regulate the reversal of chemotherapy resistance of ovarian cancer cells..

2.5 Angiogenesis and Lymphangiogenesis

Angiogenesis is an important hallmark of cancer progression, and lymphangiogenesis plays a crucial role in the metastasis of cancer cells to regional lymph nodes. Current studies have confirmed that miR-186 is involved in tumor angiogenesis and lymphangiogenesis. In prostate cancer, the prostaglandin E synthase 1 (PGES-1)/prostaglandin E2 (PGE-2) pathway promotes tumor angiogenesis through the induction of vascular endothelial growth factor (VEGF). Overexpression of miR-186 eliminates PGES-1/PGE-2-mediated new blood vessel formation by targeting VEGF, resulting in prostate cancer growth inhibition [21]. In addition to VEGF, miR-186 can inhibit angiogenesis in cancer by targeting other molecules. miR-186 can inhibit angiogenesis in ovarian cancer, but the specific mechanism is currently unclear [18].

2.6 Glycolysis

Cancer cells mainly rely on glycolysis to meet the energy requirements for proliferation and migration. This characteristic metabolic alteration in proliferative tumors is due to a hypoxic microenvironment caused by insufficient vascularization. A key mediator of cancer cells in a hypoxic microenvironment is hypoxia-inducible factor 1 (HIF-1).

As glycolysis increases in cancer cells, HIF-1 expression increases, enhancing the synthesis of glucose transporters and glycolytic enzymes. Current studies have shown that miR-186 plays a tumor suppressive role by interfering with glycolysis. In osteosarcoma cells, miR-186-mediated downregulation of HIF-1α was accompanied by a decrease in intracellular glucose and lactate levels, indicating that miR-186 may inhibit glycolysis by inhibiting HIF-1α [22]. Although HIF-1α signaling is closely related to various genitourinary tumors such as renal cancer and prostate cancer, there are currently no reports of miR-186 regulating glycolysis through HIF-1.

3 FACTORS REGULATING MIR-186 EXPRESSION IN UROGENITAL TUMORS

3.1 Long Non-Coding RNA (lncRNA)

A variety of lncRNAs are involved in the regulation of miR-186 in genitourinary system tumors. Among such lncRNAs, lncRNA PVT1 has attracted much attention. lncRNA PVT1 promotes EMT in prostate cancer by inhibiting miR-186 and upregulating Twist1 [11]. lncRNA HOXD-AS1 can directly bind to miR-186, induce the expression of PIK3R3 and promote EMT of ovarian cancer [3]. In cervical cancer, miR-186 is negatively regulated by lncRNA ANRIL [4]. 3.2 Resistin Resistin is a pro-inflammatory cytokine secreted by adipocytes and monocytes. In addition to its key role in inflammation-related diseases, resistin is also involved in the development of cancer. The chemoresistance-inducing function of resistin in ovarian cancer may be caused by the inhibition of miR-186 [18].

4 SUMMARY AND OUTLOOK

Current research shows that miR-186 is widely involved in the occurrence and development of genitourinary system tumors. miR-186 is expressed differently in different types of tumors. The dysregulation of miR-186 in patients' blood, urine, and feces makes miR-186 a non-invasive It is possible to diagnose cancer with a sexual method, and the expression of miR-186 in tissue and plasma can also be used to predict the survival of tumor patients. The biological functions of miR-186 in genitourinary tumors involve multiple cellular processes, including proliferation, apoptosis, migration, invasion, cell cycle regulation, and intracellular metabolism. In addition, miR-186 is also involved in tumor angiogenesis and lymphangiogenesis, as well as the response of cancer cells to chemotherapy. By regulating miR-186, lncRNA and resistin are involved in the occurrence and development of urogenital tumors. Nonetheless, the expression of miR-186 in bladder and prostate cancer remains controversial. Furthermore, the effects of miR-186 on various cellular processes and the complex regulatory network targeting miR-186 are still not fully understood. Current research focuses on the identification of miRNA as a diagnostic and prognostic marker. There are still few studies on the use of miRNA as a gene therapy for cancer. Before implementing miR-186 targeted gene therapy for cancer, its safety and effectiveness should be further determined. sex. In summary, miR-186 is an important factor in the occurrence and development of genitourinary system tumors and can be further studied as a new target for the treatment of urogenital system tumors.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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