

Research Status of Death Domain-associated Protein

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Abstract. Overexpression of death domain-associated protein (DAXX) is a common feature of many cancers, and it structurally has binding sites for many interactors (eg, ARTX, HDAC3). According to functional studies, DAXX interacts with a number of DNA-binding transcription factors (TFs), epigenetic regulators, core histones, and proteins involved in chromatin to induce apoptosis via the extrinsic death receptor pathway. Functions as a co-activator or transcriptional inhibitor of cobalt dipus to regulate gene expression. Current studies have found that DAXX is expressed upregulated in ovarian cancer. Additionally, research has demonstrated that DAXX increases the tumorigenicity of prostate cancer by preventing autophagy pathways. In contrast, patients with pancreatic neuroendocrine tumors have lower survival rates when their DAXX is lost. A powerful breast tumor-initiating cell (TIC) inhibitor, DAXX also inhibits the production of pluripotent and EMT genes via promoters that may bind to pluripotent TIC-related genes. As a result, DAXX has powerful carcinogenic properties and potential new therapeutic targets. This article will introduce the protein from the aspects of DAXX's structure, function, and relationship with cancer.

Keywords: DAXX, Cancer, PML-NBs, ARTX.

1. Introduction

Due to an aging population, the number of new cancer cases is expected to reach over 30 million by 2040, which will result in a 50% rise in the burden of cancer globally compared to 2020. To lessen the worldwide burden of cancer in the future, preventive and therapeutic cancer interventions are crucial.

Human understanding of tumor pathogenesis has gone through a long process, from single and physical carcinogenic theories, a carcinogenic chemical, carcinogenic viral, and mutation to multifactorial comprehensive carcinogenic theory. The most successful example comes from the study of colon cancer by Vogelstein's laboratory at Johns Hopkins University. They discovered that a number of molecular events are interspersed throughout the multi-stage process of hyperplasia, benign tumor, in situ carcinoma, and invasive carcinoma encountered in colon carcinogenesis. In contrast to the malignant Ras gene mutation and loss of the tumor-suppressor genes P53, the Ras gene mutation and loss of the tumor-suppressor genes APC and DCC were found in adenoma. Loss of heterozygosity in the tumor suppressor gene APC appears to be the first step in the development of colon tumors. Elimination of APCs may occur in germ or somatic cells, resulting in progressively increased benign adenomas. In benign adenomas, one of the cells is often mutated into the Ras oncogene, leading to additional clonal development. Subsequent deletion of tumor suppressor genes CCD and p53 promotes benign-malignant progression. The evolution of adenoma to cancer is also accompanied by DNA damage repair gene mutations and changes in DNA methylation status. Therefore, carcinogenesis of the colon is a multigenic and multi-stage process.

In 1997, a Fas protein called DAXX was first discovered. It controls apoptosis caused by the final enzyme Jun n (JNK). The embryonic development protein DAXX is expressed in bodily tissues. It interacts with a protein that has a variety of functions in the nucleus and the nucleus. DAXX not only interacts with various transcripts, visible gene regulators, major proteomes, and dye-related proteins as an additional means of inhibiting transcription or assisting activation but also proves that dielectrics die with the help of external death receptors. Factors controlling gene expression.

There is ongoing debate concerning DAXX's contribution to the growth of cancer. DAXX is increased in gliomas and ovarian cancer, according to studies.

Studies have also demonstrated that DAXX inhibits the autophagy pathway, which increases the tumorigenicity of prostate cancer. On the other hand, patients with pancreatic neuroendocrine tumors who lost DAXX had lower survival rates. By controlling the epigenetic regulation of membrane metalloendopeptidases, DAXX prevents the development of insulinoma cells. DAXX, a strong TIC inhibitor in breast cancer, may bind to the promoters of genes associated with pluripotency and TIC to reduce the expression of pluripotent and EMT genes. As a result, I believe that depending on the cell type and the environment, DAXX can either promote or hinder the growth of malignant tumors.

This article will introduce the structure of DAXX, its sublocalization in cells, its function, and its changes in cancer.

2. Structure of DAXX

A multifunctional protein with high levels of evolutionary conservation and ubiquitous expression is death domain-associated protein 6. (DAXX). DAXX is widely distributed in both healthy and cancerous cells, including heart, liver, kidney, and 293 and HeLa cell lines. It is also highly conserved in both animals and people. Transcription, cell proliferation, cell cycle regulation, fas-induced apoptosis, among other biological processes, are DAXX-related. The androgen receptor (AR), axin, HDAC1, HDAC2, the tumor suppressor gene p53, Smad4, the paired box gene 3 (Pax3), and other proteins can interact with DAXX. DAXX can interact with a wide variety of molecules to control how many genes that are involved in stress are expressed in stressed cells.

740 amino acids make up human DAXX (hDAXX), which has a molecular weight of 81.3 kDa., while mouse DAXX (mDAXX) is made up of 739 aa. hDAXX and mDAXX have 69 percent of the same amino acid sequence. The hDAXX gene is 315 kb long and has 6 introns in addition to 7 exons. hDAXX has three versions with molecular weights of 70 kDa, 97 kDa, and 120 kDa as a result of post-transcriptional modifications[1].

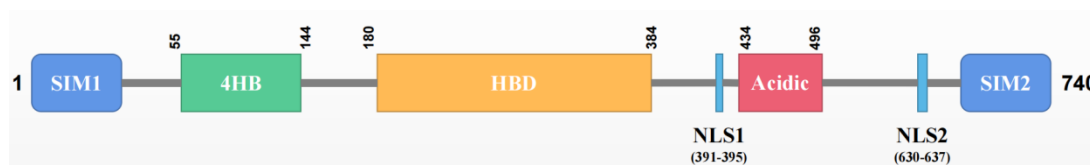


Figure 1. DAXX structure

2.1. DAXX helix beam (4HB)

Two double helix domains, one rich in acidic amino acids and the other rich in serine/proline/threonine, make up the four domains of hDAXX. Due to its four-helical structure, the serine/proline/threonine-rich domain is known as the DAXX helical bundle (DHB) or 4HB(Figure 1). It interacts with DAXX via a number of proteins with well-defined binding sites, including MDM2, RASSF1C, and p53. A portion of the interface between DAXX and RASSF1C is occupied by the binding surface that 4HB and ATRX share. ATRX's DAXX-binding domain forms a lengthy helix close to a significant portion of the hydrophobic residues in DAXX 4HB(Figure 2、 Figure 3) [2].

Promyelocytic leukemia nucleosomes (PML-NBs), which are abundant in certain proteins, separated from their surroundings, and reside in the liquid phase, are an example of intracellular membraneless entities that frequently include DAXX. In addition to being in PML-NBs, DAXX also associates with SPOP to produce a phase-separated nucleus that promotes the engagement of DAXX with certain proteins.

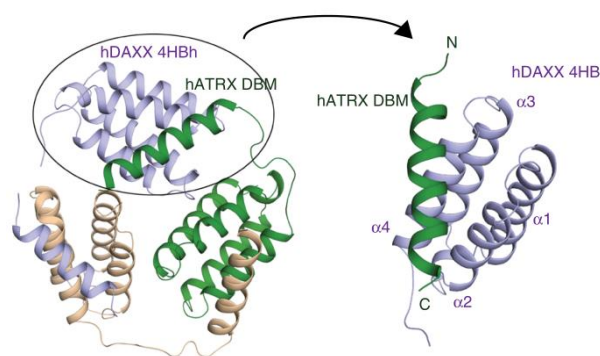


Figure 2. Depicts the intramolecular interaction between each monomer and the synthetic trimer of the hDAXX 4HB-hATRAX DBM fusion protein (left). Ribbon view of hDAXX 4HB connected to hATRAX DBM, displaying its 2 and 4 helices (right).

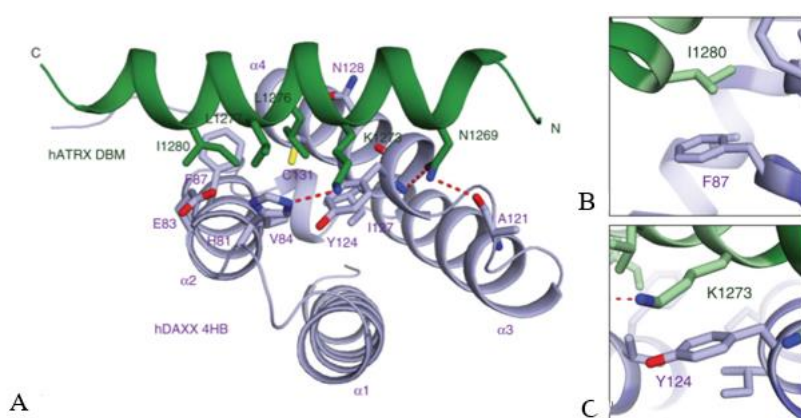


Figure 3. A、 B and C increase the contact between F87 in hDAXX 4HB and I1280 in hATRAX DBM, and between Y124 in hDAXX 4HB and K1273 in hATRAX DBM, respectively.

2.2. DAXX histone binding domain (HBD)

The DAXX core region is the portion of the index between 180 and 397. The H3.3/H4 dimer can interact with the core domain, commonly referred to as the histone binding domain (HBD)(Figure 1). The fundamental proteins that bind with DNA that are found in the nucleus of all eukaryotes are referred to as "histones." Genes for histones are highly conserved. The H2A, H2B, H3, and H4 amino acid sequences are remarkably similar in species that are not closely related to one another.

Six helical structures wrap and occupy 40% of the surface of the H3.3/H4 dimer in the HBD. The binding specificity of the H4 dimer determinant is crucial for the binding specificity of DAXX to the H3.3/H4 dimer, according to structural models and biochemical investigations. The HBDs of DAXX can only form stable structures in the core environment, according to structural modeling, and only with H3.3/H4 dimers, not with H3.3/H4 tetramers. creates stable structures that H3.3/H4 cannot employ to bind dimers. The chromatin remodelers ATRX and BRG1, both of which bind DAXX in the cellular environment, may be necessary for the H3.3/H4 dimer to function. The phrase "chromosome remodeling" refers to the molecular process that changes the packaging state of chromatin, histones in nucleosomes, and related DNA molecules during gene expression replication and recombination. H3.3 is deposited by the DAXX/ATRX complex in areas of heterochromatin with high amounts of H3K9me3 and simple GT-rich nucleotide repeats, despite the fact that H3.3 deposition is linked to active transcription. Only the HBD itself is significantly disordered in solution, despite the fact that the H3.3/H4 dimer and the six helices of the DAXX HBD work together to generate a stable structure. The stability and folding of all three of the H3.3/H4-DAXX HBD ternary complex's subunits are known to be influenced by this complex.

2.3. Acidic domain of DAXX

Near the c-terminal of HBD, DAXX has a long region of roughly 50 consecutively acidic residues (Figure 1). This acidic region is crucial for interacting with p53's lysine-rich c-terminal regulatory domain (CTD). While the acetylation of p53 CTD reduces its interaction with transcriptional inhibitors of acidic domains like DAXX, the DAXX acidic domain is crucial to DAXX-mediated gene repression. It is significant to note that whereas the sequences of the various histone chaperones are nearly never similar, they frequently contain intrinsically disordered and acidic areas. Further study is required to understand how the DAXX acidic domain increases its histone chaperone activity and other functions.

2.4. DAXX's NLS1 and NLS2

Aa sequences at residues 391-395 in DAXX make up the first NLS (NLS1), which Percy Luk Yeung et al. have shown is in charge of the nuclear localization of the n-terminal domain. The second major NLS (NLS2) is made up of the aa sequence PAKKSRKEKK at residues 627–633, and it is crucial for mediating the nuclear introduction of DAXX (Figure 1).

Percy Luk Yeung et al. research demonstrates that importin-3 directly interacts with the NLS1 and NLS2 regions of DAXX. Importin-3 may physically attach to DAXX in the cytoplasm, interact with Importin B there, and then pass through the nuclear pore to reach the nuclear cytoplasm via a Ran-GTP-dependent transport pathway [1].

3. Subcellular localization of DAXX

DAXX was initially screened by yeast double hybridization with the death region of the Fas receptor as bait and found that it connected the Fas signal to the JNK (c-Jun n-terminal kinase) pathway in the cytoplasm via ASK1. Recently, a growing body of research has shown that DAXX has been found to play the role of transcriptional co-inhibitors in the nuclear chamber, mainly through interactions with transcription factors and other nuclear factors.

3.1. PML-NBs positioning

In PML-NB, there are two proteins: DAXX and PML modified by small ubiquitin-like modifier 1 (SUMO1). The first reports of the ubiquitin-like protein modifying molecules SUMO1 and SUMOylation appeared in 1996. In eukaryotic cells ranging from yeast to humans, their changed substrate proteins have been discovered over the past 20 years, and SUMOylation has been recognized as a fairly frequent post-translational modification of proteins. Six SUMO-specific proteins—SEN1, 2, 3, 5, and 6—as well as three SUMO proteins (SUMO1/2/3) are present in higher eukaryotic cells.

DAXX and PML, as the main protein components of PML-NBs, are intimately involved in the formation and maintenance of the spherical structure of PML-NBs, as well as the localization of other proteins within PML-NBs. Lin et al. used immunoprecipitation to show that DAXX can bind to SUMO1-modified PML and thus localize in PML-NBs for the first time. SUMO Interaction Sequence (SIM) 733 I-I-V-L-S-D 740 of DAXX binds to an SUMO1 molecular surface groove formed by α -sheets (aa 33-39) and partially α -helix (aa 45-54). Intracellular DAXX is required for the preservation of various components of PML-NBs, and blocking DAXX expression can result in PML-NB dissociation.

3.2. Nucleus localization

DAXX was mostly found in the nuclear fraction of HeLa cells after they were split into cytoplasmic and mitotic chromosomal segments, nuclear, cytoplasmic, low-density microsomes, high-density microsomes, and cytoplasmic membrane fractions. Endogenous DAXX was detected via immunofluorescence in 3T3 fibroblasts, and it was discovered that the cytoplasm only displayed weak, punctate fluorescence.

4. Features of DAXX

4.1. Transcriptional suppression function

Transcriptional repression is one of DAXX's most notable roles in the nucleus (Table 1). According to Hollenbach and his co-authors, transcriptional repression involves an interaction between DAXX and the transcription factor Pax3. This study demonstrates that DAXX, when connected to DNA via the GAL4 DBD, can function as a transcriptional repressor. In transient transfection studies, the co-expression of DAXX and Pax3 led to an 80% reduction of Pax3 activity.

DAXX can also operate as a transcriptional co-activator, however overall it inhibits the transcriptional activity of a variety of proteins. Emelyanov et al. discovered that the cell type and promoter environment affect whether DAXX inhibits or activates Pax5 transcriptional activity.

Can DAXX perform this in PML-NB then? One of the many proteins that interact with DAXX is HDAC2, an important transcriptional regulator in cells. DAXX is probably implicated in transcriptional suppression through the attraction or stability of particular promoters, notably the c-met promoter, by HDAC2. DAXX interacts with PML and HDAC2 via the same carboxy terminus, therefore binding DAXX to sulfonated PML can disassemble the DAXX-HDAC2 complex and inactivate DAXX-mediated transcriptional repression.

Table 1. Transcription factors and their functions that interact with DAXX

Transcription factor	Method of interaction	Cell Line	Functional consequence
Pax3	Co-IP	COS1.NIH 3T3	Repression of Pax3-driven transcription by DAXX
Ets1	YTH;GST	COS-1	Exogenous Repression of Ets1-driven transcription by DAXX
Pax5	YTH;GST	Mouse B cells M12.4 A20. BL-2. HS-Sultan. 293T, HeLa	Depending on the cell type and promoter, DAXX either stimulates or represses the transcriptional activity of Pax5.
p53. p63. p73	YTH; GST; Co-IP	Saos2	DAXX, possibly by deacetylation, suppresses p73 and p53 transactivation in a dose-dependent manner.
P53	YTH; Co-IP	HCT116. HCT116p53, Saos2, p53/MDM2 DKO MEF	DAXX shields cells from p53-mediated apoptosis and represses p21 and pAIP 1 reporter constructs in a p53-dependent manner.
ATRX	Co-IP	HeLa	DAXX does not engage in ATRX's remodeling activities.

4.2. Pro-apoptotic function

4.2.1 Pro-apoptotic effect in the cytoplasm through the ASK1/JNK signaling pathway

The Fas death domain activates Apoptosis Signal-Regulating Kinase 1 (ASK1), which facilitates the translocation of DAXX from the nucleus to the cytoplasm. The translocated DAXX interacts with the Fas death domain to cause apoptosis, activating the Fas-DAXX-ask1-jnk1 signaling pathway. Sharma, however, found the opposite result: 4-hydroxynonenal (HNE) therapy results in a rapid and long-lasting upward regulation of DAXX in cells CRL2571. When DAXX expression is suppressed by small interfering RNA (si RNA), CRL2571 cells are more susceptible to Fas-induced apoptosis. This demonstrates that DAXX and Fas are not necessary for the signaling pathway of Fas-mediated

apoptosis. Awasthi added more evidence that HNE and DAXX interact, causing DAXX to translocate from the nucleola to the cytoplasm. DAXX links to Saf in the cytoplasm to stop apoptosis [3].

4.2.2 The function of DAXX in apoptosis induced by TGF- receptors

Through TGF-activation of murine12 hepatocyte amalgam, the JNK-induced apoptosis is mediated through the DAXX receptor and Type II TGF- receptor (TGFB2)[4]. DAXX metabolism stability appears to be improved by TGF- rather than phosphorylation of DAXX. After then, it was shown that JNK is activated by DAXX, mitotically activated protein kinases MKK4 (MAP2K4), and MKK7 via the transcriptional regulator and apoptotic protein kinase homeodomain-interacting protein kinase 2 (HIPK2) (MAP2K7). When HIPK2 and DAXX are co-domained in PML-NB, HIPK2 then directly phosphorylates DAXX to enhance TGF- receptor-induced apoptosis [5]. This process occurs when DAXX is liberated from PML-NB.

4.2.3 Function of DAXX in the nucleus that promotes apoptosis

By suppressing the expression of anti-apoptotic genes and activating less specific pathways like pro-apoptotic genes within the nucleus, DAXX may strengthen apoptosis. The involvement of DAXX in oxidative stress, cytokines (TNF and IFN), and osmotic stress has been demonstrated [6,7]. This involvement may be due to DAXX's inhibition of anti-apoptotic genes. In primary fibroblasts exposed to UV radiation, it was discovered that DAXX activates the ASK1-JNK pro-apoptotic signal within the nucleus. Under UV light, DAXX encourages p53-mediated apoptosis by suppressing p21 expression and activating proapoptotic BCL2 family members like PUMA. In the latter instance, DAXX joins forces with AXIN and HIPK2 to form a complex that enhances p53's Ser-46 phosphorylation, enhancing PUMA production and apoptosis (Figure 4) .

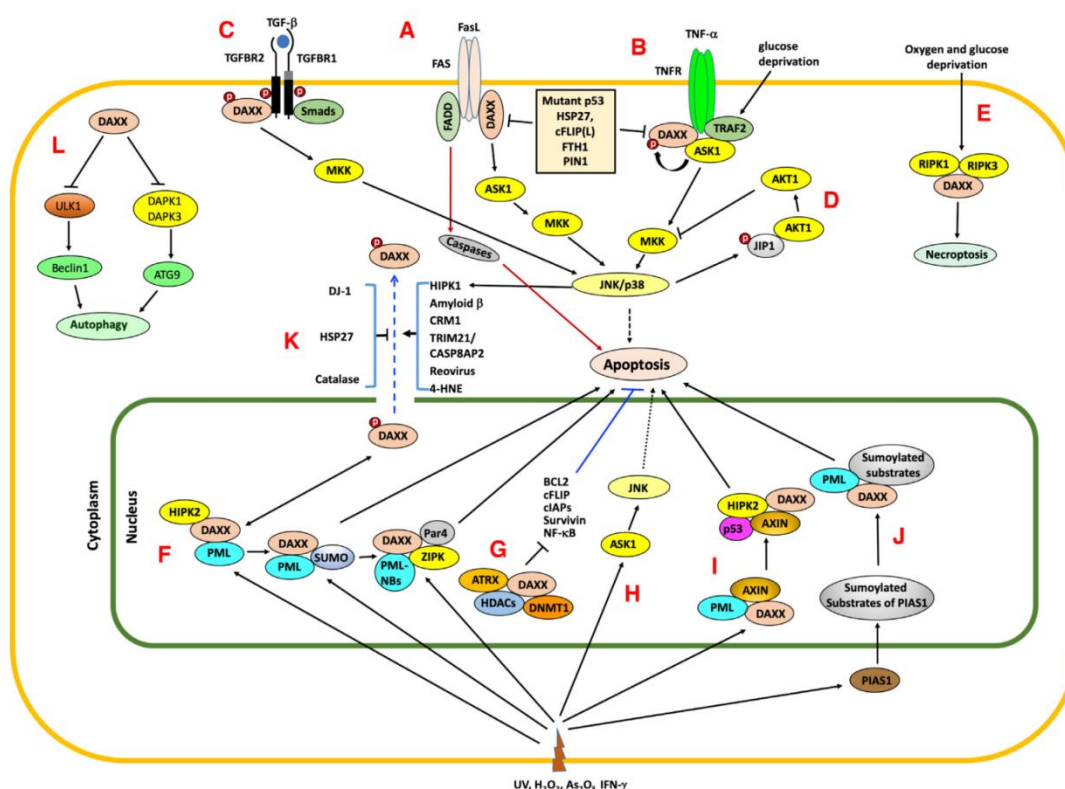


Figure 4. Several ways DAXX induces apoptosis

5. Relationship between DAXX and cancer

5.1. Pancreatic neuroendocrine tumors

Nearly 3% of all pancreatic cancers are pancreatic neuroendocrine tumors (PanNETs), which develop on the pancreas' langerhans island. 93% of patients had 5-year survival-death domain-associated proteins (DAXX) and/or α -thalassemia/mental retardation X-linked chromatin remodeling protein (ATRX) mutated in approximately 40% of sporadic PanNETs, often binding to MEN1 mutations DAXX/ATRX mutations resulting in loss of nuclear expression of this protein in tumor tissue. Deletion of ATRX/DAXX is associated with alternative lengthening of the telomere (ALT) phenotype that uses homologous recombination to maintain telomere length rather than activate telomerase.

Cellular telomere lengthening is caused by the enzyme telomerase. It is a fundamental nucleoprotein reverse transcriptase that may extend telomeres at the ends of eukaryotic chromosomes, fill in telomeres lost during DNA replication, and prolong telomere repair to prevent telomere loss during cell division, which would enhance the rate of cell division. In cells from various animals, telomeres are crucial for preserving chromosomal stability and cell viability. Telomeres can be lengthened and shortened by telomerase, which increases cell proliferation in vitro (shortened telomeres have limited ability to replicate cells). Telomerase activity is repressed in healthy human tissues and stimulated in tumors, which may be involved in the development of cancer. In order to preserve telomere stability, genome integrity, long-term cell function, and the potential for further proliferation, telomerase is crucial. The purpose of telomerase is to prolong telomere repair in order to compensate for DNA replication flaws and enhance the rate of cell division by preventing telomere loss during cell division.

Most ULMS also exhibit ALT, which is particularly useful in brain malignancies and soft tissue sarcomas. The frequent decrease of ALT and ATRX/DAXX expression in ULMS may suggest that some ULs have the potential to become cancerous lesions and are ULMS precursor lesions. Although its causal relationship is still unclear in the study of panNET's progression mechanism on DAXX and ATRX loss. Although the molecular mechanisms associated with DAXX and ATRX loss remain unclear, the definitive role of PanNET prognosis is emerging.

5.2. Ovarian cancer

Ovarian cancer, which makes up around 4% of all female systemic malignancies, is one of the most frequent tumors of the female reproductive system. It ranks third in occurrence, behind uterine body cancer and cervical cancer. But among all gynecological tumors, ovarian cancer is the leading cause of death, seriously endangering the lives of women. Ovarian cancer has no known cause, however its development may be influenced by factors like age, fertility, blood type, mental health, and environment. DAXX has been investigated as a potential regulator of cell proliferation, metastasis, and treatment resistance in ovarian cancer.

It's probable that DAXX is necessary for ovarian cancer cells to preserve their genome integrity and prevent DNA damage-induced apoptosis. Cell death is brought on by DAXX depletion, which also sets off a DNA damage response. As a result, DAXX can indirectly enhance tumor development in vivo by reducing DNA damage checkpoints and apoptosis. Additionally, via interacting with transcriptional regulators, DAXX can directly promote the proliferation of ovarian cancer cells.

According to Wei-Wei Pan et al., DAXX overexpression improved colony formation, migration, and proliferation in ovarian cancer cell lines, whereas RNA interference to remove DAXX had the reverse impact. DAXX is highly expressed in cortical tumors on the surface of human ovaries. Ovarian cancer cells overexpressing DAXX demonstrated higher carcinogenesis capacity in vivo when transplanted into nude mice, whereas the absence of DAXX prevented tumor formation. It is significant to highlight that DAXX promotes normal cells in the superficial ovarian cortex to undergo tumorigenic transformation. DAXX and PML collaborate to protect ovarian cancer cells from chemotherapy- and X-ray-induced DNA damage. Wei-Wei Pan found that the DNA damage markers

pH2AX and pCHK2 partially colocalized with DAXX-PML and that after DNA damage, ovarian cancer cells formed more nuclear PML bodies. Additionally, PML cancellation led to genomic instability in cultivated ovarian cancer cells, just like DAXX RNAi did. All of these findings clearly imply that DAXX interacts with PML to shield ovarian cancer cells from DNA damage[8].

Through the use of immunohistochemistry, Sheng-Bing Liu et al. investigated the expression of CEBP- and DAXX in human ovarian cancer tissues. They discovered that both proteins were significantly expressed in these tissues, and that CEBP's transcriptional activity increased in a channel-dependent manner. These findings imply that DAXX binds to CEBP- and encourages ascites cell survival and migration [9].

As a result, the new ovarian cancer gene DAXX encourages ovarian cancer cell proliferation and resistance to chemotherapy. As a result, controlling DAXX-nuclear PML's activity can be a useful tactic for preventing ovarian cancer recurrence and medication resistance.

5.3. Prostate cancer

Prostate cancer is the most common malignancy of the male germline, the incidence increases with age, and its incidence has obvious regional differences, higher in Europe and the United States. It is reportedly second only to lung cancer and is the second most canceric death in men. The incidence rate in China was low before, but due to the aging of the population, the incidence rate has increased in recent years, and due to the continuous improvement of the diagnostic methods of prostate cancer, such as radioimmunoassay of acid phosphatase, lactate dehydrogenase determination of prostatic fluid, ultrasound imaging of the transrectum, CT examination and improvement of prostate puncture needles, etc., prostate cancer can be diagnosed early, and the incidence of prostate cancer has also increased.

The late E3 ubiquitin ligase-promoting complex tightly controls the mitotic process in mammalian cells (APC).

In 1986, the APC gene was first discovered by Herrera on the chromosome of a patient with Gardner syndrome with rectal tumor and intellectual disability. The patient had a deletion on the long arm of chromosome 5. Later, it was found that the APC gene was the causative gene of FAP. Miyoshi et al. classified the APC gene as a tumor suppressor gene based on the common heterozygous 5q21 deletion in a variety of tumors, including colorectal tumors. However, once the transfected chromosome 5 was removed, the cell line reverted to malignant behavior, suggesting that the 5q21 region does indeed contain a suppressor gene for colon cancer. Another On the other hand, the high frequency of loss of heterozygosity in the 5q21 region in FAP cancer patients also supports the APC gene as a tumor suppressor gene. According to studies, introducing APC protein to colon cancer cells deficient in APC protein can slow the growth of tumor cells. Increased cell auto-death is the cause of the growth slowdown. It is clear that APC has the ability to regulate both cell proliferation and death. As a result, the balance between cell proliferation and cell death is somewhat affected by the deletion of the APC gene. The APC gene regulates cell count.

By transiently transfecting U2OS cells with DAXX siRNA and using immunoprecipitation, Pak Shing Kwan et al. were able to determine that DAXX, a new APC/C inhibitor, is generally overexpressed in prostate cancer. In vivo, DAXX can interact with the APC co-activators Cdc20 and Cdh1, and DAXX's binding to Cdc20 is reliant on a trustworthy disruption cassette adjacent to the protein's N-terminus. Ectopic DAXX expression can delay mitosis briefly by preventing the degradation of the APC/Cdc20 and APC/Cdh1 substrates. The ectopic expression of DAXX in non-malignant prostatic epithelial cell lines results in the induction of polyploidy under the strain of mitosis. In conclusion, DAXX may function as a novel APC/C inhibitor that promotes chromosomal instability during prostate cancer progression[10].

DAXX overexpression is frequently seen in prostate cancer tissue and may play a role in the onset of prostate cancer. It can disrupt the operation of the mitotic checkpoint and chromosomal stability.

6. Conclusion

By examining DAXX's structure and function, the main roles it plays in cell survival, apoptosis, and cancer are detailed in this review. DAXX has only been studied for little than two decades since its identification as a highly conserved multifunctional protein, and it is still unknown why it affects certain tumors in different ways. Different forms of cancer may be treated therapeutically by focusing on DAXX-mediated pathways. Developing novel approaches for creating anticancer therapeutic treatments may result from a better understanding of the mechanisms through which DAXX controls gene expression, chromatin remodeling, DNA repair, and epigenetic alteration.

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