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Review

The guanine nucleotide exchange factor Tiam1: A Janus-faced molecule in cellular signaling☆

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ABSTRACT

The Rho family of GTPases consists of several small proteins that have been described as molecular switches, playing important roles in a wide variety of fundamental cellular processes and in human diseases such as cancer. These proteins, active in the GTP conformation and inactive in the GDP form, are in turn regulated by guanine nucleotide exchange factors (GEFs), guanine nucleotide activating proteins (GAPs) and guanine dissociation inhibitors (GDIs). Two decades ago, Tiam1 (T-lymphoma invasion and metastasis) was identified as a GEF specific for Rac1 activation, but also for Cdc42 and in a lesser extent RhoA.

Acting principally upstream of Rac1, Tiam1 is mainly involved in the regulation of Rac1 mediated signaling pathways including cytoskeletal activities, cell polarity, endocytosis and membrane trafficking, cell migration, adhesion and invasion, cell growth and survival, metastasis and carcinogenesis. However, given the large number of protein interaction domains found in its structure, it is possible that Tiam1 affects cellular processes in another way than through its GEF activity by interactions with other signaling proteins.

Due to its functional diversity, Tiam1 is involved in multiple steps of tumorigenesis.

As its name suggests, Tiam1 has been shown to increase T-cell lymphoma invasion and metastasis. It also promotes migration of fibroblasts, neuronal and cancer cells. On the contrary, Tiam1-induced cell adhesion has also been described, as opposed to cell migration. Moreover, studies indicate that Tiam1 is involved in both anti-apoptotic and pro-apoptotic mechanisms.

While increasing evidence has demonstrated Tiam1's contribution to tumorigenesis and metastasis, others suggest that Tiam1 could have anti-cancer properties.

In the present review, we discuss the current knowledge about the controversial roles of Tiam1 in cellular signaling. In particular, we will focus on Tiam1's regulation, its biological functions and implication in cancer.

Contents

Abbreviations: DH, Dbl homology; JIP/IB2, c-Jun N-terminal kinase-interacting protein/islet-brain 2; GAP, GTPase-activating protein; GDP, guanosine diphosphate; GDI, guanine dissociation inhibitor; GEF, guanine nucleotide-exchange factor; GTP, guanosine triphosphate; PH, pleckstrin homology; RBD, Ras binding domain; STEF, Sif and Tiam1-like exchange factor; Tiam1, T-lymphoma invasion and metastasis.

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1. Introduction

1.1. Rho family of small GTPases

Rho GTPases are key regulators of many fundamental cellular processes, not only the regulation of actin cytoskeleton, cell division, and cell motility, but also the gene expression, vesicle trafficking and endocytosis [1]. Most of them act as molecular switches being inactive in the guanosine diphosphate (GDP) form and active in the guanosine triphosphate (GTP) conformation, allowing downstream signal transduction. Three sets of regulatory proteins tightly control Rho GTPases activity, as illustrated in Fig. 1. The guanine nucleotide-exchange factors (GEFs) promote GDP release and GTP binding, inducing a conformational change that allows downstream effectors to bind and to transduce a signal. In contrast, the GTPase-activating proteins (GAPs) stimulate the hydrolysis of GTP to GDP, promoting the inactive state. The guanine nucleotide-dissociation inhibitors (GDI) sequester GTP- or GDP-bound proteins, keeping the GTPases away from their regulators and effectors, thus blocking protein activity [2–4]. Consequently, Rho-GTPase activity is dependent on the activity of GEFs and GAPs that are themselves under tight control. For example, stimulation of multiple cell surface receptors (growth factor receptors, cytokine receptors or adhesion receptors) not only leads to GEF activation, but might also affect the negative regulators GAP and GDI.

Twenty Rho GTPase family members are identified in mammals [5], but the most extensively studied are Rac1, RhoA and Cdc42. All have at least one GEF, promoting GDP/GTP exchange. GEFs have specific Rho-GTPases affinity, meaning that one GEF can activate several GTPases or only one. Among the 70 GEFs identified in human [6], T-lymphoma and metastasis gene 1 (Tiam1), a Rac1-specific activator, is one of the most studied. This review highlights the recent progress in our understanding of the controversial roles of Tiam1 in cellular signaling. Tiam's regulation, its biological functions and implication in cancer are discussed in depth.

1.2. Tiam1: general properties

1.2.1. Expression

Tiam1 was first identified in 1994 during an in vitro search for genes that confer an invasive phenotype to murine T-lymphoma cells [7]. Tiam1 is a protein of 1591 amino acids, widely expressed in adult tissues with a higher level in brain, testis and epidermis [8]. Tiam1 mRNA is detected in mice from E10 and it has been shown that silencing Tiam1 expression in mouse embryos results in severe defect in embryonic brain development, suggesting a critical role for Tiam1 in embryogenesis [8,9]. Tiam1 is highly conserved among vertebrates, underlining the importance of its cellular function. Human and mouse gene products present 95% homology [8]. The human gene is located on chromosome 21q22.1, whereas its mouse homolog is located on chromosome 16 [10]. The closest family member of Tiam1, Sif and Tiam1-like exchange factor (STEF), also named Tiam2 is mainly expressed in neuronal cells and might also play a role in cell migration and cytoskeletal regulation

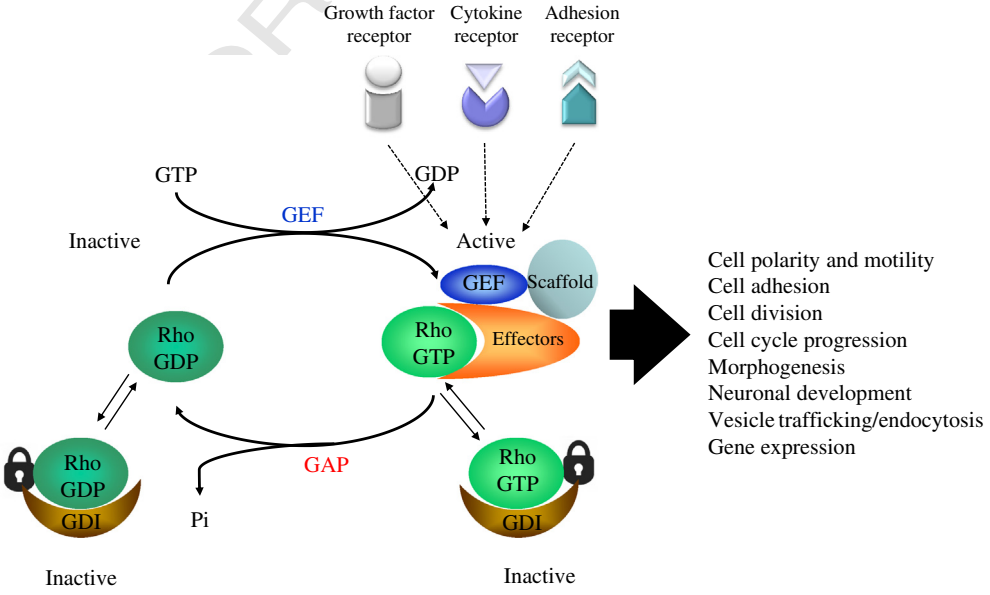

Fig. 1. Rho GTPases protein regulation. Receptors-mediated signals such as growth factor receptors, cytokine receptors or adhesion receptors might activate GEFs, facilitating the exchange of GDP to GTP. The GTP-bound Rho proteins can in its active state associate with multiple downstream effectors, leading to a wide variety of cellular responses. Membrane receptors might also affect the negative regulatory proteins: GAPs which promote the GTP hydrolysis and GDIs which sequestrate Rho proteins, leading to Rho GTPases inactivation.

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