Chapter 14
Role of TCTP for Cellular Differentiation and Cancer Therapy

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Abstract The translationally controlled tumor protein (TCTP) is a highly conserved protein that is regulated due to a high number of extracellular stimuli. TCTP has an important role for cell cycle and normal development. On the other side, tumor reversion and malignant transformation have been associated with TCTP. TCTP has been found among the 12 genes that are differentially expressed during mouse oocyte maturation, and an overexpression of this gene was reported in a wide variety of different cancer types. Its antiapoptotic effect is indicated by the interaction with several proapoptotic proteins of the Bcl-2 family and the p53 tumor suppressor protein. In this article, we draw attention to the role of TCTP in cancer, especially, focusing on cell differentiation and tumor reversion, a biological process by which highly tumorigenic cells lose their malignant phenotype. This protein has been shown to be the most strongly downregulated protein in revertant cells compared to the parental cancer cells. Decreased expression of TCTP results either in the reprogramming of cancer cells into reversion or apoptosis. As conventional chemotherapy is frequently associated with the development of drug resistance and high toxicity, the urge for the development of new or additional scientific approaches falls into place. Differentiation therapy aims at reinducing differentiation backward to the nonmalignant cellular state. Here, different approaches have been reported such as the induction of retinoid pathways and the use of histone deacetylase inhibitors. Also, PPARγ agonists and the activation of the vitamin D receptor have been reported as potential targets in differentiation therapy. As TCTP is known as the histamine-releasing factor, antihistaminic drugs have been shown to target this protein. Antihistaminic compounds, hydroxyzine and promethazine, inhibited cell growth of cancer cells and decreased TCTP expression of breast cancer and leukemia cells. Recently, we found that two antihistaminics, levomepromazine and buclizine, inhibited cancer cell growth by direct binding to TCTP and induction of cell differentiation. These data confirmed that TCTP is an exquisite target for anticancer differentiation therapy and antihistaminics have

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potential to be lead compounds for the direct interaction with TCTP as new inhibitors of human TCTP and tumor growth.

Abbreviations

ADDS	Adenylosuccinate synthase
AIF	Apoptosis-inducing factor
APL	Acute promyelocytic leukemia
ATRA	All-trans retinoic acid
Bcl-2	B-cell lymphoma 2
BMP	Bone morphogenic proteins
CH60	Mitochondrial 60 kDa heat shock protein
CHFR	Checkpoint with forkhead and ring finger domains
COF1	Cofilin-1
ENOA	α-Enolase
ER60	Probable protein disulfide isomerase
ES	Embryonic stem
FABP	Liver fatty acid-binding protein
GTA1	Glutathione S-transferase alpha
HDAC	Histone deacetylase
HSP105	Heat shock protein 105
KCRB	Creatine kinase B
Mcl-1	Myeloid cell leukemia 1
MDM2	Murine double minute 2
MPSS	Megasort and massively parallel signature sequencing
NDKA	Nucleoside diphosphate kinase A
NPM2	Nucleoplasmin 2
Oct4	Octamer-binding transcription factor 4
PDCD6IP	Programmed cell death six-interacting protein
PPARγ	Peroxisome proliferator-activated receptor-γ
PS1	Presenilin 1
RARs	Retinoic acid receptors
RMS	Rhabdomyosarcoma
SAHA	Suberoylanilide hydroxamic acid
SIAH1	Seven in absentia homologue 1
Sox2	Sex-determining region Y-box 2
STAT3	Signal transducer and activator of transcription 3
STI1	Stress-inducible phosphoprotein 1
TACC3	Transforming acidic coiled-coil protein 3
TCTP	Translationally controlled tumor protein
TSAP	Tumor suppressor-activated pathway
VDR	Vitamin D receptor

14.1 Introduction

The translationally controlled tumor protein (TCTP) encoded by the *TPT1* gene is a highly conserved protein that can be found within all eukaryotic organisms, all tissues and cell types (Oh et al. 2013; Acunzo et al. 2014). It was initially identified in Ehrlich ascites tumor cells, and no homologies to other proteins have been found at that time (Oh et al. 2013). Due to its numerous functions, it is also known as histamine-releasing factor, TPT1, p23, or fortilin (Acunzo et al. 2014; Nagano-Ito and Ichikawa 2012). It can be found in both, in the nucleus and the cytoplasm of cells, and it is regulated by a high number of extracellular stimuli. The protein interacts with itself and with a wide variety of other proteins [such as myeloid cell leukemia 1 (Mcl-1) and p53] (Acunzo et al. 2014). Furthermore, TCTP is expressed extra- and intracellularly, implicating that it is involved in many biological processes such as development (Kubiak et al. 2008; Hsu et al. 2007; Chen et al. 2007a), cell cycle (Brioudes et al. 2010; Gachet et al. 1999), cellular growth (Koziol and Gurdon 2012), protein synthesis (Cans et al. 2003), cytoskeleton (Burgess et al. 2008; Tsarova et al. 2010), immune response (MacDonald et al. 1995), cell death (Li et al. 2001; Liu et al. 2005; Yang et al. 2005), and induction of pluripotent stem cells (Acunzo et al. 2014) (Fig. 14.1). On the other hand, it has also been associated with tumor reversion and malignant transformation (Tuynder et al. 2002; Rho et al. 2011).

Its crucial biological functions have been demonstrated in several studies. Knockout of TCTP was lethal in utero in mice (Chen et al. 2007a; Susini et al. 2008), pointing to its role in normal development of organisms. Within the cell cycle, TCTP binds to tubulin and associates with the microtubules during different phases of the cell cycle (Gachet et al. 1999). In metaphase, TCTP is bound to the mitotic spindle. During the transition from metaphase to anaphase, it is dissociated from the spindle (Acunzo et al. 2014).

Phosphorylation of TCTP by PLK1 is necessary for cell cycle. Additionally, TCTP interacts with CHFR and thus prevents the entry into mitosis (Acunzo et al. 2014).

TCTP is able to interact with Mcl-1 (Li et al. 2001; Liu et al. 2005) and other members of the B-cell lymphoma 2 (Bcl-2) family (Yang et al. 2005; Susini et al. 2008) and thus plays an important role in the regulation of apoptosis. Destabilizing the tumor suppressor p53 leads to an additional antiapoptotic effect (Rho et al. 2011; Amson et al. 2011), indicating an involvement in tumorigenesis.

Besides the direct effect on the cell cycle, TCTP reduces cellular stress and protects the cell from thermal shock by binding to denatured proteins and refolding them by acting as a molecular chaperone (Gnanasekar et al. 2009). Additionally, it acts as an antioxidant by neutralizing radicals directly (Bini et al. 1997).

Due to the involvement in numerous biological cell processes, its relevance as target for cancer therapy has been discussed. Overexpression of TCTP in a large variety of cancers was reported (Acunzo et al. 2014; Nagano-Ito and Ichikawa 2012; Amson et al. 2013b; Telerman and Amson 2009; Miao et al. 2013).

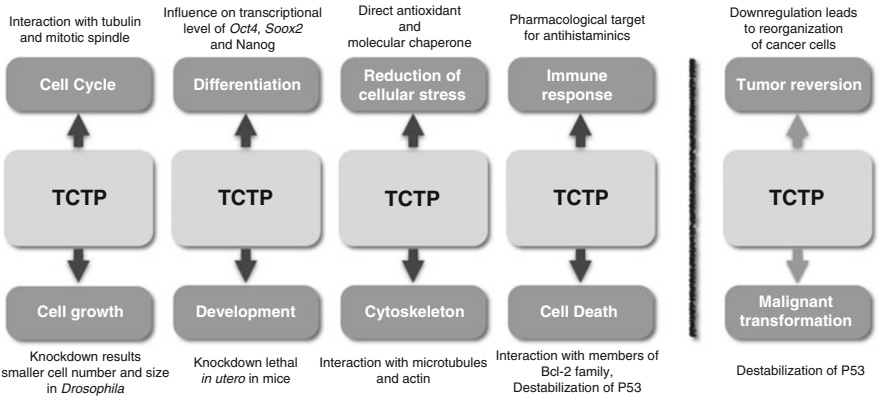

Fig. 14.1 Multiple functions of TCTP

Telerman's group demonstrated that downregulation of TCTP in MCF7 and T47D cells caused a reorganization of cells (Acunzo et al. 2014; Tuynder et al. 2002). Additionally, they showed that the protein was drastically downregulated within the process of tumor reversion and correlated with clinical and pathological parameters of the aggressiveness of breast cancer (Acunzo et al. 2014; Amson et al. 2011). This indicates a role of TCTP as prognostic factor for breast cancer (Amson et al. 2013b). A change in the expression of TCTP was associated with in vivo colon carcinogenesis. A decrease of TCTP by 2.7-fold during cell differentiation in Caco2 cells has been observed (Stierum et al. 2003), indicating the importance of the protein for the differentiation process. The limited number of tumor markers especially in colon cancer makes the retrieval for new targets more urgent (Stierum et al. 2003; Williams et al. 1996).

In other cancer types, an involvement of TCTP in tumor reversion was also found, e.g., prostate cancer, lung cancer, leukemia, erythroleukemia, glioma, lymphoma, squamous cell carcinoma, colon cancer, hepatocellular cancer, liver cancer, larynx cancer, and melanoma (Acunzo et al. 2014; Amson et al. 2013b; Miao et al. 2013). In this wide variety of cancers, higher TCTP expression levels were found in tumors compared to the corresponding normal tissues (Acunzo et al. 2014; Tuynder et al. 2002; Amson et al. 2013b; Sinha et al. 2000).

In conclusion, the involvement of TCTP in cell differentiation and tumor reversion makes it an interesting target for anticancer therapy (Acunzo et al. 2014).

14.1.1 TCTP in Differentiation Processes

Cellular differentiation is a process in the development of immature cells to more complex states. TCTP plays an important role in cell differentiation, not only in humans but also in microorganisms, plants, and animals.

TcpA, a protein with high similarity to TCTP, can be found in *Aspergillus nidulans*. TcpA plays an important role in cell cycle progression and development of this model organism. Furthermore, TcpA expression influences the balance between asexual and sexual differentiation in *A. nidulans*, further stressing its role in cell differentiation (Oh et al. 2013).

Also in plants, TCTP or homologues can be identified. In *Robinia pseudoacacia,* the TCTP homologue Rpf41 regulates symbiotic nodulation in legume, indicating an involvement of TCTP in symbiotic cell differentiation. Functional parallels in the regulation of cell division by TCTP between *Arabidopsis* and *Drosophila* were found. Here, the TCTP expression levels in the plant varied due to stress conditions such as darkness, cold, salt, drought, or heavy metals. Especially high *TCTP* gene expression was observed in physically active tissues (Chou et al. 2016). Low *TCTP* expression was found during the reversion of cells from the transformed to the normal phenotype (Chou et al. 2016). In *Arabidopsis* two isoforms AtTCTP1 and AtTCTP2 have been detected. The two TCTP homologues reveal different functions. AtTCTP1 is an important regulator of mitosis, while AtTCTP2 plays a role in vegetative reproduction (Toscano-Morales et al. 2015).

AmphiTCTP is a TCTP orthologous gene in *Amphioxus*. The expression pattern of AmphiTCTP correlated with differentiation of notochord and somite, implying a role in embryonic development (Chen et al. 2007b). In *Hydra vulgaris*, another TCTP homologue showed an expression pattern coinciding with the proliferation status (Yan et al. 2000).

TCTP is among the 12 genes that are differentially expressed during mouse oocyte maturation. The other genes are the transforming acidic coiled-coil protein 3 (TACC3), heat shock protein 105 (HSP105), programmed cell death six-interacting protein (PDCD6IP), stress-inducible phosphoprotein 1 (STI1), importin α2, adenylsuccinate synthase (ADDS), nudix, spindlin, lipocalin, lysozyme, and nucleoplasmin 2 (NPM2) (Vitale et al. 2007). Mouse embryonic stem cells represent a good model system for studying stem cell biology since murine and human embryonic stem cells share many conserved pathways in self-renewal and differentiation (Sato et al. 2003; Ginis et al. 2004). They can differentiate into two different types of neurons. Proteomic analysis of E14 cells and neurons showed that TCTP was significantly downregulated. In motor neurons, a stronger downregulation was found than in dopaminergic neurons. The TCTP expression levels were independent of the extracellular Ca^{2+}-concentrations during neuronal differentiation. This indicates an involvement of TCTP in neurogenesis through modulating tubulin expression and Ca^{2+} binding (Wang and Gao 2005). In mouse cells, TCTP expression is highly regulated at both transcriptional and translational levels by a broad range of extracellular signals (Bommer and Thiele 2004). Human embryonic stem cells represent pluripotent cells. They are able to self-renew and proliferate without limitations. Originating from the inner cell mass of the human blastocysts of the embryo, they differentiate into any fetal or adult cell type (Donovan and Gearhart 2001). A small number of key transcription factors were described for self-renewal and suppression of differentiation (Chambers et al. 2003). In embryotic stem cells, several genes are upregulated, among them octamer-binding transcription factor 4 (*Oct4*) acting as marker of pluripotency (Pesce and Schöler 2001)

and differentiation, as it is able to repress and activate the expression of different genes by directly binding to their promotor regions or indirectly by neutralizing their transcription activators (Pan et al. 2002). *Oct4* becomes silent after gastrulation in mouse and human mammalian somatic cells (Kirchhof et al. 2000). *Oct4* is highly conserved (Koziol and Gurdon 2012). For *Oct4* activation, nuclear actin polymerization is necessary in *Xenopus laevis* oocytes (Miyamoto et al. 2011). As TCTP has an actin binding site, interaction can be expected here (Koziol and Gurdon 2012). Another central player in pluripotency is Nanog, which is required for maintaining the undifferentiated state of early postimplantation embryos and ES cells (Chambers et al. 2003; Mitsui et al. 2003). It leads embryonic stem (ES) cells into self-renewal by acting in parallel with cytokine stimulation of signal transducer and activator of transcription 3 (STAT3). Nanog has exclusively been identified in ES cells (Chambers et al. 2003; Mitsui et al. 2003). In human nuclei, a change in the transcriptional level of *Oct4* and Nanog has been demonstrated under the influence of TCTP (Koziol et al. 2007). Due to its highly conserved function, an effect of TCTP on the activation of pluripotency can be predicted (Tani et al. 2007). Also, bone morphogenic proteins (BMP), which inhibit differentiation, can be seen as pluripotency markers (Masui et al. 2007). They suppress differentiation and thus lead to a higher pluripotency (Ying et al. 2003). One more important marker of pluripotency is sex-determining region Y-box 2 (Sox2), which binds Oct4 and activates genes promoting pluripotency (Nishimoto et al. 1999) and controls its inhibitors (Niwa et al. 2000). Sox2 regulates several transcription factors affecting the expression of Oct3/4 making Sox2 an essential factor for maintaining ES cells in a pluripotent state (Masui et al. 2007).

TCTP is expected to promote pluripotency in two different ways, one by directly activating pluripotency genes such as *Sox2*, *Nanog*, *Oct4*, and *Klf4* and one indirect way by inhibiting the expression of somatic genes (Koziol and Gurdon 2012).

14.2 TCTP in Cancer

14.2.1 TCTP and Tumor Reversion

Tumor reversion is a biological process, by which highly tumorigenic cells lose their malignant phenotype (Telerman and Amson 2009; Amson et al. 2013a). For instance, teratoma cells differentiated into normal somatic tissues, and tumor cells acquired the molecular circuitry that resulted in the negation of chromosomal instability, translocations, oncogene activation, and loss of tumor suppressor genes (Telerman and Amson 2009; Askanazy 1907). Telemann's group developed a series of revertants using the H1 parvovirus, which is a small DNA virus that preferentially kills tumor cells, but keeps their normal counterparts alive. They analyzed changes in gene expression (Tuynder et al. 2002, 2004; Telerman et al. 1993; Toolan 1967; Mousset and Rommelaere 1982; Nemani et al. 1996; Amson et al. 1996; Roperch et al. 1999) and identified about 300 genes as gene tumor

reversion by mRNA differential display, Megasort and massively parallel signature sequencing (MPSS) (Tuynder et al. 2002; Amson et al. 1996; Roperch et al. 1999; Liang and Pardee 1992; Brenner et al. 2000a, b; Israeli et al. 1997). P53-regulated proteins were seven in absentia homologue 1 (SIAH1), an E3 ligase and a transcriptional target of p53 (Nemani et al. 1996; Amson et al. 1996; Roperch et al. 1999; Fiucci et al. 2004), presenilin 1 (PS1), a predisposition gene for familial Alzheimer's disease (Roperch et al. 1998), tumor suppressor-activated pathway (TSAP), a transcriptional target of p53 controlling the secretion of proteins (Amson et al. 1996; Passer et al. 2003; Amzallag et al. 2004; Lespagnol et al. 2008), and translationally controlled tumor protein (TCTP), the inhibitor of p53 activity (Cans et al. 2003; Tuynder et al. 2002, 2004; Susini et al. 2008; Amson et al. 2011). Inhibition of TCTP expression increased the number of revertant cells, which regained sensitivity to contact inhibition and decreased tumor-forming capability (Telerman and Amson 2009; Tuynder et al. 2004). As TCTP was the most strongly downregulated protein in the revertant cells compared to the parental cancer cells, the effects of its inhibition in several biological and genetic models have been studied (Tuynder et al. 2002, 2004; Amson et al. 2011; Telerman and Amson 2009). Decreasing TCTP expression resulted in either reprogramming of cancer cells into revertants or apoptosis.

14.2.2 TCTP as Antiapoptotic Protein

TCTP is known to play a key role in the regulation of apoptosis. TCTP regulated antiapoptotic activity by suppressing Mcl-1 degradation through blocking its ubiquitination (Li et al. 2001; Liu et al. 2005; Yang et al. 1995). However, TCTP and Mcl-1 could independently protect cells from apoptosis (Graidist et al. 2004). TCTP interacted with other antiapoptotic proteins from the Bcl-2 family such as Bcl-xL (Yang et al. 2005) or Bax (Susini et al. 2008) (Fig. 14.2). Yang et al. identified the interaction site to the N-terminal region of TCTP and the Bcl-2 homology domain 3 of Bcl-xL and demonstrated that the TCTP N-terminal region mediates inhibition of apoptosis (Yang et al. 2005). This result corresponds to data from Zhang et al., who showed that Arg21 in the N-terminal region of TCTP was critical for TCTP binding to Mcl-1 (Zhang et al. 2002). The homodimerization of proapoptotic Bax is required for its apoptotic activity. TCTP prevented the apoptotic effect of Bax by inserting into the mitochondrial membrane and inhibiting Bax dimerization. Unlike Mcl-1 and Bcl-xL, TCTP did not directly bind Bax (Susini et al. 2008).

P53 protein is well-known as tumor suppressor. It is a transcription factor and regulates the transcription of numerous genes. It activates the transcription of DNA repair genes upon DNA damage by regulating genes involved in cell cycle and apoptosis such as Bax and Bcl-2 (Riley et al. 2008). P53 promotes apoptosis in cancer cells, whereas TCTP prevents apoptosis by repressing the transcription of p53 (Rho et al. 2011; Amson et al. 2011) (Fig. 14.2). TCTP bound p53 and prevented

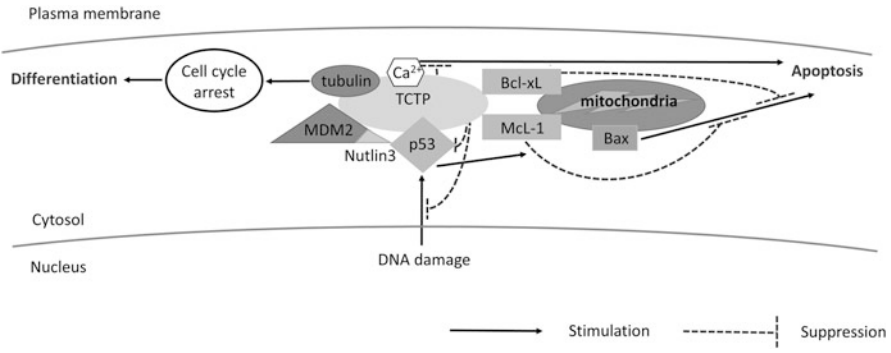

Fig. 14.2 Interaction partners of TCTP to differentiation and apoptosis regulation

apoptosis by destabilizing the protein (Rho et al. 2011). The murine double minute 2 (MDM2) is a transcriptional target of p53. If it is overexpressed, MDM2 ubiquitinates and degrades p53. TCTP directly associates with the E3 ubiquitin ligase MDM2, increasing MDM2-mediated ubiquitination of p53 and promoting its degradation (Amson et al. 2011; Amit et al. 2009) (Fig. 14.2). Nutlin-3, a protein that promotes apoptosis, blocked the interaction between MDM2 and TCTP (Funston et al. 2012) (Fig. 14.2).

14.2.3 Cell Cycle Regulation of TCTP

TCTP is involved in the cell cycle (Gachet et al. 1999). It has a tubulin-binding site that allows binding to microtubules in a cell-cycle-dependent way (Gachet et al. 1999) (Fig. 14.2). TCTP is recruited to the mitotic spindle during metaphase, but is released at the M/G1 transition (Gachet et al. 1999). TCTP interacts with the protein checkpoint by the forkhead and ring finger domains (CHFR) that binds to microtubules (Burgess et al. 2008). If microtubules are depolymerized, CHFR and TCTP interaction is reduced. This interaction senses microtubule abnormalities by CHFR that results in CHFR activation, polo-like kinase 1 (PLK1) degradation, and finally cell cycle arrest (Burgess et al. 2008). If PLK1 phosphorylation sites on TCTP were blocked, increased numbers of multinucleated cells were observed, indicating that the completion of mitosis was inhibited (Yarm 2002). This result demonstrates that TCTP is crucial for cell cycle regulation and that its phosphorylation by PLK1 is required for the precise exit from mitosis (Yarm 2002).

14.2.4 TCTP Reduces Cellular Stress

Cell death can be induced by Ca^{2+} influx. The level of TCTP is controlled by the intracellular Ca^{2+} concentration, and elevation of Ca^{2+} increased *TCTP* mRNA in cells (Xu et al. 1999). Binding of TCTP to Ca^{2+} was first reported using *Trypanosoma brucei* protein and later on using the human protein (Haghighat and Ruben 1992; Sanchez et al. 1997). Thapsigargin increased cytosolic levels by blocking the ability of the cells to pump calcium into the ER, which depletes its Ca^{2+} stores. This activated plasma membrane calcium channels allowing Ca^{2+} influx into the cytosol, thereby initiating apoptosis. The lack of TCTP resulted in exaggerated increases of Ca^{2+} in thapsigargin-challenged cells (Graidist et al. 2007). Increasing the intracellular Ca^{2+} levels beyond the normal range could damage the mitochondrial membranes and leads to the release of cytochrome C and apoptosis-inducing factor (AIF), resulting in apoptosis. Ca^{2+} binding of TCTP was required for cellular protection against thapsigargin-induced apoptosis (Graidist et al. 2007) (Fig. 14.2). TCTP binds to and scavenges Ca^{2+}, thus preventing the ion from activating downstream apoptotic execution pathways (Graidist et al. 2007) (Fig. 14.2). Thapsigargin also induced ER stress, in which unfolded proteins were accumulated in the organelle (Nagano-Ito and Ichikawa 2012). Thapsigargin decreased Ca^{2+} concentration in the ER and suppressed small molecule Ca^{2+}-dependent chaperones in the organelle, allowing accumulation of abnormal proteins, which eventually drove cells to undergo apoptosis (Nagano-Ito and Ichikawa 2012).

Therefore, it can be concluded that TCTP protects cells from ER stress-induced apoptosis by inhibiting the corresponding signal pathways.

14.3 TCTP for Differentiation Therapy

14.3.1 Approaches of Differentiation Therapy in General

Cancer cells fail to differentiate into functional mature cells, and differentiation therapy aims to reinducing differentiation backward to nonmalignant cellular states. This process is termed tumor reversion (Spira and Carducci 2003; Pierce and Wallace 1971). Differentiation therapy is based on the assumption that specific neoplastic cells exhibit aberrant patterns of differentiation and that treatment with appropriate agents results in tumor reprogramming, ultimately leading to a loss in proliferative capacity and induction of differentiation (Leszczyniecka et al. 2001). Conventional chemotherapy is frequently associated with the development of drug resistance and high toxicity, both of which limit its therapeutic efficacy (Lal et al. 1993). Stierum et al. studied protein expression changes in differentiating Caco-2 cells by proteomics approach (Stierum et al. 2003). Eleven proteins were identified including TCTP, liver fatty acid-binding protein (FABL), three forms of α-enolase (ENOA), nucleoside diphosphate kinase A (NDKA), cofilin-1 (COF1), mitochondrial 60 kDa heat shock

protein (CH60), probable protein disulfide isomerase (ER60), creatine kinase B (KCRB), and glutathione S-transferase alpha (GTA1) (Stierum et al. 2003). This differentiation-related change in phenotype of Caco-2 cells involved changes in a variety of distinct biochemical pathways (Stierum et al. 2003). The processes were related to protein folding and disulfide bridge formation, cytoskeleton formation and maintenance, nucleotide metabolism, glycolysis, as well as tumorigenesis-associated proteins (Stierum et al. 2003).

14.3.2 Retinoids

Retinoids are a class of compounds derived from vitamin A possessing the ability to regulate cell proliferation, differentiation, and apoptosis in normal and cancer cells (Garattini et al. 2007). Retinoids play a fundamental role in chemoprevention of carcinogenesis and in differentiation therapy (Hansen et al. 2000). Retinoids exert their bioactivity by binding to retinoic acid receptors (RARs) (Garattini et al. 2007). Treatment of osteosarcoma and chondrosarcoma cell lines with all-trans retinoic acid (ATRA) resulted in reversible growth inhibition and decreased colony formation (Thein and Lotan 1982; Ng et al. 1985). Clinically, ATRA is successfully applied to treat acute promyelocytic leukemia (APL) with an aberrant chromosomal translocation (Waxman 2000). This translocation results from the fusion of the *PML* gene with the *RAR* gene (*PML-RARα*) (Spira and Carducci 2003). ATRA differentiates APL cells into mature neutrophils (Huang et al. 1987a, b). Retinoids reduced cell proliferation and induced myogenic differentiation in a variety of rhabdomyosarcoma (RMS) cell lines derived from either alveolar or embryonal RMS (Luo et al. 2010; Crouch and Helman 1991; Brodowicz et al. 1999; Barlow et al. 2006).

14.3.3 Histone Deacetylase Inhibitors

Histone deacetylation by histone deacetylases (HDACs) leads to chromatin compaction. Histone deacetylation is related to transcriptional repression of tumor suppressors involved in regulating cell growth and differentiation in various cancers (Mai et al. 2005; Cress and Seto 2000). DMS53 small cell lung carcinoma cells changed their morphology upon treatment with the histone deacetylase inhibitor, trichostatin A, and showed cellular differentiation (Platta et al. 2007). Five quinolone compounds, which inhibited HDAC activity in vitro, stimulated cell differentiation at growth inhibitory concentrations in MCF-7 breast carcinoma cells (Martirosyan et al. 2004). The morphology of MCF-7 cells was changed after treatment of suberoylanilide hydroxamic acid (SAHA) or vorinostat, suggesting the induction of epithelial mammary differentiation (Munster et al. 2001).

14.3.4 PPARγ Agonists

Peroxisome proliferator-activated receptor-γ (PPARγ) is an important regulator of cell proliferation, differentiation, and apoptosis in a variety of cell types such as hepatocytes, fibroblasts, myoblasts, and adipocytes (Grommes et al. 2004; Sertznig et al. 2007). Treatment of 3T3-L1 preadipocytes and murine fibroblast cells with the PPARγ agonist, troglitazone, induced the expression of cyclin-dependent kinase inhibitors (CDKIs) p18 and p21 allowing terminal adipogenic differentiation (Morrison and Farmer 1999). Activation of PPARγ with either endogenous PPARγ agonists or synthetic agonists induced cell cycle exit by terminal differentiation of preadipocytes and fibroblast cells (Morrison and Farmer 1999; Tontonoz et al. 1994; Wahli et al. 1995). Primary human liposarcoma (LPS) cells were effectively induced to undergo terminal adipocytic differentiation after treatment of the PPARγ agonist, pioglitazone (Tontonoz et al. 1997). Furthermore, promising preclinical results about the effects in differentiation of PPARγ agonist treatment in liposarcoma have been reported in a clinical phase II trial utilizing the PPARγ agonist, rosiglitazone (Debrock et al. 2003; Dusso et al. 2005).

14.3.5 Vitamin D

Vitamin D receptor (VDR) is expressed in many cell types and tissues. It is of a small intestine, kidney, and bone and is involved in the homeostasis of calcium and minerals (Dusso et al. 2005; Nagpal et al. 2005; Samuel and Sitrin 2008). Vitamin D alters cellular proliferation through multiple mechanisms such as cell cycle progression, apoptosis, and differentiation (Dusso et al. 2005; Nagpal et al. 2005; Samuel and Sitrin 2008; Masuda and Jones 2006; Banerjee and Chatterjee 2003). Vitamin D induces cell cycle arrest by inhibiting the transition from the G1 to the S phase of the cell cycle (Bohnsack and Hirschi 2004). By affecting multiple genes, multiple effects of vitamin D on this step of the cell cycle, including p21waf1, p27kip1, cyclin D1, and so on, were observed concerning their transcription and protein stability (Bohnsack and Hirschi 2004; Liu et al. 1996; Boyle et al. 2001; Hershberger et al. 2001; Inoue et al. 1999; Rots et al. 1998; Bettoun et al. 2002). Vitamin D induced maturation of HL-60 and U937 leukemia cells (Olsson et al. 1983; Rigby et al. 1984). It also induced CDKIs such as p27kip1 and perturbated the subcellular distribution of protein phosphatases (Wang et al. 1997; Song and Norman 1998).

14.3.6 Differentiation Therapy with Antihistaminic Drugs

A novel target for differentiation therapy is TCTP, because it was the most downregulated gene in tumor reversion experiments (Tuynder et al. 2004). Since TCTP encodes for a histamine-releasing factor, Tuynder et al. hypothesized that inhibitors of the histaminic pathway could be effective against tumor cells (Tuynder et al. 2004). Antihistaminics are widely used in cancer patients as antiallergics, antidepressants, or antiemetic agents (Tuynder et al. 2004). Therefore, it is also reasonable to test their possible antiproliferative effects. Moreover, some phenothiazines, including promethazine, thioridazine, perphenazine, and chlorpromazine, revealed antiproliferative effects (Strobl et al. 1990; Gil-Ad et al. 2004; Zhelev et al. 2004). Antihistaminic compounds decreased TCTP expression, killed cancer cells, and, eventually, led to strong reversion of the malignant phenotype (Tuynder et al. 2004). Hydroxyzine and promethazine as model drugs inhibited cell growth of human leukemia U937 cells and decreased TCTP expression of breast cancer MDA-MB-231 and monocytic leukemia U937 cells (Tuynder et al. 2004). These two drugs were also investigated in vivo. The volumes of MDA-MB-231 and U937 xenograft tumors were consistently reduced by treatment with hydroxyzine or promethazine, indicating that these drugs indeed inhibited tumor growth by targeting TCTP (Tuynder et al. 2004).

We investigated a series of antihistaminic drugs as new TCTP inhibitors in a systematic way (Seo and Efferth 2016). In our study, levomepromazine and buclizine showed higher in silico binding affinities to TCTP among 12 different antihistaminic compounds including the control drugs, promethazine and hydroxyzine, by using Autodock4 and AutodockTools-1.5.7.rc1. We found that levomepromazine and buclizine bound to the same sites at TCTP as promethazine and hydroxyzine, but with higher affinities. Recombinant human TCTP protein was obtained by codon optimization, heterogeneous expression in *E. coli*, and purification using chitin affinity chromatography. We were able to experimentally validate the binding of levomepromazine and buclizine to recombinant human TCTP using microscale thermophoresis. Furthermore, we explored the effects of two selected compounds on cell growth and TCTP protein and observed indeed that they inhibited cell growth and downregulated TCTP expression in MCF-7 breast cancer cells, indicating TCTP direct binding and downregulation as causative growth-inhibitory mechanism of levomepromazine and buclizine. We also investigated the cell cycle distribution of MCF-7 cells after drug treatment using flow cytometry and found that the percentage of G1 phase cells after levomepromazine or buclizine treatment increased without showing apoptosis. The mode of the action of two compounds was investigated using annexin V/PI staining. High concentrations (IC_{50} or $2 \times IC_{50}$) of both drugs for 72 h treatment did not increase the fraction of dead cells, and most of cells were annexin V/PI negative, demonstrating that the cells were alive after treatment of two drugs. These results indicated that these two antihistaminics cause neither necrosis nor apoptosis. Therefore, they were not cytotoxic. Our cell cycle analysis and annexin V/PI staining results strongly implied

that levomepromazine and buclizine caused cell growth inhibition by G1 cell cycle arrest without induction of cell death. Moreover, trypan blue exclusion test showed that more than 90% of cells were living cells possessing intact cell membranes that excluded trypan blue staining upon treatment with IC_{50} or $2 \times IC_{50}$ concentrations of levomepromazine or buclizine for 72 h. This result is another proof that these two drugs inhibited cell growth without inducing cell death. Based on our results, we conclude that the interaction of TCTP with the apoptotic machinery was not of major mechanism for the antiproliferative effects of antihistaminic compounds. The effect of these two drugs on cell cycle arrest, annexin V/PI staining analysis, and cell viability using trypan blue staining demonstrated that cytostatic rather than cytotoxic mechanisms were operative. In order to confirm that two drugs really induced differentiation, lipid droplet staining was performed. Lipid droplets are a reliable market for functional differentiation of mammary tissues (Munster et al. 2001). Finally, we demonstrated that those two antihistaminics really induced differentiation in MCF-7 cells by increase of lipid droplets. Thus, we found that two antihistaminics, levomepromazine and buclizine, inhibited cancer cell growth by binding to TCTP and induction of cell differentiation.

On the basis of data of Tynder et al. and our study, TCTP is a novel target for anticancer differentiation therapy, and antihistaminics are promising to serve as lead compounds for cancer differentiation therapy by targeting TCTP (Tuynder et al. 2004; Seo and Efferth 2016).

14.4 Conclusions and Perspectives

Many cytotoxic agents against cancer reveal side effects such as bone marrow suppression, gastrointestinal tract lesions, hair loss, nausea, etc. because these agents are active on both malignant tumor and healthy normal cells (Thurston 2007; Jain et al. 2013). Therefore, these drugs induce cell death not only in tumors but also in normal cells (Thurston 2007; Jain et al. 2013). Since cytotoxic drugs lack sufficient tumor selectivity, they frequently cannot cure patients due to non-tolerable high side effects that prevent the application of drug doses high enough to sustainably kill all cells of a tumor.

Another treatment is differentiation therapy, which aims at reactivation of endogenous differentiation programs in cancer cells with subsequent cellular maturation and loss of the aggressive tumor phenotype (Pierce and Wallace 1971). This novel and potentially less toxic form of cancer therapy comprise agents that modify the state of differentiation and growth of cancer cells (Leszczyniecka et al. 2001). Although differentiation therapies such as retinoids, HDACI, PPARγ agonists and vitamin D have been investigated as described above, it is still relatively in its infancy.

TCTP represents an exquisite target for differentiation therapy, since downregulation of TCTP was responsible for the reprogramming of cancer cells into revertants (Tuynder et al. 2002, 2004). The antihistaminics, promethazine and

hydroxyzine, showed the inhibition of TCTP indicating that antihistaminic drugs can be a suitable class of TCTP inhibitors (Tuynder et al. 2002, 2004). Furthermore, our study demonstrated that antihistaminic drugs, levomepromazine and buclizine, inhibited the breast cancer cell line MCF-7 growth by binding to TCTP and induce cell differentiation (Seo and Efferth 2016). Those studies showed the potential that differentiation therapy with higher tumor specificity and less side effects than cytotoxic therapy can be reached using antihistaminic TCTP inhibitors.

A synergistic effect was reported between the downregulation of TCTP by siRNA and antisense oligonucleotides in combination with docetaxel treatment of prostate cancer models in vitro and in vivo (Baylot et al. 2012). This result demonstrates that TCTP knockdown with docetaxel therapy could serve as a novel strategy to treat castration-resistant prostate cancer (Baylot et al. 2012).

Hence, the combination of the targeting of TCTP with classical chemotherapy is worth to be investigated, because it might reveal synergistic effects and the opportunity of treating cancer in a more effective way with higher response rates, lower risks of tumor resistance, and fewer side effects with treatment of less concentration of cytotoxic substances.

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