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Review

The mechanisms and clinical significance of *PDCD4* in colorectal cancer

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ABSTRACT

In recent years, the incidence and mortality of colorectal cancer (CRC) have been on a global upward trend. There is an urgent need for effective tools to prevent and treat CRC and reduce morbidity and mortality of CRC patients. Recent evidence suggests that programmed cell death 4 (*PDCD4*), a novel tumor suppressor gene, inhibits tumor progression at transcriptional and translational levels and regulates multiple signal transduction pathways. However, little is known about the precise mechanisms regulating *PDCD4* expression in CRC. In addition, several studies have demonstrated that the expression of in CRC is down-regulated or even absent. *PDCD4* is therefore considered to be an independent prognostic factor in CRC and may be a potential support diagnostic tool for distinguishing in normal colon tissue, benign adenoma and CRC. This review will focus on the expression of *PDCD4* in CRC and the relevant molecular mechanisms.

1. Introduction

Colorectal cancer (CRC) is the second most common malignant tumor in women and the third in men, with approximately 600,000 deaths worldwide each year (Sung et al., 2015). According to statistics, there are an estimated 135,430 new cases and 50,260 deaths in the United States in 2017 (Siegel et al., 2017). High recurrence and metastasis rate, low early diagnosis rate, and lacking of effective treatment are responsible for the mortality of CRC. CRC is a heterogeneous disease that special genetic alterations contribute to its progression (Bovell et al., 2013). Identification of molecular mechanisms involved in the progression of CRC is helpful in improving patients' prognosis and providing targets for cancer prevention and therapy.

PDCD4 is located on human chromosome 10q25.2 and regulates apoptosis considering as a novel tumor suppressor gene (Cmarik et al., 1999). Under normal physiological conditions, PDCD4 protein is mainly located in the nucleus. When the cellular microenvironment changes, such as malignant proliferation of cells, it can be transferred to the cytoplasm through the nuclear export signals (Wang et al., 2011). *PDCD4* can inhibit the eukaryotic translation initiation factor-4A (*eIF4A*) helicase activity by binding to the N-terminal domain of eIF4A via a conserved α-helix MA-3 structure in the protein, thereby limiting the synthesis of ribosomal recombination and protein (Zakowicz et al., 2005). Additionally, *PDCD4* can also directly bind to the ribosome of tumor cells and affect the translation process without depending on the *eIF4A* pathway, leading to apoptosis of tumor cells (Wedeken et al., 2010). To better understand the molecular mechanisms of *PDCD4* in the development of CRC, this review will summarize the related research

Abbreviations: **Abbreviations**, **Full name in English**; 3′-UTR, 3′-untranslated region; AA, asiatic acid; AOM, azoxymethane; AP-1, activating protein 1; AR, aldose reductase; ATF, activating transcription factor; Bcl-2, B-cell lymphoma 2; CAC, colitis-associated CRC; CDK1, cyclin dependent kinase 1; CKI1, cyclin dependent kinase inhibitor 1; COX-2, cyclooxygenase-2; CRC, colorectal cancer; CSC, CRC stem cells; DFS, disease free survival; DSS, dextran sodium sulfate; eIF4A, eukaryotic initiation factor-4A; GβL, G protein beta subunit-like; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; IECs, intestinal epithelial cells; IGF-1R, insulin-like growth factor 1 receptor; IL-6, interleukin 6; IL-8, interleukin 8; ITGβ4, Integrin, beta 4; JDP, Jun dimerization protein; MAP4K1, mitogen-activated protein kinase kinase kinase kinase 1; miRNAs, microRNAs; mTOR, mammalian target of rapamycin; mTORC2, mammalian target of rapamycin complex 2; NES, nuclear export signals; NF-κB, nuclear factor kappa-light-chain-enhancer; OS, overall survival; PDCD4, programmed cell death4; PGE2, prostaglandin E2; PKB, protein kinase B; PTEN, phosphatase and tensin homolog; Rictor, rapamycin-insensitive companion of mTOR; S6K1, S6 kinase beta-1; Sin1, stress-activated protein kinase interacting protein 1; SP, side population; STAT3, signal transducer and activator of transcription3; TCF4, T-cell factor 4; TGFβR2, transforming growth factor beta receptor 2; TNF-α, tumor necrosis factor alpha; UC, ulcerative colitis; uPAR, urokinase-type plasminogen activator receptor

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progress of *PDCD4* in CRC development in recent years.

2. Potential downstream mechanisms of *PDCD4* in CRC

2.1. PDCD4-MAP4K1/c-Jun/AP1 pathway

Activating protein 1 (*AP1*), a heterodimer consisting of the proteins of *c-Fos*, *c-Jun*, activating transcription factor (*ATF*) and Jun dimerization protein (*JDP*) families, is a transcription factor that can regulate the expression of a variety of stimulatory response genes such as cytokines, growth factors, stress response factors, and control many cellular processes including proliferation, differentiation and apoptosis (Ameyar et al., 2003; Hess et al., 2004). *PDCD4* can block the activation of *c-Jun* and the transcriptional activation of *AP1* by blocking the transcription of Mitogen-activated protein kinase kinase kinase kinase 1 (*MAP4K1*), which inhibits the invasion, metastasis and extracellular matrix protease activity of human CRC cells (Yang et al., 2006). Reduced *PDCD4* expression promotes the activation of β-catenin/T-cell factor 4 (*TCF4*) and *AP1*-dependent transcription (Wang et al., 2008). Further research showed that the increased Snail expression by knockdown of *PDCD4* leads to the down-regulation of E-cadherin resulting in activating β-catenin/TCF4-dependent transcription, and stimulates the expression of *c-Myc* and Urokinase-type plasminogen activator receptor (*uPAR*) (Wang et al., 2010). Down-regulation of *c-Myc* can reverse the expression of *MAP4K1* and the activation of *AP1* in *PDCD4* knockdown cells (Wang et al., 2012). Furthermore, knockdown of *PDCD4* results in the transformation of HT29 cells into fibroblast-like cells, and enhancing the invasiveness of CRC cells (Wang et al., 2008). Additionally, it has been found that curcumin can inhibit the proliferation, invasion and metastasis of tumor cells by acting on *AP1* and inhibiting the transcriptional regulation of miR-21 to stabilize the expression of *PDCD4* in CRC (Mudduluru et al., 2011) (Fig. 1).

2.2. PDCD4-PI3K/Akt/mTOR pathway

Akt, also known as protein kinase B (*PKB*), a serine/threonine-specific protein kinase, involves in glucose metabolism, apoptosis, cell proliferation, transcription and cell migration by binding and regulating the downstream effectors, such as nuclear factor kappa-light-chain-enhancer (*NF-κB*) of activated B cells and B-cell lymphoma 2 (*Bcl-2*) family proteins (Song et al., 2005). The activity of Akt is mainly monitored by mammalian target of rapamycin complex 2 (*mTORC2*) which consists of G protein beta subunit-like (*GβL*), mammalian target of rapamycin (*mTOR*), stress-activated protein kinase interacting protein 1 (*Sin1*) and rapamycin-insensitive companion of mTOR (*Rictor*) (Gaubitz et al., 2016). Studies have shown that *PDCD4* may regulate *PI3K-mTOR* signaling pathway involved in the proliferation and invasion of CRC (Schmid et al., 2011a; Wang et al., 2017). Furthermore, in CRC cells, *PDCD4* can inhibit the activation of ribosomal protein S6 kinase beta-1 (*S6K1*), a downstream effector of *PI3K/Akt/mTOR* signaling pathway, thereby overcoming the therapeutic resistance of insulin-like growth factor 1 receptor (*IGF-1R*) to CRC (Zhang et al., 2015). In addition, asiatic acid (AA) is reported to regulate *PDCD4* inhibition of CRC cell proliferation, migration, and induce apoptosis through the *PI3K/Akt/mTOR/S6K1* signaling pathway (Hao et al., 2018). The result of luciferase reporter showed that *PDCD4* inhibits *Sin1* translation by suppressing *eIF4A*, and it is functionally important for suppression of *mTORC2* activity and invasion. Moreover, directly inhibiting *eIF4A* by the use of Silvestrol can significantly inhibit *Sin1* translation and reduce the invasion of CRC (Wang et al., 2017). It is suggested that *PDCD4/PI3K/Akt/mTOR* pathway plays an important role in the development of CRC. (Fig. 2).

2.3. NF-κB-IL-6-STAT3-miR-21-PDCD4 feedback loop pathway

There is evidence that long-term chronic inflammation promotes cancer (Hanahan and Weinberg, 2011). Study has shown that the expression of *PDCD4* is decreased in mouse colon tissue in response to dextran sodium sulfate (DSS) induced colitis (Schmid et al., 2011b). In colitis-associated CRC (CAC) model induced by DSS and azoxymethane (AOM), *PDCD4* deficiency not only aggravates the acute DSS-induced acute colitis but also accelerates epithelial cell proliferation during malignant transformation and promotes DSS-induced CAC (Wang et al., 2016a). As is well-known, interleukin 6 (*IL-6*), a pro-inflammatory cytokine, is produced primarily by innate immune system cells such as monocytes and macrophages, and is significantly up-regulated in inflammatory bowel disease (IBD) and CRC (Chung and Chang, 2003; Francescone et al., 2015). In the CRC mouse model, *IL-6* enhances epithelial cell survival and proliferation through signal transducer and activator of transcription 3 (*STAT3*) signaling in colonic epithelial cells, promoting tumorigenesis (Bollrath et al., 2009; Grivennikov et al., 2009a). *STAT3* mediates the expression of various genes that respond to cell stimulation and therefore plays a critical role in many cellular processes such as cell growth and apoptosis (Yuan et al., 2004). A study further indicated, miR-21 promotes *NF-κB* activation and *IL-6* expression by inhibiting *PDCD4* expression in CAC models (Shi et al., 2016). NF-κB proteins are involved in the control of immune and inflammatory responses, developmental processes, cellular growth, and apoptosis (Barnes and Karin, 1997). In myeloid cells, the inactivation of NF-κB inhibits the production of tumor necrosis factor alpha (*TNF-α*) and *IL-6* and prevents the proliferation of intestinal epithelial cells (IECs) during CAC induction (Shi et al., 2016). Asangani et al. (Asangani et al., 2008) reported for the first time that miR-21 down-regulates *PDCD4* by targeting its 3′-untranslated region (3′-UTR), thus promoting CRC invasion, vascular invasion and metastasis. It has also been found that overexpression of miR-21 down-regulates *PDCD4* by targeting transforming growth factor beta receptor 2 (*TGFβR2*) (Yu et al., 2012). The study found that *PDCD4* inhibits *NF-κB* activation by interacting with *p65* in gliomas, and *IL-6* is produced after *NF-κB* activation in intestinal myeloid cells, promoting CAC tumor proliferation and survival (Grivennikov et al., 2009b; Hwang et al., 2014). Previous studies have shown that *NF-κB/p65* and *STAT3* bind directly to the miR-21 promoter and induce the expression miR-21 (Yang et al., 2010; Ou et al., 2014). Up-regulation of miR-21 also activates *NF-κB* and extracellularly regulates protein kinase signaling in malignant cells, and *STAT3*-driven miR-21 transactivation is found in CRC (Iliopoulos et al., 2010; Ling et al., 2012). A study further demonstrated that *IL-6* enhances *NF-κB* activation, whereas *STAT3* is a target of *IL-6* and miR-21, suggesting a positive feedback loop to promote tumor growth (Iliopoulos et al., 2009; Iliopoulos et al., 2010). It was found that *PDCD4* deficiency up-

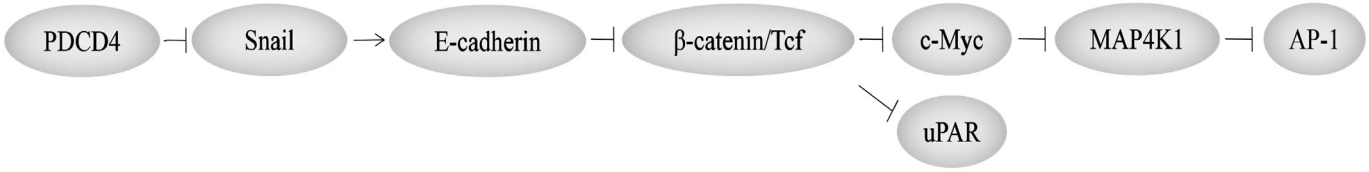

Fig. 1. *PDCD4* reduces the expression of *Snail* and leads to up-regulation of *E-cadherin*, inhibition of *β-catenin/TCF4*-dependent transcription, and decrease of the expression of *c-Myc* and *uPAR*. Down-regulated *c-Myc* subsequently inhibits *MAP4K1* expression, thereby inhibiting *AP-1* transcription to impede CRC proliferation, promotion and invasion.