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Review Article

Regulatory Role Played by the mRNA Binding Protein Tristetraprolin in the Skin and its Involvement in Different Diseases

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ABSTRACT

The mRNA binding protein Tristetraprolin (TTP), encoded by the ZFP36 gene, plays a fundamental regulatory role in a wide variety of cellular processes by means of its widespread expression in different tissues, and of its ability to post transcriptionally regulate the stability, and therefore the expression, of multiple specific target mRNAs. Because of these features, TTP expression and activity are strictly regulated, and malfunctions of such mechanisms underlie different pathologies. Here we recapitulate the role of TTP in the skin, and its involvement in different conditions, with special reference to psoriasis and cancer.

Keywords: Tristetraprolin; ZFP36; Skin; Psoriasis; Cancer

INTRODUCTION

A general overview on tristetraprolin

ZFP36, encoding the mRNA binding protein Tristetraprolin (TTP), is the most studied member of a wider family of genes. The ZFP36 family of RNA-binding proteins consists of ZFP36 (TTP, TIS11), ZFP36L1 (BRF-1, TIS11b), ZFP36L2 (BRF-2, TIS11d), and ZFP36L3 (only in rodents) [1,2]. The gene family is ancient and highly conserved, suggesting that it plays a fundamental role in a variety of organisms.

The main functional feature of TTP is its ability to bind specific mRNAs carrying a specific ARE (AU-Rich Element) sequence (the nonamer UUAUUUAUU) in their 3' untranslated region (3'-UTR). Binding of TTP to target mRNAs leads to their degradation [1,2]. AREs are quite common and are present in a high number of mRNAs encoding proteins that play the most different functions. This also accounts for the involvement of TTP in very different physiological and pathological processes.

TTP's activity undergoes tight regulation. The first level of regulation resides in the fact that TTP's mRNA carries AREs in its own 3'-UTR, therefore it is capable to self-limit its own expression by binding and degrading its own mRNA [3]. This negative feedback mechanism also suggests that TTP expression can be induced by the same pathways whose activity TTP regulates. In other words, in the processes where TTP is involved, what it does is switching off those processes and then switching off itself. Another regulatory mechanism is mediated by phosphorylation. TTP is extensively phosphorylated by several kinases [4,5] and this event affects both its localization and activity. It has been demonstrated that p38 MAPK is able to phosphorylate TTP on specific serine residues, thereby inhibiting its mRNA decay activity [6,7]. Considering that TTP can degrade its own mRNA, the inhibition of the mRNA decay activity by phosphorylation may lead to TTP stabilization. Therefore, high levels of TTP expression do not necessarily mean high mRNA decay activity.

TTP has been linked to cell proliferation, differentiation and death, together with many other cell processes. Nonetheless, it has been very well characterized for its role in the regulation of inflammation. TTP is capable of switching off inflammation by inducing the degradation of mRNAs encoding multiple proinflammatory cytokines, such as TNF, IL-1β, IL-6, or IL-23 [2,8]. Deregulation of these processes due to alteration of TTP expression account for its involvement in several diseases characterized by a relevant inflammatory component, such as arthritis, dermatitis, autoimmune diseases [9], psoriasis [10-12], rheumatoid arthritis [13] and in cancer [2]. As far as cancer is concerned, with a few exceptions, in general TTP is

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downregulated and seems to behave as a tumor suppressor, although so far not so many mutations affecting the gene have been described.

TTP IN SKIN DISEASES

TTP is widely expressed in the skin, both in keratinocytes [14], and in fibroblasts [10]. In this context, TTP has been described as a critical regulator of tumorigenesis by controlling both inflammation and oncogenic pathways of neoplastic epidermal cells [15]. Alterations of TTP expression have been described in melanoma [16] and in squamous cell carcinoma (SCC) [17,18], but they have also been described in psoriasis [10], which is a disease characterized by inflammation and by an increased proliferation of the keratinocyte compartment, but that does not evolve towards malignant transformation. This observation seems to be particularly relevant and suggests that, in cancer, TTP inactivation, that provides an advantage for neoplastic cells in terms of inflammation and cell proliferation, is rather a consequence of primary mutations that lead to pathways' deregulation, than an initiating event leading transformation. In contrast, in psoriasis, TTP down-regulation might indeed underlie the chronic inflammatory state without a malignant transformation.

To better analyze these aspects, it would be useful to further study the mechanisms leading to TTP down-regulation in cancer and inflammatory diseases. Not many studies suggest the presence of mutations of the gene [19], while epigenetic causes have been proposed [20]. It has been proposed that in cancer TTP down-regulation is a consequence of other pathways' deregulation, for instance Wnt/CTNNB1 in SCC [17]. Indeed, it has been demonstrated that in 3 different SCC cell lines a correlation between the Wnt/CTNNB1 signal transduction pathway and ZFP36 is mediated by three transcriptional repressors (SNAI1, SLUG and TWIST) that are induced by CTNNB1 pathway and that in turn modulate ZFP36 expression by binding to its promoter [17], correlating TTP downregulation to the epithelial-mesenchymal transition. Recently, it has been confirmed that ZFP36 expression is downregulated in human primary SCC [15]. In particular, it has been identified a tumor-specific keratinocyte (TSK) population with no counterpart in normal skin [21]. It has been also observed a very similar expression pattern for TTP paralogs, ZFP36L1 and ZFP36L2. In sharp contrast, the expression of ELAVL1, that encodes for another ARE-binding protein with opposite functions, was higher in tumor cells and in TSKs in particular [15]. Globally, these results suggest that human SCC is characterized by an ARE-mediated mRNA regulation completely dysregulated.

These findings envisaged a key role of TTP in cutaneous carcinogenesis. Indeed, it has been nicely demonstrated that an overexpression of endogenous TTP protected mice from cutaneous chemical carcinogenesis [15]. Using the well-known two steps chemical carcinogenesis protocol by the mean of continuous application of DMBA/TPA, the formation of multiple papillomas was strikingly reduced and delayed in the Zfp36ΔARE mice, which constitutively overexpress TTP. On the other hand, a selective TTP deletion in epidermal cells in Zfp36ΔEP mice resulted in a dramatic increase in DMBA/TPA tumorigenesis, with a rapid tumor formation, major increase in tumor size, and progression to carcinomas compared to control animals and to mice with TTP downregulation exclusively in immune cells [15]. Finally, in SCC, the increase of the systemic inflammatory state is not central to the increase of tumorigenesis in mouse models.

To better define the mechanisms that lead to TTP downregulation, methylation [10] and the role of long non-coding RNAs have been suggested [22]. We have recently observed that TTP is downregulated in fibroblasts isolated from lesional psoriasis skin compared to those deriving from healthy individuals [10]. Moreover, we provided evidence that ZFP36 undergoes methylation in psoriasis, by virtue of the presence of long stretches of CpG dinucleotides both in the promoter and the coding region. In particular, we confirmed this aspect by the 5-aza assay performed on either normal or psoriatic fibroblasts, which determined an increase of TTP in psoriatic cells, both at the mRNA and protein level. In addition, we analyzed the methylation profile of ZFP36 promoter region through bisulfite sequencing, which revealed an increased methylation rate of a specific CpG site (-785° C) in psoriatic samples compared to healthy controls. This methylation could interfere with nearby activators of transcription, leading to a TTP downregulation in psoriatic fibroblasts. The methylation status of ZFP36 promoter in keratinocytes and other skin cells is still under evaluation and remains to be determined. However, it is known that mice with conditional deletion of TTP at the keratinocyte level (Zfp36ΔEP mice) developed augmented inflammation in the imiquimod-induced psoriasis model, unlike DC-restricted (CD11c-Cre, Zfp36ΔDC) or myeloid cell-restricted (LysM-Cre, Zfp36ΔM) TTP ablation mice [12]. More interestingly, Zfp36ΔEP mice spontaneously and progressively developed an important inflammation status that involves skin and joints in a systemic fashion. It seems that keratinocyte-derived TNF can drive these different systemic pathological features.

DISCUSSION AND CONCLUSION

TTP and its paralogs are certainly very interesting proteins. TTP is widely expressed and, via its mRNA decay activity, targets multiple mRNAs, therefore conditioning many fundamental pathways. For these reasons, there is a wide literature that highlights the role of TTP in physiological processes like proliferation, differentiation, inflammation, cell death and metabolism.

The activity of TTP is tightly regulated. In fact, TTP is capable of self-limiting its own transcription, owing to the presence of AREs in its 3'-UTR; TTP's activity is regulated by phosphorylation and, often, high levels of TTP expression do not correlate with high mRNA decay activity. Moreover, TTP is capable of shuttling between the cytoplasm and the nucleus. While the mRNA decay activity is cytoplasmic, its role in the nucleus has not been completely elucidated. Another relevant aspect is that TTP is indeed expressed in a variety of tissues, but usually it is not stably expressed. Rather its expression is induced following the activation of specific pathways and it is then repressed once that it has exerted its effect. All these features make studying TTP difficult. The analysis of expression

databases in search of TTP expression can be misleading. Over-expression experiments can provide elusive results, because obtaining high TTP levels might trigger regulatory events inhibiting the mRNA decay activity, therefore experimental models with tightly regulated TTP expression are required. In this sense, several animal models modulating the expression of TTP and specific mutants in various tissues were very helpful in highlighting TTP's function and regulation in a very convincing manner.

TTP is also involved in much pathology, in particular cancer and inflammatory diseases and syndromes, where, generally, its deregulation depends on its down-regulation. This observation pushed to describe TTP in cancer as a sort of tumor suppressor. TTP cannot be considered a typical tumor suppressor, since, so far, no specific mutations or genomic loss events have been described. Moreover, although in general TTP is downregulated in cancer, there are a few exceptions in literature. This controversy might again depend on the complexity and variety of the processes regulated by TTP, and on the technical issues previously mentioned that make studying TTP complex.

TTP is also downregulated in a number of inflammatory diseases that are not directly related to cancer. The skin is a good example, since TTP seems to be downregulated both in cancer and in psoriasis and related co-morbidities. In cancer, TTP down-regulation is related to epithelial-to-mesenchymal transition, cell death deregulation and other events, without apparently affecting the inflammatory status, while in psoriasis it appears to underlie the chronic inflammatory state. The mechanisms underlying TTP downregulation are far from being clear. In substance, it seems that inactivating TTP is a very common sport for many different inflammatory and proliferative diseases, and that there is more than one way to play it.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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