Results and Problems in Cell Differentiation 64

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TCTP/tpt1 - Remodeling Signaling from Stem Cell to Disease

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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 Weitzman 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 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 Tuynder 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 (Tuynder et al. 2004, 2002). The next step was to provide a differential analysis of gene expression between the malignant and the revertant cells (Tuynder 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 Polymorphysme 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 Tuynder 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 (Tuynder 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