TCTP, Cell Biology and Disease

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Translationally controlled tumour protein (TCTP) is multifunctional protein expressed in essentially all eukaryotic organisms. It is a cytoprotective protein that is involved in many basic biological processes, such as cellular stress responses, growth and development. Dysregulation of TCTP occurs in various disease processes, and recently the participation of TCTP in several cancer-promoting pathways has been unveiled. Understanding the core biological functions of TCTP, the mechanisms underlying its cellular regulation and its participation in disease processes is essential for the design of effective anti-cancer strategies that may involve targeting of TCTP. To provide a current overview of the knowledge in this area, we published a review article in *Cells*, which represents a detailed compilation of the recent progress in this field . Here, we give a brief overview on the core findings that are reported in this article.

Keywords: TCTP (also HRF or fortilin) ; growth and development ; biological stress reactions ; regulation of protein synthesis ; cancer ; cardiovascular diseases ; allergic diseases

1. TCTP

TCTP, also referred to, as ‘histamine releasing factor’ (HRF), ‘fortilin’ or ‘P23’, was first discovered almost 40 years ago. The protein is not related to any other known protein family, and it took about two decades, until the first papers about cell biological functions of TCTP were published. These early-described functions, reported around the beginning of the century, comprised its cell cycle-dependent association with the cytoskeleton, its anti-apoptotic activity, its association with the translational machinery, and its activity as a cancer-promoting agent. Since then, a large number of interacting proteins and hence additional functional aspects of TCTP have been described, apart from its participation in various disease processes. In 2017, the first ‘TCTP book’ was published, comprising 16 review articles that covered a wide range of topics relating to this protein [1]. Yet another review focused on the involvement of TCTP (fortilin) in diseases other than cancer [2]. Since this time, a considerable number of new papers reported novel aspects of the biological functions of TCTP, of the mechanisms that are involved in regulating cellular TCTP levels, and on how dysregulation of the protein may contribute to various disease processes. Here we summarise the core points of these recent findings, as described in more detail in our review article [3]:

2. Cell biological functions of TCTP

Growth and development: The involvement of TCTP in the cell division process, its role in stabilising polar spindle microtubules and the importance of mitotic phosphorylation of TCTP by Plk1 were known for quite some time. A recent paper also established a regulatory role of TCTP at the G1/S transition of the cell cycle in plants and insects [4]. Several interesting examples of TCTP’s involvement in organ development were published recently. These include a role of TCTP in *Drosophila* for the proliferation of intestinal stem cells and tissue regeneration [5], the importance of the protein for development of the nervous system in vertebrates, specifically its role in axon guidance of the visual system [6], and as local signal to initiate lateral root formation in plants [7].

Protein synthesis: One of the early functional observations on TCTP was its interaction with translation elongation factor EF1A and its guanine nucleotide exchange factor EF1B [8]. Meanwhile, detailed structural studies confirmed that the binding to EF1B is the most conserved interaction of TCTP. The recently discovered interactions of TCTP with two additional ribosomal factors further substantiated its association with the translational machinery. These factors are EF1A2, an isoform of EF1A preferentially expressed in neuronal tissues [9], and RACK1 [10], a ribosome-associated protein located closely to the mRNA entry site of the ribosome. It is likely that TCTP modulates EF1A activity and thus translation rates generally. However, whether this differentially affects the translation of specific mRNAs remains an open question.

Protein stability regulation: TCTP is well-known to regulate the stability of a series of client proteins [3]. It stabilises proteins by interfering with their ubiquitination and thus targeting to the proteasome, for example the anti-apoptotic protein Mcl-1 and hypoxia-inducible factor HIF1α. On the other hand, TCTP can also actively promote the degradation of proteins, such as tumour suppressor protein p53 [11] or cell cycle protein phosphatase Cdc25 [12], by enhancing their ubiquitination.

Biological stress responses: The role of TCTP as an anti-apoptotic protein was established very early and was confirmed in several additional papers [1]. TCTP is able to protect cells in a range of specific stress conditions, such as in DNA damage [13][14] or the unfolded protein response in the ER [15]. Similarly, TCTP partially protected plants under salt and osmotic stress conditions [16]. The involvement of TCTP in autophagy, another cell homeostatic mechanism, was recently studied in a few papers [17], although its precise effect on autophagy is still a matter of debate [3].

3. Regulation of cellular TCTP levels

Since TCTP is involved in various stress responses, it is not surprising that its cellular levels are highly regulated upon alterations of cell physiologic conditions. Whilst the initial observations on TCTP indicated that its synthesis is translationally regulated, we now know that TCTP may be regulated at all levels of gene expression, as well as by protein stability regulation.

Transcriptional regulation: An early study showed that TCTP is regulated through cAMP-PKA signalling via transcription factor CREB [18]. More recently, two additional transcription factors that regulate TCTP synthesis were described, i.e. the tumour suppressor protein p53, which negatively regulates TCTP expression [11], and the insulin-response element binding protein 1 (IRE-BP1) [10].

Translational regulation: The following control mechanisms have been reported to regulate TCTP mRNA translation: 1. Growth factor-dependent induction of TCTP synthesis is activated through the mTORC1 signalling pathway [19], which requires the 5'-terminal oligopyrimidine tract (5'-TOP) of the mRNA. 2. Due to the structured nature of the TCTP mRNA, its translation is negatively regulated through activation of protein kinase R (PKR), resulting in localised phosphorylation of initiation factor eIF2α [20]. 3. The differential expression of two TCTP paralogs within the life cycle of Trypanosomes is based on mRNA stability regulation [21]. 4. TCTP mRNA translation may also be regulated by certain micro-RNAs, particularly in cancer [3]; 5. Long-distance transport of TCTP mRNA and its localised expression was shown to be important for lateral root formation in plants [7]; where the signal for transport is provided by m^5C-methylation of the TCTP mRNA [22].

Protein stability regulation: Cellular TCTP levels may also be regulated via stability regulation of the protein itself. Two other cytoprotective proteins, Mcl-1 and Hsp27, were reported to stabilise TCTP [3], and recently it was shown that, under serum starvation conditions, TCTP is targeted for lysosomal degradation through chaperone-mediated autophagy (CMA) [23]. Drug-dependent degradation of TCTP via the ubiquitin-proteasome pathway was also observed, e.g. induced by dihydroartemsinin (DHA) [24].

4. Dysregulation of TCTP in diseases

Mechanisms of cancer promotion: The importance of TCTP for cancer development was initially demonstrated by the finding that inhibition of TCTP is an important part of the tumour reprogramming/reversion process, where cancer cells revert to cells with a significant decrease in their malignant phenotype [25]. Since then, numerous examples have been published showing that TCTP is overexpressed in cancers [26] and that, in cancer patients, a high TCTP status is associated with a poor outcome [3]. Several core biological processes participate in cancer development, and TCTP was shown to be involved in almost all of them: 1. TCTP activates the mTOR pathway[27] and is important for orderly cell cycle progression [12]. 2. TCTP is involved in DNA damage repair [14] and in maintaining genome stability [13]. 3. As an anti-apoptotic protein, TCTP protects cancer cells in stress conditions, and an important mechanism here is its antagonism to the tumour suppressor protein p53 [11]. 4. TCTP is involved in maintaining the stemness in both normal [5] and cancer [11] stem cells. 5. TCTP also has a role in promoting epithelial to mesenchymal transition (EMT) and cell migration and metastasis [28]. 6. Elevated TCTP levels in cancer cells contribute to the development of increased radio- or chemoresistance [3].

TCTP in cardiovascular and metabolic diseases: Dysregulation of TCTP furthermore plays a role in disease conditions other than cancer. The cytoprotective and growth-promoting properties of TCTP may contribute to disease prevention. For example, cardiomyocyte-specific overexpression of TCTP reduced the susceptibility to cardiac dysfunction in mice [29]. Similarly, specific knockout of TCTP in mouse pancreatic β-cells resulted in reduced cell proliferation, in a decreased insulin production and eventually in hyperglycaemia [30]. Examples of TCTP promoting disease include atherosclerosis,

where TCTP was found to prevent apoptosis and hence the reduction of macrophages, one of the main players in atherosclerotic lesions [31]. In another study, TCTP overexpression resulted in systemic hypertension, which also promotes atherosclerosis in mice [32]. TCTP is a disease-causing factor in pulmonary arterial hypertension (PAH), a lethal condition, by driving the excessive proliferation of pulmonary endothelial cells [33]. In diabetic nephropathy, TCTP promotes podocyte growth, and TCTP knockdown prevented the development of nephropathy in diabetic mice [34].

TCTP/HRF in allergic and immune diseases: The extracellular function of TCTP as histamine releasing factor (HRF) was discovered as early as 1995. Since then, various activities of TCTP/HRF in triggering cellular responses in the context of allergic and other immune disorders have been reported [35]. However, a more in-depth understanding of the role of TCTP in these processes have only been achieved within the last ten years, and this comprises the following core points [36]: 1. It is the dimeric form of TCTP/HRF, which exerts this extracellular function. 2. HRF binds to a subset of IgE molecules on the surface of mast cells, triggering the release of histamine. 3. The role of TCTP/HRF in the following allergic and immune disorders has been confirmed: Asthma, atopic dermatitis, food allergy and chronic urticaria [36].

5. Applications and Influences

Given the involvement of TCTP in several cancer-promoting processes, it is obvious that TCTP is potentially an important target for cancer treatment. Several established drugs are known to target TCTP, typically for ubiquitination and proteasomal degradation. Examples are sertraline and thioridazine, which are able to reduce TCTP and hence, induce apoptosis of cancer cells [37], and sertraline is currently being tested in phase I/II clinical studies. The anti-malarial drug dihydroartemisinin (DHA), which has also anti-cancer activity, is able to promote the degradation of human TCTP (fortilin) [24]. This prompted initial studies to test derivatives of artemisinin against TCTP, either alone or in combination therapy, e.g. for breast cancer [38]. Yet another approach, i.e. the use of TCTP-antisense oligonucleotides, is being explored as a strategy against prostate cancer [39]. Regarding the extracellular function of TCTP as a histamine-releasing factor (HRF), a number of peptide and other inhibitors of HRF have been tested and show some promise in alleviating symptoms elicited by this molecule in the context of allergic diseases [36] .

As TCTP is not a tumour-*specific* protein, but is involved in several core biological processes, it is important to understand its normal biological function as well as its cellular regulation, when designing anti-cancer strategies, which include targeting this protein. To serve this purpose, we anticipate that this review article will provide a useful compilation of the current knowledge in this area.

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