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What Does Translationally Controlled Tumor Protein (Tctp) Promise? Is Tumor Reversion Possible?

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Abstract

Cancer research mainly interests understanding how a normal cell becomes malignant. Here is another question: How does a tumor cell quit the malignant state and return? The answer may be that the reprogramming of tumor cells. In the process of tumor reversion, expressions profiles of many gene can provide reprogramming of tumor cells to the revertants.

Recent studies suggested that most strongly downregulated protein in the revertant cells is TCTP. Essentially, TCTP is a house-keeping gene expressed in some cells including not only tumor cells but also erythrocytes, and encodes for a hydrophilic protein of 18–23 kDa. TCTP transcripts accumulate in the resting cells and the cells are rapidly translated, if necessary, into the protein. TCTP protein is expressed at low levels in resting cells and high levels in proliferating cells.

Overexpression of TCTP leads to inhibition of etoposide-induced apoptosis, thus reducing TCTP expression either results in apoptosis or reprogramming of cancer cells to the revertants. Additionally, pharmacological studies have shown that agents that reduce TCTP levels kill tumor cells. Other suggested molecular mechanisms in relation to tumor reversion of TCTP are: TCTP is a tubulin-binding protein that associates with microtubules in a cell-cycle; TCTP is directly interact with PLK1 and required for the normal progression of cytokinesis; TCTP binds to the MCL1 protein involved in the programmed cell death; and shows structural similarity to channel-forming helices of the pro-apoptotic protein Bax.

In conclusion, TCTP is a key player in the process of tumor reversion and also may provide the new strategies in cancer treatment by identification of new pharmaceutical compounds able to reduce its expression and kill malignant cells.

Keywords: TCTP, tumor reversion, reprogramming of cancer cells

INTRODUCTION

Cancer is a disease in which cells lose their organization by gaining unlimited proliferation ability. With the 2011 update, we know that carcinogenesis includes following ten basic hallmarks; 1) Sustaining Proliferative Signaling, 2) Evading Growth Suppressors, 3) Avoiding immune destruction, 4) Enabling replicative immortality, 5) Tumor-promoting inflammation, 6) Activating invasion and metastasis, 7) Inducing angiogenesis, 8) Genome instability and mutation, 9) Resisting cell death, 10) Deregulation cellular energetics [1].

With the formation of one and more or all of these causes, a normal cell becomes malignant and the tumorigenesis begins. Once the normal cell gains malignant properties, it rapidly formed to tumor and grows and invades the surrounding tissues and organs. Many cancers are also diagnosed at this stage. After cancer is diagnosed, all methods such as chemotherapy, radiotherapy and surgery aim to kill cancer tissues and cells. Most of the studies to date have investigated the carcinogenesis and, treatments aimed at killing cancer cells [1-5].

Even at this time, the Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation [6].

So is there another way? Are tumor cells capable of reverting from their malignant state? The answer is yes. Moreover, the concept of tumor reversion is not new, but there is a renewed challenge in the era of system biology [7, 8].

What is the tumor reversion?

Tumor reversion is a biological process in which the tumorigenic cells lose their malignant phenotype substantially or completely [4]. Tumor reversion was first discovered by Askanazy in the early 20th century. Later, in the 1950s, Braun et al. describe the healing of tumor cells. Next, Pierce et al. showed that tumor cells could differentiate into benign tissues [9]. Another important study for cancer reversion was described by Mintz et al. in 1975. In this study, blastocysts injected into embryonal carcinoma cells were found to develop successfully in normal organs and tissues [7, 10].

In the process of tumor reversion, a cancer or tumor cell is transformed into a revertant cells by activation of certain specific genes and deactivation of some other specific genes. The tumor reversal at the molecular level can be considered as a process of cellular reprogramming of cancer cells. Studies in the last decade have reported a total of 263 genes involved in tumor reversal by activation or inhibition [11].

Translationally Controlled Tumor Protein (TCTP)

Recent studies suggested that most strongly downregulated protein in the revertant cells is TCTP. Essentially, TCTP is a calcium-binding and tubulin binding protein and encoded by an 829 bp long gene located on chromosome 13q14, called TPT1 for a hydrophilic protein of 18–23 kDa [11-13].

TCTP was also named histamine release factor (HRF), fortilin, P21, P23, TPT-1 and Q23. This protein is referred to as TCTP because its mRNA is translationally controlled. Although TCTP is present everywhere in tissue and cell types, its expression is relatively low in lung, colon and cell lines from normal cells [14].

TCTP plays an important role in many cellular physiological processes such as cancer, cell proliferation, stress response, gene regulation, and heat shock response. TCTP also has an extracellular function such as histamine release [14-17].

What is the link between TCTP and cancer?

As is known, apoptosis is programmed cell death, and the aged, physically impaired or unwanted cells die in this way. When apoptotic death disrupted, an imbalance between life and death of cells can lead to cancer. In other words, if cells escape apoptosis and do not die as programmed, they become immortal and become cancerous [5].

The main feature of TCTP is that it is an anti-apoptotic protein. TCTP is able to inhibit mitochondrial apoptosis by regulating the relevant signal pathways. TCTP might also protect cells from ER stress-induced apoptosis by inhibiting the signal pathway. Moreover, TCTP inhibits p53-dependent apoptosis by downregulating the protein (Figure 1) [14].

Genetic changes play an important role in cancer. Two of the main gene types that are effective in cancers are oncogene and tumor suppressor genes. We call oncogenes which cause uncontrolled growth and proliferation of cells by losing their control as a result of mutations or epigenetic changes while they are normally involved in cell growth and proliferation. Tumor suppressor genes are normal genes that slow cell division, repair DNA errors, or control when cells die. When tumor suppressor genes do not function properly, cells can become cancerous [18-20]. One of the well-known tumor suppressors is p53 and abnormalities of the TP53 gene (which codes for the p53 protein) have been found in more than half of human cancers [14].

Herein, the other main carcinogenic feature of TCTP is acting as an oncogene. It is also closely associated with tumor suppressor p53 and there is a negative feedback loop between P53 and TCTP. In other words, TCTP can promote p53 degradation and, p53 can directly suppress TCTP transcription (Figure 1) [21, 22].

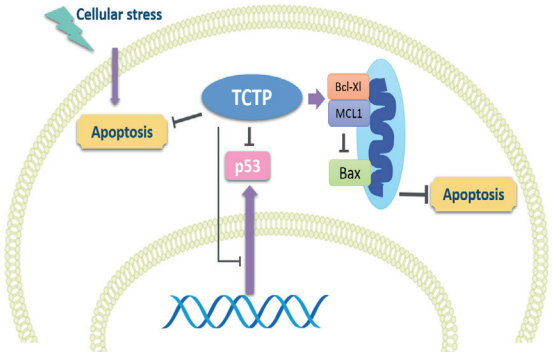

Figure1: TCTP protects cells from cell death by inhibiting apoptosis: TCTP inhibits cell death induced by cell stress and protect cells from apoptosis. TCTP also inhibits apoptosis by stabilizing antiapoptotic Bcl-2 family proteins, MCL1 and Bcl-xL and by inhibiting activation of proapoptotic Bax protein (Figure is redrawn according to reference) [14].

TCTP in tumor reversion

Nowadays, many studies have shown that TCTP is a potential target for tumor reversal. TCTP is an anti-apoptotic protein that is highly expressed in many cancer cells. The expression of TCTP is regulated by various stimulants, including dioxin, heavy metals, growth factors, and vitamin D. The TCTP gene was significantly reduced in tumor revertant cells, and it was suggested that inhibiting TCTP expression could transform cancer cells into normal phenotypes [13].

Gnanasekar et al. evaluated the effects on cell proliferation and apoptosis in prostate cancer cells reducing the effect of the TCTP gene with small interference RNAs (siRNA). As a result of the study, it was found that transfection with siRNA significantly decreased the expression of both TCTP mRNA and protein levels of TCTP and increased apoptosis [13].

In another study, Tuynder et al. found that two drugs (sertraline and thioridazine), which are actually used on psychiatry and are effective on tumor cells, bind directly to TCTP and thus inhibit the growth of cancer cells through the p53 pathway [23].

In another study conducted by Tuynder et al., It was emphasized that TCTP level was associated with cellular reprogramming. When the TCTP level was decreased with antisense or siRNA in the breast cancer cells, it was found that the deteriorated cell placement returned to normal [24].

CONCLUSION

Although the initial evidence of tumor reversion has been reported more than a hundred years ago and so far has accumulated many biological evidence, the underlying mechanism is still largely unknown. Probably, TCTP targets and modulates many proteins at the same time. However, it has been proved that TCTP is closely related to cell death and cancer and can provide tumor reversion. At this point, there is need more work about the determination of the molecular mechanism of TCTP and discovery of synthetic or nano-medical inhibitors.

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