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Research on the mechanism of DTL in the occurrence and development of cancer

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Abstract. DTL (denticleless E3 ubiquitin protein ligase homolog) is an E3 ubiquitin ligase that is highly expressed in a variety of tumors and is closely related to the occurrence and development of tumors. Here, we review the latest progress in DTL regulation in various cancer data, including the mechanisms by which changes in its expression affect multiple pathways, ultimately leading to cell cycle arrest and tumor proliferation. Future research should further elucidate the molecular mechanism of DTL and its relationship with tumorigenesis, which is of great significance for the prevention, diagnosis and treatment of tumors. In addition, multi-omics data need to be used to further explore the differential expression and regulatory network of DTL at the single cell level, which is crucial for finding tumor suppressor drug targets.

Keywords: DTL, Cancer, cell cycle, oncogene, biomarker.

1. Introduction

Cancer is one of the leading causes of death worldwide today. According to statistics from the World Health Organization, there were 19.29 million new cancer cases and 9.96 million deaths worldwide in 2020[1]. Although cancer diagnosis and treatment methods have continued to improve in recent years, the prognosis of most cancer patients is still poor, and the 5-year survival rate is generally not high. Therefore, in-depth study of the molecular mechanisms of cancer occurrence and development and finding key targets for inhibiting cancer are of great significance for improving the prognosis of cancer patients.

The cell cycle is the basis of eukaryotic cell proliferation and plays a vital role in maintaining the homeostasis of body tissues. Cell cycle disorder is one of the important characteristics of cancer [2]. A large number of studies have shown that abnormal expression of cell cycle-related genes and proteins is common in various cancers, leading to imbalance of cell cycle checkpoints, causing excessive cell proliferation and causing tumors[3]. Therefore, abnormal cell cycle regulation is considered to be a key driver of cancer development. The development of anticancer drugs targeting cell cycle-related molecules has become an important direction in cancer treatment research.

DTL (denticleless E3 ubiquitin protein ligase homolog) is an important cell cycle regulator discovered in recent years. DTL belongs to the DCAF (DDB1 and CUL4 associated factors) family and

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can serve as a substrate receptor for CRL4 (cullin-RING ubiquitin ligase 4), mediating the ubiquitination and degradation of a variety of cell cycle-related proteins, such as CDT1, p21, Set8, etc. , thus playing an important role in DNA replication, DNA damage repair, cell cycle checkpoints and other processes [4,5]. Studies have found that DTL is highly expressed in a variety of human tumor tissues, suggesting that it may play an important role in the occurrence and development of cancer. Studies have confirmed that DTL inhibits DNA re-replication by regulating the degradation of CDT1, maintains genome stability, and plays a key role in inhibiting tumorigenesis [6]. In addition, DTL can also degrade p21 and Set8 through ubiquitination, relieve G1/S and G2/M checkpoint blocks, and promote cell cycle progression [7,8]. These functional abnormalities of DTL may be its important pathogenic mechanism in cancer.

In view of the important role of DTL in cell cycle regulation and cancer occurrence, in-depth elucidation of the molecular mechanism of DTL and its relationship with cancer is of great significance for the prevention, diagnosis and treatment of cancer. This article will systematically summarize the research progress of DTL, focus on the role and mechanism of DTL in cell cycle regulation and cancer development, and look forward to its application prospects as a new target for anti-cancer drugs, providing a reference for future DTL-related cancer research.

2. DTL overexpression promotes cancer progression

DTL (denticleless E3 ubiquitin protein ligase homolog) is an E3 ubiquitin ligase that is highly expressed in a variety of tumors and is closely related to the occurrence and development of tumors. Studies have shown that miR-203 can target the 3'UTR of DTL. region, inhibiting its expression [9]. The overexpression of DTL can degrade multiple tumor suppressor genes through ubiquitination, thereby promoting the proliferation, invasion and metastasis of tumor cells.

PDCD4 (programmed cell death 4) is an important tumor suppressor gene that can inhibit the proliferation and invasion of tumor cells [10,11]. Studies have found that DTL can directly interact with PDCD4 and mediate its ubiquitination and degradation [12]. Overexpression of DTL leads to a significant decrease in PDCD4 protein levels, thereby releasing the inhibitory effect of PDCD4 on tumor cell proliferation and invasion and promoting tumor progression. In addition, DTL can also induce epithelial epithelial cell death by activating the RAC1-JNK-FOXO1 signaling pathway. Mesenchymal transition (EMT), enhances the migration and invasion ability of tumor cells [13]. In addition to PDCD4, DTL can also ubiquitinate and degrade another tumor suppressor gene p21 [14]. p21 is a cyclin-dependent kinase inhibitor. It can block the cell cycle process. By degrading p21, DTL relieves its inhibition on the cell cycle and promotes tumor cell proliferation [14]. In addition, DTL can also induce epithelial-mesenchymal transition by activating the RAC1-JNK-FOXO1 signaling pathway (EMT), enhancing the migration and invasion capabilities of tumor cells [13].

In recent years, more and more studies have shown that the DTL (Denticleless E3 Ubiquitin Protein Ligase) gene is overexpressed in various cancers such as lung cancer, liver cancer, and gastric cancer, and promotes cancer progression.

In 2008, Ueki et al. [15] first reported that DTL is highly expressed in breast cancer tissues, and knocking down DTL can inhibit the proliferation and invasion of breast cancer cells. Subsequently, Perez-Peaamp et al. [16] used gene expression and functional annotation analysis to identify genes differentially expressed in the ubiquitin pathway between normal breast and basal-like tumors and found that UBE2T and DTL were expanded in approximately 12% of breast tumors. increase.

Hepatocellular carcinoma is another common tumor with overexpression of DTL. Li et al. found that DTL is highly expressed in liver cancer tissues and is related to tumor stage, vascular invasion and recurrence. The overall survival of liver cancer patients with high expression of DTL is significantly shortened. In terms of clinical manifestations, DTL is related to the overall survival of HCC patients, and patients with high DTL expression have shorter survival times. Mechanistic studies have shown that DTL deletion leads to the destruction of mitotic proteins and the upregulation of the cell cycle arrest gene p21, and targeting DTL reduces cell cycle regulatory factors and chromosome segregation genes, resulting in an increase in cell micronuclei. In this regard, Chen et al. suggested inhibiting the growth of cancer cells through down-regulation of TPX2 [17]. The mRNA expression of the CUL4 complex,

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including DTL, is increased, and patient survival time is poor. The final experiment showed that E2F1 mediates DTL to promote the invasion and metastasis of liver cancer cells [18], which also provides evidence for DTL as a prognostic marker and therapeutic target for liver cancer. points provide the basis.

In non-small cell lung cancer, miR-203 is transferred into tumor cells through extracellular vesicles (EVs) secreted by human umbilical vein endothelial cells (HUVECs), targeting the expression of DTL, thereby upregulating the protein level of PDCD4, inhibiting Malignant phenotype of tumor cells[9,10,19].

Regarding the role of DTL in colorectal cancer, Baraniskin et al. found in 2014 [20] that DTL mRNA is highly expressed in colorectal cancer tissue and is positively correlated with tumor stage. Knocking down DTL inhibits the proliferation and colony formation ability of colorectal cancer cells. In 2017, Kobayashi et al. [21] reported that DTL promotes epithelial-to-mesenchymal transition (EMT) and metastasis of colorectal cancer cells by regulating the Wnt/β-catenin pathway.

In cervical adenocarcinoma, high expression of DTL is associated with depth of tumor invasion, lymph node metastasis, and poor prognosis [13]. These findings suggest that DTL may become a potential therapeutic target against metastasis of cervical adenocarcinoma [11]. 2023 Luo et al. [22] used real-time quantitative polymerase chain reaction (qRT-PCR) to detect the expression of circ-acyclic E3 ubiquitin protein ligase homolog (circ-DTL), miR-758-3p and DCUN1D1. It was found that Circ-DTL acts as a tumor promoter in cervical cancer development by regulating the miR-758-3p/DCUN1D1 pathway. Knockdown of circ-DTL can inhibit the growth, migration and invasion of cervical cancer cells, and promote cell cycle arrest and apoptosis. In bladder cancer, Luo confirmed through in vitro and in vivo experiments that DTL may promote BCa progression through the AKT/mTOR pathway[23].

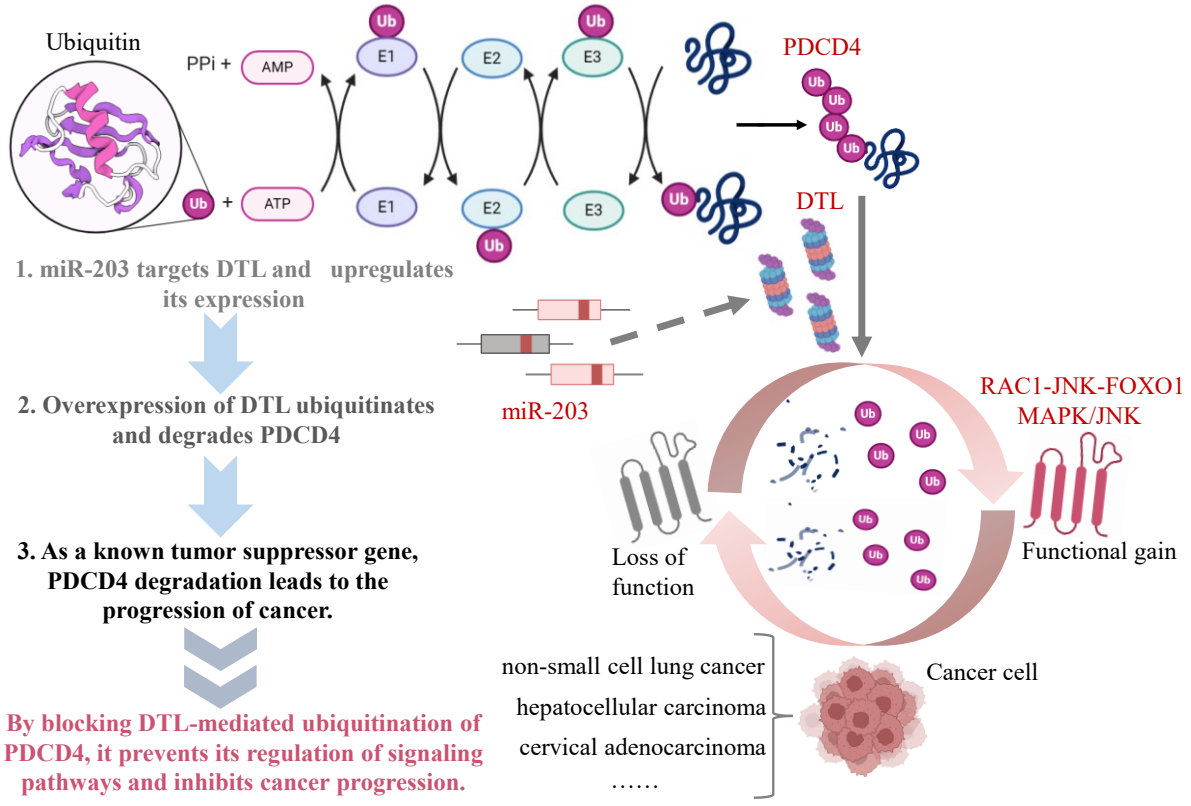

Figure 1. Mechanisms of pro-cancer response by miR-203→DTL→PDCD4 axis

The above views all confirm that the "miR-203→DTL→PDCD4" reaction chain plays an important role in tumor progression (Figure 3.1). miR-203 targets the expression of DTL, and DTL overexpression can ubiquitinate and degrade multiple Tumor suppressor genes such as PDCD4, p21, etc. relieve their

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inhibitory effects on tumor cell proliferation, invasion and metastasis, and promote tumor progression through various mechanisms such as inducing EMT and reshaping the tumor immune microenvironment[10,13,19]. In-depth Studying the miRNA-DTL-tumor suppressor gene axis will help elucidate the molecular mechanism of tumor development and provide new ideas and strategies for tumor diagnosis, prognosis assessment and targeted therapy. In addition to the above-mentioned cancers, DTL is also involved in melanoma [24], colorectal cancer [20], ovarian cancer[16] and other cancers are also highly expressed, promoting the proliferation, invasion, migration and drug resistance of cancer cells. In the future, more clinical samples and animal model experiments are needed to further verify the feasibility and effectiveness of DTL as a tumor marker and therapeutic target.

3. The regulatory mechanism of DTL on the cell cycle

DTL is also a protein that plays an important role in cell cycle regulation. The latest research shows that DTL mainly maintains genome stability through two different mechanisms. On the one hand, DTL is an important component of the CUL4-DDB1 ubiquitin ligase complex, to prevent repeated DNA replication by regulating the level of CDT1 [6]; on the other hand, DTL is also essential in the G2/M checkpoint activation process induced by DNA damage [6].

During normal cell growth, DTL forms a complex with CUL4-DDB1 and degrades CDT1 through the ubiquitination pathway, thus inhibiting the initiation of DNA replication mediated by CDT1 and preventing repeated replication of the genome [6,25]. CDT1 is a DNA replication It is necessary for the formation of the pre-replication complex, and the strict regulation of CDT1 levels is crucial to ensure that DNA is only replicated once per cell cycle. Studies have found that knocking down DTL will lead to an increase in CDT1 protein levels, causing Part of the DNA is replicated repeatedly, eventually leading to an increase in DNA content >4N [6]. In addition, DTL deletion can also lead to a series of phenotypes such as delayed G2 phase, excessive centromere replication, and spindle multipolarization. These phenotypes It is very similar to the overexpression of CDT1 or the deletion of Geminin (the inhibitor of CDT1)[26,27]. These results strongly prove that the DTL-CUL4-DDB1 complex inhibits DNA repeat replication and maintains genome stability by degrading CDT1.

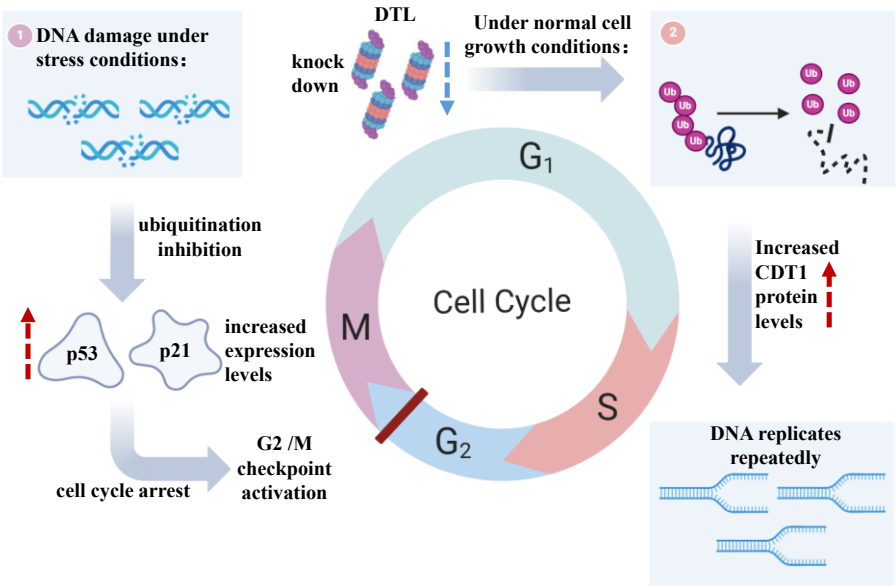

Figure 2. Two main mechanisms by which DTL regulates the cell cycle

In addition to regulating CDT1, DTL also plays an irreplaceable role in the G2/M checkpoint induced by DNA damage. Studies have found in zebrafish embryos that DTL mutants cannot effectively block the mitotic process after ionizing radiation treatment, showing showed obvious G2/M checkpoint defects [6]. Further knocking down DTL in human cells also destroyed the G2/M checkpoint induced by

ionizing radiation. Interestingly, this function does not seem to be related to CDT1, because in Although knocking down DTL and CDT1 simultaneously in zebrafish embryos can rescue the cell cycle defects caused by DTL deletion, it cannot restore the G2/M checkpoint. This suggests that DTL may activate the DNA damage checkpoint by regulating other substrates[25]. The latest research shows that DTL may trigger G2 arrest by stabilizing p53 and p21 [25]. DTL interacts with the MDM2-p53 ubiquitination complex, and knocking down DTL will lead to the inhibition of p53 ubiquitination, p53 and p21 levels increase, thereby causing cell cycle arrest [26].

4. Summary

In summary, as an important component of the CUL4-DDB1 ubiquitin ligase complex, DTL mainly maintains genome stability in two ways: first, under DNA damage stress conditions, DTL participates in the G2/M checkpoint Activation blocks the mitosis process and buys time for DNA repair; secondly, during normal cell growth, DTL participates in ubiquitination and degradation of CDT1 to prevent repeated DNA replication. These two processes complement each other and jointly ensure the integrity and stability of the genome. The loss of DTL function will lead to increased genome instability and may promote the occurrence and development of tumors. Therefore, it is necessary to conduct in-depth research on the molecular mechanism of DTL and its relationship with tumorigenesis. , is of great significance for the prevention, diagnosis and treatment of tumors. Future work also needs to further elucidate the regulatory network between DTL and other cell cycle and DNA repair factors, as well as the role and mechanism of DTL abnormalities in tumorigenesis.

With the rapid development of single-cell level methods at this stage, whole-genome visualization and imaging technology enables the intuitive characterization of gene expression and the spatial organization and folding of the genome in various types of cells. Single-cell transcriptomics (scRNA-seq) [28–30] and single-cell chromosome conformation capture technology (scHi-C) [31,32] provide a new perspective and powerful tool for in-depth understanding of the role of DTL in the development of cancer. The tumor microenvironment plays a key role in tumor progression [33–35]. Using scRNA-seq technology to analyze the expression pattern of DTL in tumor cells and microenvironment cells (such as immune cells, stromal cells) will help understand the interaction between DTL expression and the tumor microenvironment, and provide clues for the development of new cancer immunotherapy strategies[36,37]. Faced with the heterogeneity caused by multicellular subtypes in tumor tissue, using scRNA-seq technology to analyze the expression patterns of DTL in cells of different tumor subtypes will help to understand its role in the formation and maintenance of tumor heterogeneity. Combining scRNA-seq and scHi-C for DTL regulatory network analysis, scRNA-seq can provide gene expression information at the single cell level, while scHi-C can reveal the relationship between the 3D structure of chromosomes and gene expression regulation. By integrating the two types of data [38], a multi-modal regulatory network of DTL at the single cell level can be constructed [39], which opens up broad prospects for exploring DTL as a cancer marker and therapeutic target. Future research should make full use of these new technologies to understand the role of DTL in tumor occurrence and development in a multi-dimensional and dynamic manner, build a more accurate prognostic model, and explore more effective prevention and treatment strategies, ultimately benefiting cancer patients.

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