ISSN: 2637-6067 DOI: 10.6918/IJOSSER.202108_4(8).0039

Research Progress of Smac and XIAP of Endometrial Carcinoma

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Abstract

Endometrial carcinoma (EC) is a common malignant tumor in gynecology. For the early detection of endometrial carcinoma, the prognosis is relatively good. However, for advanced endometrial cancer, recurrent endometrial cancer and special types of endometrial cancer, the treatment effect is not good, the prognosis is still not ideal, there is an urgent need for other treatments to prolong the survival time. There is apoptosis escape due to the malignant proliferation of many kinds of tumor cells. Therefore, starting from the pathways involved in apoptosis signal transduction, targeted regulation of apoptosis is a hot field of tumor research. As an important member of apoptosis pathway, second mitochondria-derived activator of caspases (Smac), X-linked inhibitor of apoptosis protein (XIAP) plays an important role in the process of apoptosis and is a research hotspot of targeted therapy. This article reviews the new progress in basic research and clinical trials of endometrial carcinoma in recent years.

Keywords

Endometrial carcinoma; Apoptosis; Targeted therapy; Smac; XIAP.

1. Introduction

Endometrial carcinoma (EC) is an epithelial tumor caused by malignant transformation of the endometrium. It is reported that the incidence of endometrial carcinoma has reached the fourth place in developed countries [1], of which 3/4 are women over 50 years old. The China National Cancer Center reported that in recent years, due to changes in people's lifestyle and diet, as well as the unconscious accumulation of hormone foods and drugs in the body, the prevalence rate of EC is rising every year and getting younger, seriously affecting the life expectancy of older women and the reproductive health of women of childbearing age. Families and society are under great pressure and burden for this [2]. The etiology of EC is not very clear. The differential expression of many genes and transcription, the abnormal regulation of cellular signal transduction pathway and the loss of homeostasis of cell microenvironment may lead to the occurrence and development of EC. Normal endometrial epithelial cells are closely related to a variety of gene proteins and multiple signal transduction pathways in the evolution of atypical hyperplasia and even malignant tumor and further invasion and metastasis. The interaction between them is complex, and they play an important role in carcinogenesis or inhibition of cancer. In-depth study of the signal transduction pathway and gene protein expression in the process of endometrial malignant transformation, invasion and metastasis, and explore the mechanism of this process may provide some scientific theoretical basis for the study of EC molecular targeted therapy.

2. Overview of Apoptotic Pathway

Apoptosis is a programmed death of cells under the regulation of genes, which is indispensable to the body. The mechanism of apoptosis is highly conserved. Various signals that induce apoptosis act on cells. After a series of regulation, most of them are activated by induced

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cascade of caspase (Caspase), resulting in programmed degradation of DNA, nuclear pyknosis, fragmentation and other apoptotic manifestations. According to the different initiation stages of apoptosis, different apoptotic pathways can be divided into: 1. Apoptosis pathway involved in mitochondria: as the energy supply of cells, mitochondria is closely related to apoptosis. Apoptosis caused directly by affecting the structure and function of mitochondria is called endogenous pathway. In this pathway, the pro-apoptotic protein binds to the anti-apoptotic protein Bcl-2, antagonizes the anti-apoptotic function, and makes the mitochondrial outer membrane permeate, resulting in the release of cytochrome C (Cyt-c), apoptosis-inducing factor (AIF) and the second mitochondrial activating factor (Smac) of cysteine protease, leading to cell apoptosis. Among them, Smac induces IAPs inactivation and apoptosis by directly binding to the inhibitor of apoptosis protein (IAPs). At present, the regulatory mechanism of this pathway is not completely clear, and the release of mitochondrial proteins is also the key to the study of mitochondrial pathway regulating apoptosis.2. Death receptor-mediated apoptosis pathway: apoptosis signal is directly transmitted to the cell membrane, combined with a specific death receptor and then directly transmitted to the cell to initiate apoptosis, also known as exogenous pathway [3]. And the internal and external pathways are interconnected and interact with each other, which can promote apoptosis together. 3. Endoplasmic reticulum-mediated apoptosis: endoplasmic reticulum (ER), as the main "repository" of intracellular calcium, is a protein quality control system dependent on protein chaperone. Protein chaperones can quickly identify and identify misfolded proteins and help them fold correctly. If the folding process fails, the misfolded proteins will accumulate in the ER cavity, called "ER stress". When there is calcium imbalance in ER or protein accumulation in ER, Caspase-12, will be expressed on the ER membrane and activated by Caspase-7 moved from the cytoplasm, and the activated Caspase-12 further activates Caspase-3, and causes apoptosis. 4. Perforin / granzyme pathway: completed by cytotoxic T cells, which establishes a transmembrane pathway with target cells by secreting perforin, and then granzyme An or B enters the cell and induces apoptosis. Granzyme A can destroy the Caspase-independent apoptosis pathway activated by single-stranded DNA,. Granzyme B can hydrolyze the aspartic acid residue of pro-Caspase-10 and activate it into Caspase-10. At the same time, granzyme B can also use the mitochondrial apoptosis pathway to specifically cleave Bid, and further induce the release of Cyt-c in the mitochondria to amplify the cell death signal. secondly, it can also activate Caspase-3 and completely bypass the upstream signal transduction pathway and directly enter the executive stage of inducing cell apoptosis [4]. From the above apoptosis pathway, we can see that apoptosis is the result of the participation of multiple pathways, and the error of any link may lead to the error of apoptosis and induce the occurrence of tumor.

3. The Overview of Smac

Smac/DIABLO protein was found separately by Du and Verhagen and published in Cells magazine in 2000. The two proteins were identified as the same protein by sequence comparison. Human Smac gene is encoded at 12q24.31, which plays a biological role in the release of Smac protein from mitochondria into cytoplasm under the action of apoptosis-inducing factors from 122692209 to 122712068 [5]. At present, it is believed that the pro-apoptotic effect of Smac is mainly achieved by binding to the baculoviral IAP repeat, (BIR) structure of IAPs baculovirus to promote the release of Caspases, which has a high affinity [6]. Haplotype Smac protein can only block one BIR structure, while in dimer state, Smac can bind to the BIR-2 and BIR-3 domains of X-linked apoptotic protein at the same time, effectively relieving the inhibition of XIAP on Caspase. So as to exert the biological activity of promoting apoptosis [7]. The main active structure of Smac is the four residues of N-terminal [8]. Some scholars think that [9] the N-terminal is the functional region and the C-terminal is the auxiliary region.

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4. Smac and Endometrial Carcinoma

The important regulatory function of Smac in apoptosis has led to the study of its expression in different cancers and the relationship between clinicopathological factors and prognosis. Feng Haili et al detected the relative expression of SmacmRNA in EC tissues and normal tissues adjacent to cancer by RT-qPCR method, and found that the expression of SmacmRNA in EC tissues was significantly lower than that in adjacent normal tissues, and the relative expression of SmacmRNA decreased with the increase of clinical stage, decreased degree of differentiation, increased depth of myometrial invasion and lymph node metastasis of EC [10]. Wang Xiaohua [11] detected the expression of Smac in endometrial carcinoma, atypical hyperplasia and normal endometrium by fluorescence quantitative PCR, and found that the expression of Smac in endometrial carcinoma, atypical hyperplasia and normal endometrium was significantly lower than that in the latter two groups. By analyzing the relationship between the relative expression and the clinicopathological features of EC, it was found that the relative expression was not related to myometrial invasion, but the others were consistent with Feng Haili [10]. It is suggested that Smac may be involved in the invasion and metastasis of endometrial adenocarcinoma.

5. Research Status of Smac Simulations

Because Smac interacts with IAPs and antagonizes the anti-apoptotic activity of IAPs in cells, leading to apoptosis, a mimic with similar N-terminal structure of Smac has been developed. Its application is considered to be the first Smac mimic compound containing 8 amino acids in cancer in 2000 [12]. At present, eight Smac mimics have been developed and their anticancer activities have been evaluated in different preclinical and clinical studies. Smac mimics are divided into two categories according to the number of Smac mimic groups. One is a monovalent compound that contains a Smac mimic part. The second is a bivalent compound, which is a Smac simulation element connected by a joint. Among them, the anticancer activities of 6 compounds have been confirmed in clinical trials, and the anticancer activities of bivalent compounds are high, and their representatives have carried out a number of clinical phase I and phase II experiments, respectively. its anticancer effect has also been confirmed in cervical cancer, oral squamous cell carcinoma, liver cancer, sarcoma, leukemia and other cancer cells [13]. And Mrkvov á Z [14] et al used tumor necrosis factor-α and Smac mimics in drug-resistant cells by knocking out the death domain of Fas-related proteins or all cysteine aspartate proteases: LCL161, found that this drug resistance could be reversed. It is suggested that the combined application of tumor necrosis factor-α and Smac mimics can reduce the drug resistance of tumor cells. It can be seen that Smac mimics may play a role in the treatment of endometrial adenocarcinoma. Potential treatments.

6. The Overview of XIAP

IAPs was first discovered by Crook in 1993 and attracted much attention because of its ability to inhibit virus-induced apoptosis and allow virus proliferation. There are 8 kinds of human IAPs. What they have in common is that the N-terminal has one to three BIR domains, and in addition to NAIP, Survivin and Bruce, they all have a ring finger structure (RING domain) at the C-terminal. XIAP, expressed in most adult tissues, can directly regulate apoptosis by binding to Caspases-3,-7 and-9. It belongs to the most potent IAPs family protein. XIAP gene encodes 497 amino acids in Xq25,. Its characteristic domain is BIR domain and RING domain. Its N-terminal is connected by three cysteines and one histidine, and is divided into three domains: BIR1, BIR2 and BIR3. These three domains are the basic structures in which XIAP plays a role. They resist apoptosis by affecting the interaction between DNA and protein and between protein and

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protein. There is a bridge between BIR structures, Linker, which can directly bind to Caspase and inhibit its activation and apoptosis. The RING domain composed of 3 cystine and 1 histidine at the XIAPC- terminal, or 4 cystine and 1 zinc atom has UbE3 activity, which can ubiquitinate the target protein and block apoptosis [15]. IAPs is the only known family of endogenous Caspases inhibitors. Among them, XIAP is the most specific and effective inhibitor of Caspases apoptosis.

7. XIAP and Endometrial Carcinoma

As the most effective Caspase inhibitor in the IAPs family, XIAP has been widely studied. Celine [16] et al found that XIAP is highly expressed in endometrial carcinoma epithelial cells cultured in vitro, so it is speculated that the high expression of XIAP is related to endometrial carcinoma. Feng Haili [17] used RT-qPCR to detect the expression of XIAPmRNA in endometrial carcinoma and adjacent normal tissues. It was found that the relative expression in endometrial carcinoma was significantly higher than that in adjacent normal tissues. In endometrial carcinoma, the higher the clinical stage, the lower the degree of differentiation, the deeper the depth of myometrial invasion and the positive lymph node metastasis, the higher the expression rate. It is suggested that the high expression of XIAP may promote the occurrence and development of endometrial adenocarcinoma and accelerate the invasion and metastasis of endometrial adenocarcinoma.

8. Research status of Anti-tumor Targeted Therapy of XIAP

So far, XIAP is considered to be the most effective anti-apoptosis factor in existence, and it plays an important role in preventing cell death. More and more studies have taken XIAP as the target of anti-tumor therapy. At present, the main research directions of tumor inhibition through XIAP are focused on the following three aspects: small molecule inhibitors, antisense oligonucleotide inhibitors (Antisenseoligonucleotideinhibitors, AON) and XIAP gene silencing [18]. Among them, small molecular inhibitors play an anti-apoptotic effect by binding to the BIR or RING domain of XIAP. At present, most of the researches are Smac simulations, ARTS simulations and so on. AON is a synthetic target sequence that specifically binds to the DNA or mRNA of XIAP to inhibit the expression of XIAP, which is regulated at the genetic level to achieve the purpose of tumor suppression. XIAP gene silencing is the use of RNA interference technology to silence XIAP gene, so as to reverse the drug resistance caused by XIAP mutation, increase the sensitivity to chemotherapy, and improve the prognosis of patients [19].

9. Prospect

The treatment of endometrial cancer often has different treatment options according to the patients' pathological type, metastasis and their own status, including standard surgical treatment, postoperative supplementary radiotherapy, chemotherapy and hormone therapy. Most of the chemotherapeutic drugs are based on platinum, but the drug resistance of chemotherapeutic drugs leads to the increase of treatment failure rate. In order to improve the quality of life and survival time of patients with metastatic and recurrent endometrial cancer, targeted therapy has been paid more and more attention and research. A number of experimental studies suggest that Smac and XIAP are involved in the occurrence and development of endometrial carcinoma. at present, the study of Smac mimics has entered the clinical phase I and II trials, while the research on XIAP as the therapeutic target is relatively diversified and various methods. based on the study of targeted therapy based on these molecular typing, the therapeutic efficacy of advanced endometrial carcinoma, recurrent

ISSN: 2637-6067 DOI: 10.6918/IJOSSER.202108_4(8).0039

endometrial carcinoma and special types of endometrial carcinoma is expected to be further improved. And achieve accurate medical goals more quickly.

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ISSN: 2637-6067 DOI: 10.6918/IJOSSER.202108_4(8).0039

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