Roles of programmed cell death protein 5 in inflammation and cancer (Review)

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Abstract. PDCD5 (programmed cell death 5) is an apoptosis related gene cloned in 1999 from a human leukemic cell line. PDCD5 protein containing 125 amino acid (aa) residues sharing significant homology to the corresponding proteins of species. Decreased expression of PDCD5 has been found in many human tumors, including breast, gastric cancer, astrocytic glioma, chronic myelogenous leukemia and hepatocellular carcinoma. In recent years, increased number of studies have shown the functions and mechanisms of PDCD5 protein in cancer cells, such as paraptosis, cell cycle and immunoregulation. In the present review, we provide a comprehensive review on the role of PDCD5 in cancer tissues and cells. This review summarizes the recent studies of the roles of PDCD5 in inflammation and cancer. We mainly focus on discoveries related to molecular mechanisms of PDCD5 protein. We also discuss some discrepancies between the current studies. Overall, the current available data will open new perspectives for a better understanding of PDCD5 in cancer.

Contents

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1. Introduction

Programmed cell death 5 (PDCD5), also designated TF-1 cell apoptosis-related gene-19 (TFAR19), is an apoptosis-related gene cloned in 1999 from the human leukemic cell line TF-1 (accession number AF014955 in GenBank) (1). Human *PDCD5* gene is located on chromosome 19q12-q13.1 (2), and the integrated PDCD5 protein contains 125 amino acid (aa) residues (3). The wide expression pattern of PDCD5 protein in various cell lines indicated that it is a regulator in pathological and physiological processed (4). Decreased expression of *PDCD5* has been found in many human tumors, including breast (5), gastric cancer (6), astrocytic glioma (7), chronic myelogenous leukemia (8) and hepatocellular carcinoma (9) (Figs. 1 and 2). Previous studies also showed that *PDCD5* is involved in paraptosis (10), cell cycle regulation (11), ischemia/reperfusion (4), immunoregulation (12) and viral infection (13).

However, the molecular mechanism of PDCD5 regulation during inflammation and cancer is very complex. According to the published literature, PDCD5 is essential for inflammation and cancer through regulating apoptosis. The present review is structured to provide a comprehensive overview of the functions and the mechanisms of PDCD5 in inflammation and cancer.

2. Properties of PDCD5

PDCD5 protein containing 125 amino acid (aa) residues shares significant homology with the corresponding proteins of species ranging from yeast to mice (1) (Fig. 3). Human PDCD5 protein can be divided into three structural regions: a rigid core region (residues 41-101 aa), C-terminal residues (102-125 aa) and N-terminal residues (3-40 aa) (3) (Fig. 4). In the study of Liu *et al* (14), it was found that the sequence region of PDCD5 (Asp^{3}-Ala^{19}) contains four leucine residues, three alanine residues, and two polar amino acid residues by using NMR methods. They also found that PDCD5 without N-terminal residues significantly attenuates the apoptosis-promoting effects on myeloblastic leukemia HL-60 cells (14). The C-terminal region of PDCD5 (Val^{109}-Val^{116}) includes four basic residues, which mediate the ability of the protein to bind to heparin, is important for PDCD5 to translocate through plasma membranes (15). The nuclear translocation of

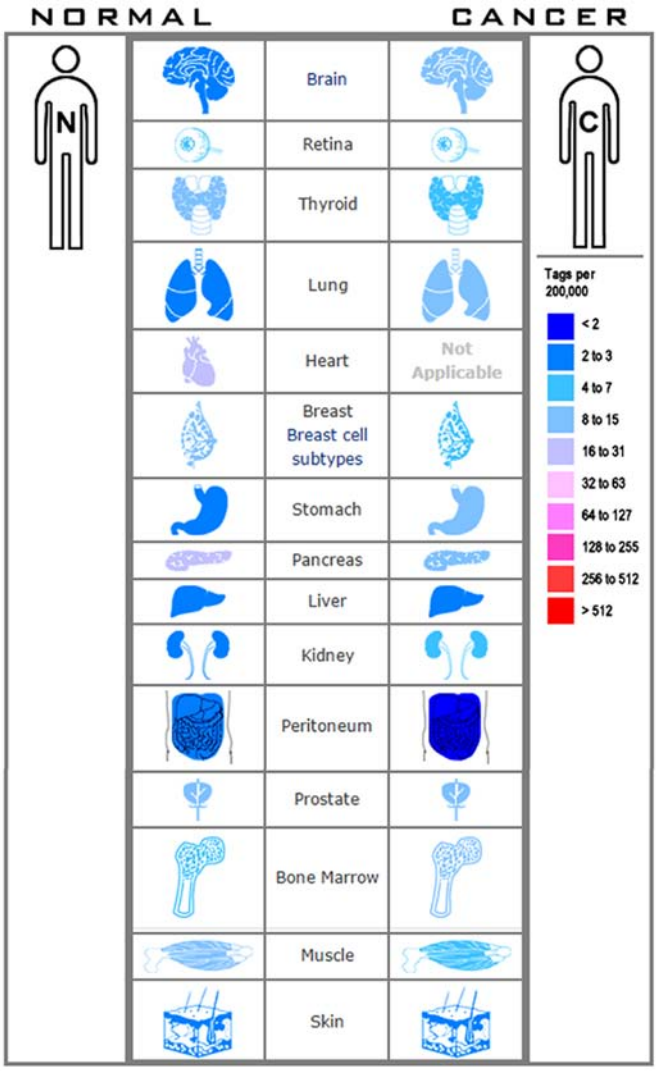

Figure 1. Expression profile for PDCD5 in human cancers.

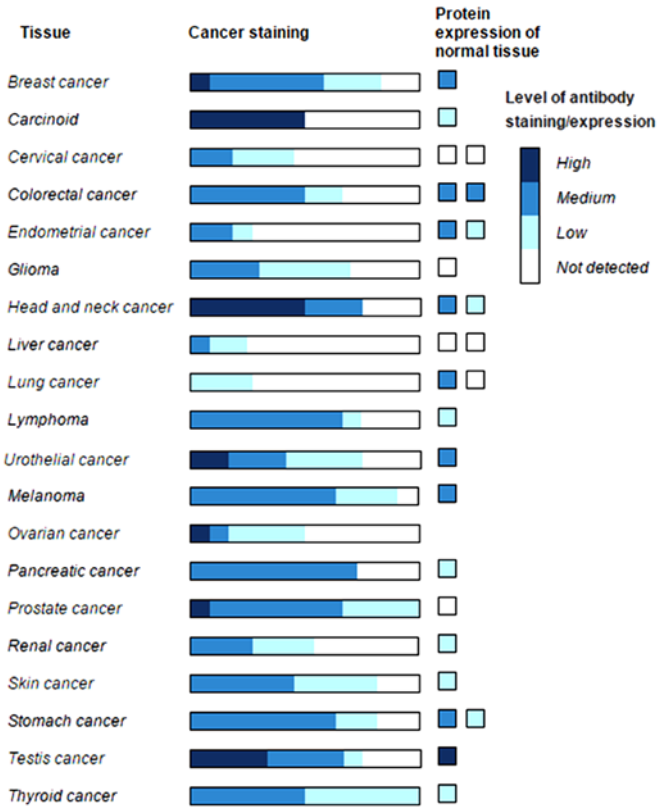

Figure 2. Ideograph of PDCD5 protein was generated by using Peptide Atlas.

PDCD5 is an early event of the apoptotic process, and may be a novel early marker for apoptosis (16).

3. PDCD5 and inflammation

Osteoarthritis (OA) is one of the most common chronic health conditions and a leading cause of pain and disability among adults (17). The main cause of OA is that articular chondrocytes lose proliferative capacity while maintaining the ability to produce proinflammatory mediators and matrix degrading enzymes (18). Cheng *et al* (19) found the enhancement of PDCD5 expression in OA cartilage compared with that in normal healthy cartilage. In the study of Yi *et al* (20) they also found that the level of PDCD5 was negatively correlated with the rate of chondrocyte apoptosis. These results indicated that PDCD5 is involved in the pathogenesis of OA.

PDCD5 also plays an important role in rheumatoid arthritis. Rheumatoid arthritis (RA) is a chronic systemic inflammatory joint disease characterized by hyperplasia of synovial tissue, inflammatory infiltrates and a progressive destruction of cartilage and bone (21). PDCD5 expression was low in RA patient-derived synovial tissue and cultured fibroblast-like synoviocytes (22). Plasma and synovial fluid PDCD5 abnormal expression and dysfunction may be correlated to tumor necrosis factor-α (TNF-α) in RA patients (23). PDCD5 level was also negatively correlated with proinflammatory cytokine interleukin (IL)-17 levels both in serum and synovial fluid of RA patients (24). These results indicated that plasma and synovial fluid PDCD5 could be useful for monitoring the activity and progression of RA. Xiao *et al* (25) found that overexpression of PDCD5 increased the level of Foxp3 protein and percentage of $Foxp3^+$ regulatory T (Treg) cells, and suppressed Th17 and Th1 responses in PDCD5 transgenic mice. A recent study showed that recombinant human PDCD5 (rhPDCD5) protein has prophylactic and therapeutic properties in a mouse model of multiple sclerosis by inhibiting Th1/Th17 differentiation and inducing apoptosis of predominantly pathogenic T cells (13).

The results of the present studies confirmed that PDCD5 serves as a guardian of immunological functions and that the PDCD5-FOXP3-Treg axis may be a therapeutic target for inflammation.

4. Antitumor function of PDCD5

Hematological oncology. PDCD5 is apoptosis-related gene originally cloned in 1999 from TF-1 human leukemic cell line undergoing apoptosis (1). From then on, PDCD5 was demonstrated to promote apoptosis in cancer cells in many studies. Ruan *et al* (8) found that *PDCD5* mRNA was lower in both acute myeloid leukemia (AML) and chronic myeloid leukemia

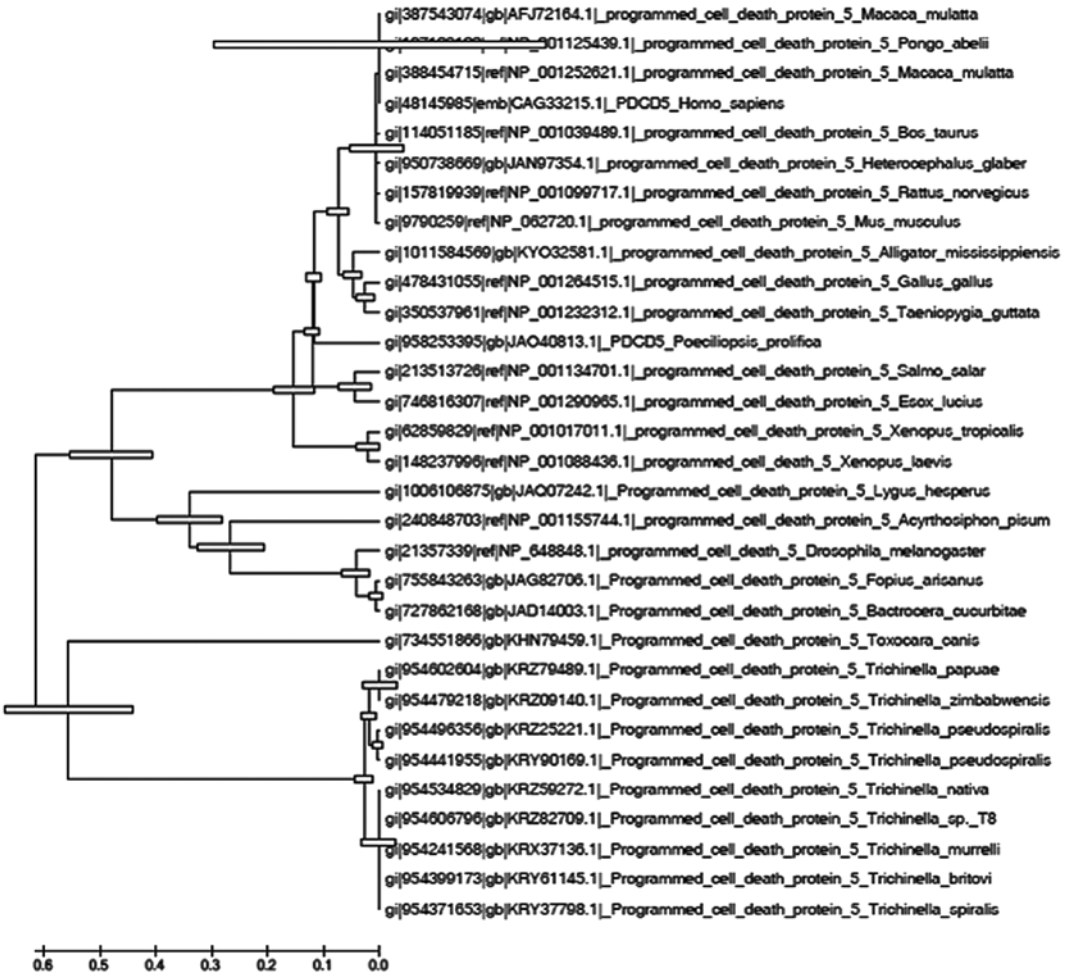

Figure 3. Multiple sequence alignments of PDCD5 by using the MEGA 5.1 software.

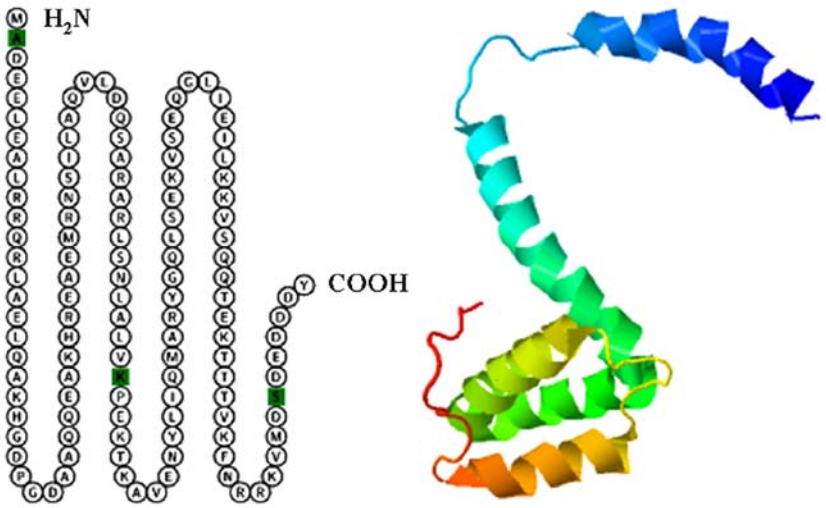

Figure 4. Structure of PDCD5 protein in RCSB Protein Data Bank.

(CML) marrow cells than that in normal donor marrow cells. They also observed a synergistic effect on apoptotic cell death in human CML K562 cells after combination therapy with adenovirus-mediated PDCD5 and idarubicin *in vitro* and *in vivo* (26). Shi *et al* (27) found that rhPDCD5 protein sensitizes K562 cells to apoptosis induced by chemotherapeutic drugs *in vitro* and *in vivo*.

Bone tumor. Osteosarcoma is the most frequent malignant bone tumor (28). Zhao *et al* (30) found that adenovirus-delivered

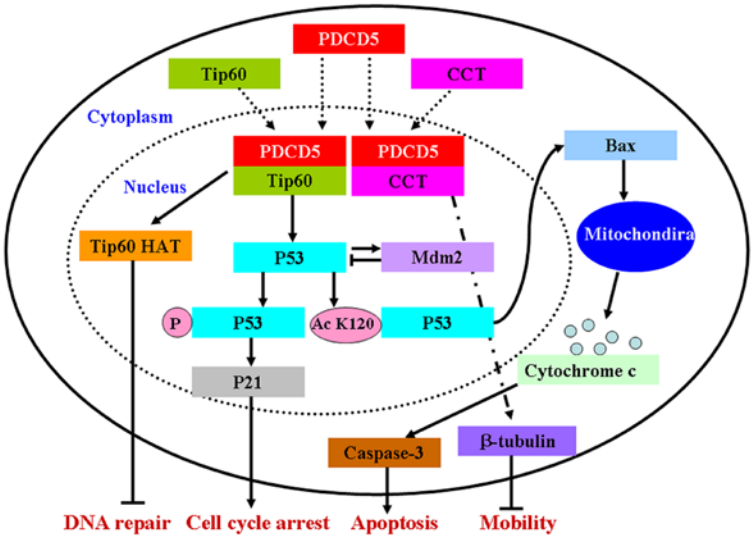

Figure 5. Schematic representation of the antitumor mechanisms of PDCD5 in cancer cells.

PDCD5 could counteract adriamycin resistance of osteosarcoma cells (Saos-2) by inhibiting P-glycoprotein (Pgp) expression. In the study of Han *et al* (29), they confirmed that various PDCD5 fragments [integrated (1-125 aa), truncated 1 (1-101 aa), and truncated 2 (41-125 aa)] could inhibit proliferation, and induce apoptosis and cell cycle arrest in the osteosarcoma cell line MG-63, and these effects were related to suppression of the Ras/Raf/MEK/ERK signaling pathway. This is an interesting result which showed that PDCD5 could induce apoptosis independently. Chondrosarcoma is the second most common primary malignant bone tumor after osteosarcoma (31). Compared with matched normal bone tissues, Chen *et al* (32) found that the levels of PDCD5 mRNA and protein were significantly decreased in chondrosarcoma tissues. PDCD5 was an independent prognostic factor in chondrosarcoma (32). In the following study, Chen *et al* (33) found that rhPDCD5 protein sensitizes chondrosarcomas to cisplatin chemotherapy *in vitro* and *in vivo*. These results indicated that PDCD5 may be used as a molecular marker in the diagnosis and prognosis of bone tumors.

Thoracic malignancy. The rs1862214 polymorphism in *PDCD5* is predictive for lung cancer risk and prognosis, and that *PDCD5* may represent a novel tumor suppressor gene influencing lung cancer (33). However, in the study of Nanba *et al* (34), they found that the rs1862214 SNP of *PDCD5* in Japanese population is not related to the risk of lung cancer. These results suggested the different roles of *PDCD5* in the pathogenesis of lung cancer in different ethnicity. The levels of PDCD5 mRNA and protein were also significantly decreased in laryngeal squamous cell carcinoma, indicating that PDCD5 may have an important role in the pathogenesis and development of laryngeal squamous cell carcinoma (35). Wang *et al* (36) confirmed that rhPDCD5 protein enhances the paclitaxel sensitivity of breast cancer *in vitro* and *in vivo*.

Abdominal tumor. Fu *et al* (9) demonstrated that PDCD5 expression is correlated with clinicopathological features and it may be a useful predictor of prognosis in patients with hepatocellular carcinoma after surgical resection. A recent study showed that PDCD5 could increase cisplatin sensitivity and decrease invasion in hepatic cancer cells (37). Compared with matched normal tissues, gastric cancer tissues contained lower level of PDCD5 protein (6). The survival rate of the patients with gastric cancer was dependent upon the expression level of PDCD5 (6). Xu *et al* (38) also found that PDCD5 sensitizes gastric cancer cells to cisplatin-induced apoptosis. Another study showed that combination of PDCD5 and cisplatin enhances apoptosis in colorectal cancer cells by activating the mitochondrial signaling pathway (39). A recent study of our team indicated that serum levels of PDCD5 protein were related with circulating $CD133^+$ cells in gastric cancer patients (40).

Other tumors. Human glioma is one of the most frequent primary tumors of the central nervous system (7). A reduced expression of *PDCD5* mRNA was found in glioma compared with normal brain tissue (41). Li *et al* (42) confirmed that PDCD5 promotes cisplatin-induced apoptosis in glioma cells (U87, U251 and T98G) by activating mitochondrial apoptotic pathway. PDCD5 mRNA and protein expression were downregulated in ovarian (43) and prostate cancer (44). rhPDCD5 protein increases doxorubicin-induced apoptosis in ovarian cancer SKOV3 cells (44). Notably, a recent study of Gao *et al* (45) confirmed that reduced PDCD5 protein is correlated with the degree of tumor differentiation in endometrioid endometrial carcinoma.

5. The antitumor mechanisms of PDCD5

Chen *et al* (46) found that PDCD5 exerts its effects through the pathway of mitochondria by modulating Bax translocation, cytochrome *c* release and caspase-3 activation. In the study of Xu *et al* (47), it was found that PDCD5 may play a dual role in the Tip60 pathway: under normal growth conditions, PDCD5 contributes to maintaining a basal pool of Tip60 and histone acetyltransferase (HAT) activity; after DNA damage, PDCD5 functions as a Tip60

coactivator to promote apoptosis through the Tip60-p53 pathway. Zhuge *et al* (48) found that PDCD5 interactions with Tip60 can accelerate DNA damage-induced apoptosis. A recent study showed that PDCD5 interacts with p53 and functions as a positive regulator in the p53 pathway (11). PDCD5 prevents ubiquitination of p53 in the cytoplasm by sequestering murine double minute 2 (Mdm2), thereby increasing p53 stability (49). Genetic deletion of PDCD5 abrogates etoposide-induced p53 stabilization in gastric cancer cells (50). Furthermore, Park *et al* (51) found that PDCD5 knockdown greatly attenuated the effect of OTU deubiquitinase 5 (OTUD5) on p53 activation. These results indicated an essential role of PDCD5 in p53 activation.

Tracy *et al* (52) found that PDCD5 interacts with the cytosolic chaperonin containing tailless complex polypeptide 1 (CCT). PDCD5-CCT complex could exert its apoptotic function, at least in part through inhibition of β-tubulin folding (52). In the study of Fu *et al* (53), it was found that recombinant human PDCD5 exhibits an antitumor role in hepatocellular carcinoma cells via clathrin-dependent endocytosis.

PDCD5 inhibits the proliferation of cancer cells by the mitochondrial apoptotic pathway and the NF-κB pathway (54,55).

Collectively, these studies provide compelling evidence of the antitumor mechanisms of PDCD5. Better understanding of these mechanisms could create novel therapeutic opportunities in treating cancer cells (Fig. 5).

6. Future perspectives

To date, cancer is still a fatal disease, and relapse rates in patients remain high regardless of the intensity of treatment. In recent years, PDCD5 has received increased attention in the molecular biology of cancer. Based on previous results and concepts, PDCD5 could be used as a prognostic marker for cancers. We believe that these data will open new perspectives for a better understanding of PDCD5. However, we are only at the beginning of understanding the precise roles of PDCD5 in cancer cells. Current results did not have sufficient certainty to permit their use in cancer patients. Thus, PDCD5 safety and efficacy in cancer treatment may be significant issues in future studies.

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