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Review

Tribbles: A family of kinase-like proteins with potent signalling regulatory function

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Abstract

The recent identification of tribbles as regulators of signal processing systems and physiological processes, including development, together with their potential involvement in diabetes and cancer, has generated considerable interest in these proteins. Tribbles have been reported to regulate activation of a number of intracellular signalling pathways with roles extending from mitosis and cell activation to apoptosis and modulation of gene expression. The current review summarises our current understanding of interactions between tribbles and various other proteins. Since our understanding on the molecular basis of tribbles function is far from complete, we also describe a bioinformatic analysis of various segments of tribbles proteins, which has revealed a number of highly conserved peptide motifs with potentially important functional roles.

Keywords: Tribbles; Tribbles proteins

Contents

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1. Introduction

A range of molecular mechanisms has evolved to precisely regulate the spatio/temporal aspects of cellular activation and cell function. These strategies involve enzymes possessing catalytic activity and regulator proteins, which themselves may not have a catalytic function but rather bind to other proteins and modulate their action. Examples of catalytic signal transducers include kinases, phosphatases and lipases; examples of signalling systems acting solely by physical association with other proteins include receptor binding proteins like MyD88 or Mal, and adaptors/scaffolds, such as JIP or KSR proteins.

The recently described family of proteins, Tribbles (trb) seems to have a very special, uncertain position in this classification. Whilst trb proteins have a single kinase-like domain, it is uncertain if this has catalytic activity; additionally, they lack the protein–protein interaction domains (SH2, SH3, PDZ, etc…) that are typical feature of many other kinases and adaptor/scaffold proteins. The emerging literature on tribbles suggests some unique functional "niche" for these proteins in modulating the activity and possibly the balance of activation between a number of key signalling pathways. The potential lack of enzyme activity, together with the lack of interaction domains is very unusual and conceptually very interesting since a large number of functional interactions – both negative and positive– between Tribbles and different signalling pathways have been reported in a variety of cellular systems. Despite the increasing body of experimental evidence, the detailed molecular basis of these interactions is yet to be defined. Therefore, whilst our understanding on the molecular mode of tribbles action is still in its infancy, we believe that the current literature gives some important insights to the complex mechanisms of modulation of cell function.

In this review we summarise the current literature on molecular interactions between tribbles and other proteins. Further, we report results of an extensive *in silico* analysis of all available tribbles protein sequences with the aim to identify evolutionally (and therefore functionally) conserved peptide motifs in tribbles proteins. Findings are linked to experimental data, where available. Since the major part of the tribbles protein sequence encodes for a kinase-like domain, a 3D computer model of this domain is presented and the possible functional implications are discussed.

2. Identification of tribbles

Members of the tribbles protein family have been identified by three independent strategies. The first approach is based on the characterisation of genes, which are differentially expressed in various physiological situations. These studies showed canine trb-2 as a differentially expressed gene in mitogen stimulated thyroids [1], downregulation of bovine trb-2 in granulosa cells of chorionic gonadotropin stimulated dominant follicles [2], altered expression of mouse trb-3 in fatty liver dystrophy (fld) mouse [3] and induction of rat trb-3 during neuronal cell death [4].

The second strategy involves functional screens. Such reports identified *Drosophila tribbles* as a major regulator of morphogenesis [5–8] and human trb-1 as a modulator of MAPK signalling pathways [9,10].

The third set of studies is based on interaction screens. Results of these demonstrate interactions between tribbles and a large number of signalling proteins, as detailed below.

3. Tribbles action in vivo

Whilst the focus of this review is on molecular interactions between tribbles and other proteins, it is also important to highlight some of the *in vivo* data on tribbles function, which comes from developmental studies. *Tribbles* in *Drosophila* regulates *string* during morphogenesis [5,6]. *String* is the fly orthologue of mammalian *cdc 25*, a phosphatase, which plays a key role in regulating cell cycle progression beyond G2 by dephosphorylating, and thus activating, the cyclin-dependent kinase, *cdk 1*. In embryonic development, expression of *string* is generally linked to the progression of mitosis. However, whilst high levels of this protein are expressed in the gastrulating mesoderm anlage during morphogenesis, the migrating cells do not divide. *Tribbles* was identified as regulator of *string*, hence this process. This regulatory role was also reported in a different developmental setting, during oogenesis. This process involves a set of highly specialised cell divisions, the number of which is regulated by tribbles expression levels [6].

Interestingly, wing development in flies also appears to be modulated by *tribbles*. When *trb* is overexpressed in the posterior compartment of the wing imaginal disk, the wing is made up of fewer but larger cells, compared to controls. This enlarged phenotype was also seen by our group when studying trb-3 overexpressing HeLa cells [9].

The role of a tribbles orthologues, trb-2 was investigated in a vertebrate model of development, *Xenopus* [17]. In contrast to the *Drosophila* phenotype, microinjection of the fertilised *Xenopus* embryos with an antisense morpholino against trb-2 led to delayed (and not accelerated) cell division. Defects in the development of the eye and the nervous system were also seen.

Although the molecular details of tribbles action in the above processes are poorly understood, the various reports clearly show an important regulatory role for tribbles in development and in regulation of fundamental aspects of cellular physiology, such as cell size.

4. Tribbles interacting proteins

4.1. Drosophila tribbles

Although the molecular mechanism of tribbles action is yet to be determined, Mata et al. elegantly showed that the turnover of *string* and another *cdc 25* homologue, *twine*, is regulated by *trb in vitro* and *in vivo* [6].

A functional interaction between *tribbles* and another protein *slbo*, a C/EBP homologue bZIP transcription factor was reported by Roth et al. [7]. They show that overexpressed *tribbles* stimulated *slbo* ubiquitination. Further, direct physical interaction between overexpressed *tribbles* and *slbo* was demonstrated. Roth and colleagues show that precise regulation of *slbo* levels