The role of the cancer stem cell marker USP22 in tumors

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Ubiquitin specific peptidase 22 (USP22) is one of the 11 known death-from-cancer signature genes. USP22 is also considered a cancer stem cell marker and is highly expressed in a variety of tumor types. USP22 alters the expression of tumor-associated genes (e.g., proto-oncogenes and tumor suppressor genes) and promotes tumor cell proliferation, invasion and metastasis via the modification of cell cycle activity and the activation of a variety of signaling pathways. In patients with tumors, USP22 expression is related to lymphatic metastasis, clinical stage of tumors, survival rate and a number of other factors. In addition, USP22 is considered an indicator of a poor prognosis and thus may be used to evaluate the prognosis of patients with tumors. As a potential cancer stem cell marker, USP22 may serve as a novel target for tumor therapies. Finally, USP22 also plays an important role in tumor development and progression.

Keywords: USP22; stem cell; biological functions; tumor prognosis and treatment

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The basic biological characteristics of USP22

The ubiquitin-proteasome pathway is one of the 3 major pathways of protein degradation in organisms. Deubiquitinating enzymes (DUBs) cleave the bonds between ubiquitinated protein substrates and single ubiquitin or polyubiquitin chains. After hydrolysis, the released ubiquitin molecules may be recycled, where they re-enter the cycle of protein regulation [1, 2]. USP22 is a type of deubiquitinating hydrolase. In 2005, Gennadi et al. examined 1153 patients with different types of tumors using mRNA microarray technology and discovered 11 death-from-cancer signature genes that were involved in tumor development and progression. USP22 is one of these death-from-cancer signature genes [3]. A high level of USP22 expression in tumor cells generally indicates a poor prognosis. Therefore, as a recently established cancer stem cell marker, USP22 may serve as a novel target for tumor therapies [4].

In humans, the USP22 gene is located on chromosome 17 (17p11.2) and contains 14 exons. The complementary DNA (cDNA) of the human USP22 gene consists of 1578 bases and encodes a 525-amino acid-long protein with a molecular mass of approximately 60 kDa. The USP22 protein contains a carboxyl-terminal ubiquitin hydrolase domain, which defines the C-19 class of peptidases, and an amino-terminal zinc finger domain. The zinc finger domain is a ubiquitous structural motif that is present in molecules that belong to the family of ubiquitin-specific modification enzymes and serves as the structural basis for the mediation of interactions.
between a molecule and its target protein substrates [5-7]. The USP22 homologs in yeasts, fruit flies and rodents are termed ubiquitin carboxyl-terminal hydrolase 8 (Ubp8), Nonstop and Usp22, respectively, all of which possess biological characteristics similar to human USP22.

As a subunit of the human Spt-Ada-Gcn5-acetyltransferase (hSAGA) complex, USP22 mediates the deubiquitination of histones H2A and H2B [8,9]. The hSAGA complex is a transcriptional cofactor complex that facilitates the docking of the transcription machinery onto the target gene promoter; this cofactor also activates gene transcription through the covalent modification of specific amino acid residues located in histone tails. Under normal circumstances, the H2A deubiquitinating enzyme USP22 is coordinately expressed with ubiquitin ligase, which is conducive to the maintenance of the transcription of certain critical genes in the context of polycomb protein-mediated control of gene expression [10]. Histone ubiquitination is a common post-translational modification of proteins in eukaryotic cells. Histone ubiquitination regulates cell division and differentiation, signal transduction, transcriptional activation, DNA repair and stress responses [11-13]. The imbalance between histone ubiquitination and deubiquitination may induce the activation of proto-oncogenes and may affect the functions of tumor suppressor genes and their products, thereby promoting tumorigenesis.

USP22 expression in normal tissues and tumors

In humans, USP22 is widely distributed in normal tissues. The myocardium, lung, nervous system and reproductive system all express USP22, as do early embryos. However, the expression level of USP22 varies among normal adult tissues. USP22 is moderately expressed in the heart and skeletal muscle, while it is weakly expressed in the lungs and liver [14]. Studies have also shown that the mouse homolog Usp22 is highly expressed in the murine brain. Our unpublished data show that USP22 is expressed in the nuclei of the highly proliferative basal cells in normal colonic mucosal crypts and in the oral mucosa. The expression pattern of USP22 is similar to that of the cell proliferation marker Ki-67, indicating that positive cells display stem cell characteristics. Recent studies have shown that USP22 is highly expressed in a variety of tumor tissues, including cervical cancer [15], colorectal cancer [16], breast cancer [17], oral squamous cell carcinoma [18], thyroid cancer [19], non-small cell lung cancer [20] and liver cancer [21].

The biological functions and roles of USP22 in tumors

Gennadi et al. have identified 11 death-from-cancer signature genes, all of which are able to predict therapy failure, high disease incidence and recurrence after surgical resection in both humans and animal models. It is worth noting that most of the death-from-cancer signature genes are regulated by the polycomb complex protein BMI-1 (B lymphoma Mo-MLV insertion region 1 homolog), which has been associated with stem cell functions in normal tissues and in tumors [22]. Therefore, many believe that death-from-cancer signature genes may be used to identify cancer stem cells [10]. USP22 is highly expressed during tumorigenesis, and the roles of USP22 in tumors include regulation of the cell cycle and alteration of the expression levels of various tumor-related regulatory factors.

USP22 is a positive regulatory factor that promotes the proliferation of tumor cells. The deubiquitinating enzyme activity of USP22 promotes the proliferation of HeLa cervical cancer cells, which has been confirmed using an activity-decreased mutant (Y513C) and an activity-deleted mutant (C185S) [23]. The inhibition of USP22 expression results in the downregulation of SAGA-mediated transcriptional activation [9]. Xu et al. manipulated USP22 protein levels using micro-RNA (miRNA) interference technology. Their results showed that the knock down of the USP22 gene inhibited the proliferation of human colon cancer cells, induced cell cycle arrest in G1 phase, decreased the apoptosis of tumor cells, and downregulated the expression of the major vault protein (MVP) [24]. The silencing of USP22 expression has been achieved in the bladder cancer cell line EJ using asymmetric interfering RNA (aiRNA), resulting in G0/G1 cell cycle arrest. In addition, the silencing of USP22 expression induces the upregulation of p53 and p21 expression through the downregulation of mouse double minute 2 homolog (MDM2), which interrupts the cell cycle in EJ cells and eventually inhibits the proliferation of these human bladder cancer cells [25]. In a study conducted by Ning et al., the enhancement of the localization of β-catenin to the nucleus in pancreatic cancer cells upregulates the expression of forkhead box protein M1 (FoxM1) and promotes the expression of USP22, facilitating entry of these cells into G1/S phase [26].

USP22 affects cellular signaling pathways and regulates the expression of tumor-associated factors. The transcriptional activation function of the proto-oncogene c-Myc and the tumor suppressor function of the p53 gene rely on hSAGA activity. Therefore, the deubiquitinating enzyme activity of USP22 has a major impact on the expression of c-Myc and p53 target genes. In cultured cervical cancer-derived HeLa cells, the deubiquitinating enzyme activity of USP22 is related to the levels of BMI-1, c-Myc, cyclin D2 and p53 [23]. USP22 has also been found to be highly expressed in gastric cancer tissues. In addition, a
synergistic effect has been observed between c-Myc protein expression and USP22 expression in gastric cancer tissues [27]. In another study, USP22 induced the inhibition of BMI-1, which was accompanied by the upregulation of the p16INK4a and p14ARF proteins and the subsequent decrease in the levels of E2F1 and p53 [28]. In addition, treatment of the cells with small interfering RNA against USP22 (USP22-siRNA) resulted in the downregulation of the expression of c-Myc target genes. That particular study states that USP22 may act as an oncogene in human colon cancer cells and may regulate the cell cycle through the following pathways: the BMI-1-mediated INK4a/ARF pathway and the Akt protein kinase signaling pathway. Survivin is a member of the inhibitor of apoptosis (IAP) gene family. Survivin is highly expressed in a variety of cancer tissues and is associated with a poor prognosis [21, 29-32]. Our results show that USP22 regulates the expression of survivin in hepatoma cells, which is likely mediated by BMI-1. In addition, the downregulation of USP22 expression in hepatoma cells leads to a decrease in the level of cyclin B protein and an increase in the level of p21 protein [21]. The literature also shows that USP22 may affect p21 expression via the ubiquitination of FUSE-binding protein 1 (FBP1) [33]. USP22 is capable of reducing the acetylation level of p53 through the removal of polyubiquitin chains from Sirt1 and the subsequent stabilization of Sirt1, inhibiting p53 function [34]. The p38 mitogen-activated protein kinase (MAPK) pathway is an important regulatory mechanism of a variety of cellular responses. Current studies have reported that p38 MAPK acts upstream of USP22 and exerts an inhibitory effect on the transcription of USP22 and its downstream genes through the specificity protein 1 (Sp1)-binding site in USP22. For example, p38 MAPK downregulates BMI-1 and cyclin D1 in a post-transcriptional manner [35].

In summary, the current literature shows that in various tumor cells of different origins, high USP22 expression alters the expression of proto-oncogenes, tumor suppressor genes, cyclins and other tumor-associated proteins (e.g., c-Myc, p53, cyclin B, BMI-1 and survivin) through a variety of pathways. Therefore, it was deduced that USP22 may be a cancer stem cell marker and may promote tumor proliferation and progression. However, complex cell signaling pathways are involved in the process of tumorigenesis. At present, many details remain unclear and require further experimental verification.

**USP22, tumor prognosis and treatment**

USP22 is a novel molecular marker that is used to predict disease progression and patient prognosis. The role of USP22 as a molecular marker has been confirmed by numerous studies. In oral cancer, laryngeal squamous cell carcinoma and hepatocellular carcinoma, high USP22 expression is related to lymph node metastasis and patient prognosis [18, 21, 36]. In patients with stage II pancreatic ductal adenocarcinoma, USP22/FoxM1 expression is related to tumor size, lymph node metastasis and overall survival rate. Moreover, USP22/FoxM1 co-expression is an independent adverse prognostic factor [26]. USP22 promotes the proliferation of cancer cells and enhances the invasiveness of cancer cells in pulmonary adenocarcinoma; additionally, USP22 induces epithelial-mesenchymal transition (EMT) in pulmonary adenocarcinoma cells. In addition, high USP22 expression is associated with a poor prognosis [36]. Because USP22 plays a vital role in tumor cell proliferation, invasion and lymphatic metastasis, the study of the signaling pathways that control USP22 expression and the development of drugs or other strategies that can regulate USP22 expression may have potential clinical significance.

**Conclusions**

USP22 is highly expressed in a variety of tumor types and is one of the known death-from-cancer signature genes. USP22 is a putative cancer stem cell marker. USP22 alters the expression of proto-oncogenes, tumor suppressor genes, cyclins and other tumor-associated molecules. USP22 also promotes tumor cell proliferation, invasion and metastasis via the modulation of cell cycle activity and the activation of a variety of signaling pathways. In addition, USP22 may be used as an independent marker or as a composite factor for the prognostic evaluation of patients with tumors. However, the specific mechanisms of action of USP22 in tumor development and progression are currently unclear. Further experimental studies and clinical observations will be conducive to the clarification of the role of USP22 in tumors and will provide new directions for treatment.

**Conflicting interests**

The authors have declared that no conflict of interests exists.

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**Author contributions**

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