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TIS11/TTP gene family
It's never too late for tumor suppressors

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Proteins belonging to the TIS11/TTP/ZFP gene family were originally described as important negative regulators of the inflammatory response,[1] owing to their ability to bind specific AU-rich elements located in the 3'-UTR region of mRNAs encoding a variety of pro-inflammatory proteins, thereby triggering their deadenylation and subsequent degradation. Over the years, the number of their putative and validated targets, among which there are several oncogenes,[2,3] grew significantly and they became more and more involved in the control of a growing number of cellular processes encompassing differentiation,[4] apoptosis[5] and even angiogenesis.[6] In addition, many evidences were published suggesting that the expression of TIS11/TTP genes is often decreased in many cancers compared to normal tissues.[7] Altogether, these data are pushing several researchers, the present writer included, to suggest with reasonable confidence that these proteins might represent a novel group of tumor suppressor genes. And indeed this hypothesis seems to be correct, since family members ZFP36 and ZFP36L1 are really capable of binding and triggering degradation of different mRNAs encoding a number of oncogenes or genes involved in proliferation and apoptosis pathways. Nevertheless, before accepting this idea, there is at least one question that requires an answer. In fact, the scientific community is used to call "oncogenes" those mutated or overexpressed genes whose deregulated activity is sufficient to determine a change in cell physiology that can ultimately lead to tumor transformation. So, if ZFP36 and ZFP36L1 are capable of downregulating the expression of several among these genes at once, they should, when overexpressed, determine a dramatic influence on the behavior of cells. In other words, how come we didn't focus our attention on these tumor suppressors before? The answer to this question probably resides in at least two issues that still require to be fully understood, that could explain why experiments aimed to restore the expression of ZFPs in cancer cells do determine a regression of the tumor phenotype, but not always as severe as one could expect considering the broad range of target genes mRNAs that could be degraded. The first issue involves a possible interplay occurring between ZFPs and mRNA binding proteins belonging to other families, such as HuR, that act by stabilizing their mRNA targets and that are known to play a positive role in the genesis of cancer.[8] This idea allows to hypothesize the existence of a network of mRNA binding proteins whose final balance, similarly to what happens in the control of apoptosis mediated by bcl family genes, determines the fate of the host cell. The second issue involves the control of TIS11/TTP genes expression. Genes belonging to this family are transiently expressed in physiological conditions to cease the cellular response to growth factors[9] or to control the inflammatory response.[1] Such observations suggest a tight regulation at the promoter level, where in both ZFP36 and ZFP36L1 genes wide CpG islands are also present, and an equally tight regulation at the post transcriptional and possibly post-translational levels. In particular, ZFPs carry AU-rich elements in their own 3'-UTR mRNAs, therefore they are capable of autolimiting their own expression. This is often observed in overexpression assays where the increase of ectopic ZFP36 expression is coupled to a decrease of the endogenous protein and mRNA. The nature of TIS11/TTP genes, the complexity of their regulation and the volatility of their endogenous expression eventually explain why these genes were not recognized as tumor suppressors before. Therefore, although studies aimed to find, validate and describe new targets of TIS11/TTP proteins will remain important, the real challenge now is to understand how these genes are regulated in order to fully exploit their anti-oncogenic potential. In general, the study of the TIS11/TTP family confirms that mRNA stability is a field of growing importance to develop novel therapeutic approaches to understand and treat cancer.

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