

Adam Telerman  
Robert Amson *Editors*

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# TCTP/tpt1 - Remodeling Signaling from Stem Cell to Disease

# **Results and Problems in Cell Differentiation**

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Adam Telerman • Robert Amson  
Editors

# TCTP/tpt1 - Remodeling Signaling from Stem Cell to Disease

 Springer

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# Contents

<b>1</b>	<b>Introduction: How We Encountered TCTP and Our Purpose in Studying It</b> . . . . .	<b>1</b>
	Adam Telerman and Robert Amson	
1.1	The Initial Years: The Tumor Reversion Project . . . . .	2
1.2	Learning to Work with High-Throughput Technology and the First Molecular Data . . . . .	3
1.3	The Year 2000: Giving a Decisive Turn into the Understanding of the Tumor Reversion Program . . . . .	3
1.4	The P53-TCTP Reciprocal Negative Feedback Loop and the Clinical Significance . . . . .	4
1.5	Conclusion and Perspectives . . . . .	5
	References . . . . .	6
<b>2</b>	<b>Structural Insights into TCTP and Its Interactions with Ligands and Proteins</b> . . . . .	<b>9</b>
	Nadine Assrir, Florian Malard, and Ewen Lescop	
2.1	Introduction . . . . .	9
2.2	Sequence and Structure of TCTP . . . . .	10
2.2.1	Description of the Structure of TCTP . . . . .	10
2.2.2	Structural Homologues of TCTP . . . . .	12
2.2.3	Functional Elements Within TCTP Sequence . . . . .	17
2.3	Binding Properties and Structural Aspects of TCTP in Complex with Ions, Small Molecules, Carbohydrates, Peptides, and Nucleic Acids . . . . .	21
2.3.1	Calcium Binding . . . . .	21
2.3.2	Antihistaminic Drugs and the Related Sertraline/Thioridazine . . . . .	23
2.3.3	Peptides . . . . .	26
2.3.4	Heme, Artemisinine, and Analogs . . . . .	26
2.3.5	Nucleic Acids . . . . .	27

2.3.6	<i>Bombyx mori</i> TCTP as a Binding Platform for Saccharides . . . . .	28
2.4	Structural Aspects of TCTP in Complex with Proteins . . . . .	29
2.4.1	TCTP Directly Interacts with Dozens of Proteins . . . . .	29
2.4.2	Structural Information on Native Complexes . . . . .	35
2.4.3	TCTP Tends to Self-associate . . . . .	38
2.5	Conclusions . . . . .	38
	References . . . . .	40
<b>3</b>	<b>Structure-Function Relationship of TCTP . . . . .</b>	<b>47</b>
	Beatriz Xoconostle-Cázares and Roberto Ruiz-Medrano	
3.1	Introduction . . . . .	48
3.2	Conserved Functions of TCTP Across Kingdoms . . . . .	49
3.3	Taxon-Specific Functions of TCTP . . . . .	50
3.3.1	Fungi . . . . .	51
3.3.2	Plants . . . . .	52
3.3.3	Blood-Borne and Other Vertebrate Parasites . . . . .	55
3.4	Non-cell Autonomous Functions of TCTP . . . . .	60
3.5	Perspectives . . . . .	63
	References . . . . .	64
<b>4</b>	<b>The Translational Controlled Tumour Protein TCTP: Biological Functions and Regulation . . . . .</b>	<b>69</b>
	Ulrich-Axel Bommer	
4.1	Introduction . . . . .	70
4.1.1	The ‘Translationally Controlled Tumour Protein TCTP’: Names and History . . . . .	71
4.1.2	Gene Structure and mRNA . . . . .	72
4.1.3	Molecular Structure, Conservation and Interactions . . . . .	74
4.2	Biological Functions of TCTP . . . . .	75
4.2.1	Maintaining Cell Homeostasis and Survival . . . . .	75
4.2.2	Involvement in the Cell Cycle and in Early Development . . . . .	81
4.2.3	TCTP in Cell Growth Regulation, Protein Synthesis and Degradation . . . . .	85
4.2.4	Extracellular Functions of TCTP . . . . .	88
4.3	Involvement of TCTP in Disease Processes . . . . .	91
4.3.1	TCTP in Human Cancer . . . . .	91
4.3.2	Participation in Immunological Reactions . . . . .	98
4.3.3	TCTP in Lower Animals and Parasitic Infections . . . . .	100
4.3.4	TCTP in Other (Patho)physiological Processes . . . . .	103
4.4	Regulation of Cellular TCTP Levels . . . . .	105
4.4.1	Cell Physiologic Conditions That Result in Regulation of TCTP Levels . . . . .	105
4.4.2	Mechanisms Involved in Regulation of Cellular TCTP Levels . . . . .	105

4.5	Synopsis . . . . .	112
	References . . . . .	114
<b>5</b>	<b>Current Understanding of the TCTP Interactome . . . . .</b>	<b>127</b>
	Siting Li and Feng Ge	
5.1	Introduction . . . . .	127
5.2	Global Interactome Profiling Methods . . . . .	128
5.3	The Current Knowledge of the TCTP Interactome . . . . .	129
	5.3.1 Chaperone Proteins . . . . .	130
	5.3.2 Nucleic Acid-Binding Proteins . . . . .	130
	5.3.3 Cytoskeletal Proteins . . . . .	130
	5.3.4 Other Functions . . . . .	132
5.4	Concluding Remarks . . . . .	133
	References . . . . .	133
<b>6</b>	<b>Role and Fate of TCTP in Protein Degradative Pathways . . . . .</b>	<b>137</b>
	Michel Vidal	
6.1	Introduction . . . . .	138
6.2	TCTP as Protein Stabilizer . . . . .	138
	6.2.1 TCTP Masks the Ubiquitination Sites of Its Partners . . . . .	139
	6.2.2 TCTP Binding Leads to E3 Ligase Degradation . . . . .	140
	6.2.3 Mmi1/ScTCTP Modulates Proteasome Activity . . . . .	140
6.3	TCTP as Degradation Inducer . . . . .	141
6.4	TCTP Degradation . . . . .	142
6.5	Conclusion . . . . .	144
	References . . . . .	146
<b>7</b>	<b>Roles of the Translationally Controlled Tumor Protein (TCTP) in Plant Development . . . . .</b>	<b>149</b>
	Léo Betsch, Julie Savarin, Mohammed Bendahmane, and Judit Szecsi	
7.1	Introduction . . . . .	149
7.2	Features of Plant TCTP Genes . . . . .	150
7.3	TCTP Is Essential for Plant Development . . . . .	154
7.4	Role of TCTP in Plant Signaling . . . . .	158
	7.4.1 Is TCTP a Component of the TOR Pathway? . . . . .	158
	7.4.2 Role of TCTP in Hormone Signaling . . . . .	160
	7.4.3 Response to Abiotic and Biotic Stresses . . . . .	162
7.5	Conclusion . . . . .	166
	References . . . . .	166
<b>8</b>	<b>Function of Translationally Controlled Tumor Protein in Organ Growth: Lessons from Drosophila Studies . . . . .</b>	<b>173</b>
	Kwang-Wook Choi, Sung-Tae Hong, and Thao Phuong Le	
8.1	Introduction . . . . .	173
8.2	Identification of <i>Drosophila</i> Tctp Function in Organ Growth . . . . .	174



8.3	Role of Tctp in TOR Signaling . . . . .	175
8.4	Regulation of Tctp Function by 14-3-3 . . . . .	178
8.5	Effects of 14-3-3 Isoforms and Tctp on Cyclin E . . . . .	181
8.6	Tctp Function in DNA Damage Control . . . . .	181
8.7	Tctp in Chromatin Remodeling and Genome Stability . . . . .	184
8.8	Concluding Remarks . . . . .	185
	References . . . . .	187
<b>9</b>	<b>Translationally Controlled Tumor Protein (TCTP/HRF) in Animal Venoms . . . . .</b>	<b>193</b>
	Andrea Senff-Ribeiro	
9.1	Introduction . . . . .	193
9.2	<i>Loxosceles intermedia</i> TCTP . . . . .	194
9.3	Other TCTPs Found in Animal Venoms . . . . .	196
9.4	Perspectives . . . . .	198
	References . . . . .	199
<b>10</b>	<b>Tctp in Neuronal Circuitry Assembly . . . . .</b>	<b>201</b>
	Cláudio Gouveia Roque and Christine E. Holt	
10.1	Introduction . . . . .	202
10.1.1	Features of Axon Development . . . . .	202
10.1.2	Axonal mRNA Localization: One in Thousands . . . . .	202
10.1.3	Axon Guidance and Cancer: Shared Features . . . . .	205
10.1.4	Axonal Mitochondria . . . . .	207
10.2	TCTP in Neuronal Circuitry Assembly . . . . .	207
10.3	Summary and Future Directions . . . . .	212
	References . . . . .	213
<b>11</b>	<b>Elusive Role of TCTP Protein and mRNA in Cell Cycle and Cytoskeleton Regulation . . . . .</b>	<b>217</b>
	Jacek Z. Kubiak and Malgorzata Kloc	
11.1	TCTP and Cell Cycle . . . . .	218
11.1.1	The Role of TCTP Protein . . . . .	218
11.1.2	The Role of TCTP mRNA . . . . .	220
11.2	TCTP and Cytoskeleton . . . . .	221
11.2.1	TCTP and Microtubules . . . . .	222
11.2.2	TCTP and Actin . . . . .	223
11.3	Conclusions . . . . .	223
	References . . . . .	223
<b>12</b>	<b>The Translationally Controlled Tumor Protein and the Cellular Response to Ionizing Radiation-Induced DNA Damage . . . . .</b>	<b>227</b>
	Jie Zhang, Grace Shim, Sonia M. de Toledo, and Edouard I. Azzam	
12.1	Introduction . . . . .	228
12.2	Primary Effects of Ionizing Radiation . . . . .	230
12.2.1	Direct and Indirect Effects of Ionizing Radiation . . . . .	230

12.3	Endogenous and Radiation-Induced DNA Alterations . . . . .	232
12.3.1	DNA Damage Response Pathways and DNA Damage Repair Mechanisms . . . . .	233
12.4	TCTP and the Sensing of Genotoxic Stress . . . . .	237
12.5	TCTP and the Repair of DNA Damage . . . . .	240
12.6	TCTP and Control of Cell Cycle Progression Under Normal and Stress Conditions . . . . .	242
12.7	TCTP and Cell Death . . . . .	244
12.8	Perspective . . . . .	245
	References . . . . .	247
<b>13</b>	<b>TCTP Has a Crucial Role in the Different Stages of Prostate Cancer Malignant Progression . . . . .</b>	<b>255</b>
	Virginie Baylot, Sara Karaki, and Palma Rocchi	
13.1	TCTP Is Upregulated in Prostate Cancer . . . . .	256
13.2	TCTP: A Promising Target in Castration-Resistant Prostate Cancer . . . . .	256
13.2.1	TCTP Mediates Heat Shock Protein 27 Cytoprotective Function in CRPC . . . . .	256
13.2.2	TCTP and P53 in CRPC: “Neither Can Live While the Other Survives” . . . . .	257
13.2.3	Development of a TCTP Antisense Oligonucleotide for Clinical Applications . . . . .	259
13.3	Discussion . . . . .	260
	References . . . . .	260
<b>14</b>	<b>Role of TCTP for Cellular Differentiation and Cancer Therapy . . . . .</b>	<b>263</b>
	Ean-Jeong Seo, Nicolas Fischer, and Thomas Efferth	
14.1	Introduction . . . . .	265
14.1.1	TCTP in Differentiation Processes . . . . .	266
14.2	TCTP in Cancer . . . . .	268
14.2.1	TCTP and Tumor Reversion . . . . .	268
14.2.2	TCTP as Antiapoptotic Protein . . . . .	269
14.2.3	Cell Cycle Regulation of TCTP . . . . .	270
14.2.4	TCTP Reduces Cellular Stress . . . . .	271
14.3	TCTP for Differentiation Therapy . . . . .	271
14.3.1	Approaches of Differentiation Therapy in General . . . . .	271
14.3.2	Retinoids . . . . .	272
14.3.3	Histone Deacetylase Inhibitors . . . . .	272
14.3.4	PPAR $\gamma$ Agonists . . . . .	273
14.3.5	Vitamin D . . . . .	273
14.3.6	Differentiation Therapy with Antihistaminic Drugs . . . . .	274
14.4	Conclusions and Perspectives . . . . .	275
	References . . . . .	276

<b>15 Targeting TCTP with Sertraline and Thioridazine in Cancer Treatment</b> . . . . .	283
Robert Amson, Christian Auclair, Fabrice André, Judith Karp, and Adam Telerman	
15.1 Introduction . . . . .	283
15.2 Experimental Approach . . . . .	284
15.3 Conclusion and Therapeutic Perspectives . . . . .	288
References . . . . .	289
<b>16 History of Histamine-Releasing Factor (HRF)/Translationally Controlled Tumor Protein (TCTP) Including a Potential Therapeutic Target in Asthma and Allergy</b> . . . . .	291
Susan M. MacDonald	
16.1 Introduction/Cloning . . . . .	292
16.2 Clinical Relevance of HRF/TCTP . . . . .	293
16.3 HRF/TCTP Extracellular Functions . . . . .	294
16.4 Other Functions of HRF/TCTP (Mainly Intracellular) . . . . .	295
16.5 An Inducible HRF/TCTP Transgenic Mouse . . . . .	296
16.6 The Importance of Ship-1 on HRF/TCTP Signaling . . . . .	298
16.7 Additional Intracellular Signaling by HRF/TCTP . . . . .	300
16.8 HRF/TCTP as a Therapeutic Target . . . . .	301
16.9 Summary . . . . .	303
References . . . . .	304
<b>Conclusion</b> . . . . .	309

# Chapter 1

## Introduction: How We Encountered TCTP and Our Purpose in Studying It

Adam Telerman and Robert Amson

**Abstract** In this brief introduction, we describe our encounter with TCTP. Back in 2000, we discovered TCTP in two quite different ways: first, we looked at protein partners of TSAP6 and one of them was TCTP. Then, in collaboration with Sidney Brenner, we performed a high-throughput differential screening comparing the parental cancer cells with revertants. The results indicated that TCTP was of the most differentially expressed genes. These two approaches were carried out only months apart. They guided our research and led to the discoveries of drugs that inhibit the function of TCTP. Much of the preclinical data on sertraline as an inhibitor of TCTP in cancer were obtained with Judith Karp at Johns Hopkins. This drug is now given in combination with Ara-C to patients in a phase I clinical trial for Acute Myeloid Leukemia. We will here detail how all this happened in our lab while working around one central project: tumor reversion.

It is both fascinating and challenging to edit the very first book on a protein. The implication of Translationally Controlled Tumor Protein (TCTP) in disease was discovered by Susan MacDonald at Johns Hopkins University: she identified it as the histamine-releasing factor (HRF) (MacDonald et al. 1995). Only later its function in cancer and more specifically in tumor reversion was discovered (Tuynder et al. 2001a, b, 2002, 2004; Amson et al. 2013a, b; Telerman and Amson 2009). Today, we know much more about TCTP and the mechanisms by which it controls cell fate. The fact that it is present in all eukaryotes, in stem cells, and that it interacts with the apoptotic machinery—including members of the Bcl2 family as well as p53-mdm2—makes of it a key-protein in regulatory processes (Amson et al. 2012b; Cans et al. 2003; Susini et al. 2008; Thebault et al. 2016).

In this book, we gave voice to some of the scientists that provided the most significant advances in the field. We have chosen not to devote chapters on describing the genetic and biologic studies on TCTP done in our laboratory,

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which have already been reviewed extensively. Our single chapter concerns TCTP as a target in the treatment of cancer and the clinical study that we initiated together with Judith Karp, from Johns Hopkins.

Our introduction sheds light, for the first time, on how those discoveries were made in our laboratory. Indeed, we have been asked numerous times to describe those events in detail, since this could be relevant for young researchers in planning their work.

## 1.1 The Initial Years: The Tumor Reversion Project

When we were doing our postdoctoral training at the Weizman Institute of Science, the vast majority of the investigators in the field of cancer sought to understand how a normal cell becomes a tumor cell. At that time, oncogenes were the main focus of research in almost every oncology laboratory worldwide. When we decided to set up our laboratory, it seemed to us pointless to concentrate our efforts on a project in which some of the strongest intellects in the field of biology had already made such tremendous contributions to answer that question. We thought that there was a different way to proceed in cancer research: not trying to understand how a normal cell becomes malignant, but rather how a malignant cell can quit its malignant phenotype (Telerman et al. 1993a, b, c). This laid the basis of the tumor reversion project (Telerman and Amson 2009). Max Askanazy had already provided at the beginning of the twentieth century the most striking example of tumor reversion (Askanazy 1907; Telerman and Amson 2009). He observed that ovarian carcinoma was composed of a homogeneous tumor cell population at an early stage, and that ultimately these cells differentiate into teeth and hairs. This quite unbelievable observation turned out to be of dramatic importance. If an ovarian carcinoma cell could become hair or teeth, it meant that those cancer cells could be entirely reprogrammed. It is precisely this reprogramming at the genetic and molecular level that became our project for almost 30 years now. In the 1950–1960s, Armin Braun (1951, 1959, 1965) confirmed tumor reversion in plants. Later, a series of investigators found in cellular systems, consisting mostly of *in vitro* cultures, that in very rare instances cancer cells transformed by oncogenes could lose their malignant phenotype (Bissell and Labarge 2005; Brinster 1974; Ge et al. 2011; Hendrix et al. 2007; Macpherson 1965; Mintz and Illmensee 1975; Pierce and Dixon 1959; Telerman and Amson 2009; Weaver et al. 1997). In most of the cases, this was due to the loss of the transforming oncogene, but not in all cases.

When we started our laboratory we found that there was a desperate need for the proper biological models to study the molecular pathways of tumor reversion. This is why we sought to obtain parental malignant cells and derive from those the revertant ones. Another laboratory in Brussels studied at that time a quite peculiar virus: the H1 Parvovirus that kills preferentially cancer cells while sparing their normal counterparts (Mousset and Rommelaere 1982; Toolan 1967). We thought that we could use the H1 Parvovirus as a negative selective agent that would kill the

malignant cells but spare those that would have reverted and lost some of their malignant properties. With the help of Marcel Tuynnder we started the experiments with the human erythroleukemia cell line K562 and after three rounds of infection with the Parvovirus we succeeded in rescuing the cells with a suppressed malignant phenotype, which we called “KS” for “K562 Suppressed” (Telerman et al. 1993a, b, c). In the following years, we expanded the experiment to different types of cancer—leukemia, breast, colon, lung, and melanoma (Tuynnder et al. 2004, 2002). The next step was to provide a differential analysis of gene expression between the malignant and the revertant cells (Tuynnder et al. 2002).

## **1.2 Learning to Work with High-Throughput Technology and the First Molecular Data**

In 1994 after publishing our first work on tumor reversion we moved to Paris, France, to join Daniel Cohen and Jean Dausset at the Fondation Jean Dausset—Centre d’Etude du Polymorphisme Humain. Daniel Cohen had made a tremendous contribution in creating a human genome center with the highest scientific standards and the most up-to-date technology and we could learn from the way they envisaged the progress in biology. Things had to be fast, precise, efficient, and large scale. We used the method of Liang and Pardee (1992) to make a first differential gene analysis using Moshe Oren’s system of M1/LTR6 cells (Yonish-Rouach et al. 1991). This yielded with the first ten differentially expressed genes that have later been proven to be so useful for our studies of tumor reversion (Telerman et al. 1996; Amson et al. 2000, 1996; Linares-Cruz et al. 1998; Nemani et al. 1996; Roperch et al. 1998, 1999). Another inspiring mentor, Georges Charpak, helped us in quantifying these data in such an elegant way with his new developed technology (Amson et al. 1996).

## **1.3 The Year 2000: Giving a Decisive Turn into the Understanding of the Tumor Reversion Program**

We divided our laboratory in several groups. Marcel Tuynnder was focused on the biological models of tumor reversion and their characterization. Laurent Susini was working on the differential gene expression analysis, Giusy Fiucci on the murine knockout models, and the crystallography and Brent Passer on the yeast two hybrid analysis.

We teamed up with Sydney Brenner that had just developed the Megasort and MPSS screening strategies (Brenner et al. 2000a, b). Laurie Goodman from Brenner’s lab came to Paris with a short list of the ten mostly differentially expressed genes between the U937 cancer cells and their revertants, the US cells (Tuynnder et al. 2000, 2001a, b). At the top of the list was Translationally Controlled

Tumor Protein (TCTP) with 248 signals in the parental U937 cancer cells versus 2 in the revertant US cells using Megasort, and this was proportional to the amount of mRNA. Decreasing TCTP by siRNA induced cell death in the parental U937 cells and a reprogramming of breast cancer cells into structures with a similar architecture of normal cells. These results were presented at the Annual Meeting on Oncogenes, Frederick, Maryland, USA, June 2001 and also at the Conference on Programmed Cell Death, Cold Spring Harbor, September 2001. The work on the anti-apoptotic of TCTP has been confirmed by another group a couple of months later; unfortunately, they changed the name of TCTP and invented a new one (Li et al. 2001).

Meanwhile, on the other side of our laboratory, Brent Passer was investigating one of the genes we had previously identified, TSAP6 (Amson et al. 1996; Amzallag et al. 2004; Passer et al. 2003). Among the potential partner proteins of TSAP6 Brent found the Histamine Releasing Factor (HRF) (MacDonald et al. 1995) that was just another name for TCTP. Brent had come to these results before we received the short list from Sydney Brenner. Later, we found that TSAP6 was promoting the secretion of TCTP via the exosomal pathway (Amzallag et al. 2004; Lespagnol et al. 2008). As explained later in the book, it was this HRF function of TCTP that led us to the discovery of the first drugs inhibiting the function of TCTP.

## **1.4 The P53-TCTP Reciprocal Negative Feedback Loop and the Clinical Significance**

It took us a long time to understand how TCTP functions and what are the molecular mechanisms that it regulates (Amson et al. 2013b). We first observed that in different biological models, increasing P53 was decreasing TCTP (Amson et al. 2012a). In contrast, overexpression of TCTP strongly decreased P53. So we tried to understand what was really going on; Alexandra Lespagnol found that the promoter of TCTP has a consensus-binding site for P53 and that this results in a negative regulation of TCTP. On the other side, TCTP promotes the degradation of P53 by stabilizing MDM2. Together with Pier Paolo Di Fiore, Salvatore Pece, and Jean-Christophe Marine, we investigated the details of these mechanisms and most importantly how it applied to stem cell biology and breast cancer, this time in patients. TCTP was highly expressed in normal breast stem cells and in breast cancer like stem cells. Decreasing TCTP inhibited the colony forming efficiency in mammosphere assays. Di Fiore's group also made the observation that in a cohort of 508 breast cancer patients, tumors with high levels of TCTP induced a more aggressive disease and a poor prognosis. Accordingly, low levels of TCTP led to a significantly better survival. TCTP stands as a prognostic marker on its own.

The search for a drug targeting TCTP in cancer treatment is addressed further in this book and deserves a chapter on its own. Briefly, as soon as we saw that decreasing TCTP could be of potential clinical relevance, we searched for