TRIM Proteins Family

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TRIM (TRIpartite Motif-containing) proteins family is one of the largest groups of E3 ubiquitin ligases. Among them, interest in TRIM8 has greatly increased in recent years. TRIM8 functions are not limited to ubiquitination, and it has a role either as an oncogene or as a tumor suppressor gene, acting as a “double-edged weapon”. This is linked to its involvement in the selective regulation of three pivotal cellular signaling pathways: the p53 tumor suppressor, NF-κB and JAK-STAT pathways.

TRIM8 TRIM proteins

1. Introduction

A delicate balance between protein synthesis and degradation is essential to maintain cell homeostasis. Deregulation of protein homeostasis in favor of either protein synthesis or protein degradation is detrimental, although in different ways. The role of the Ubiquitin–Proteasome System (UPS) is central in maintaining protein homeostasis, and alteration of the UPS has been linked to several pathological conditions.

Ubiquitination is one of the most prevalent post-translational protein modifications. It plays a key role in several cellular processes and physiological responses in inflammatory disorders, neurodegeneration, cancer, autoimmunity, infection and other human diseases. Ubiquitination can target proteins for degradation via the proteasome or selective autophagy, alter subcellular localization, affect activity and regulate interactions with other proteins.

The E3 Ub ligases function in association with an E1 ubiquitin-activating enzyme and an E2 ubiquitin-conjugating enzyme. There are only two human genes coding for E1 enzymes, 30–50 genes for E2 and over 600 E3 ligase genes, which constitute about 3% of human protein coding genes. These types of E3 ligases differ from each other depending on the type of catalytic domains: Really Interesting New Gene (RING), Homologous to E6-AP Carboxyl Terminus (HECT) or Ring-Between-Ring (RBR). The high number of E3 ligases is associated to their specificity in selectively targeting protein substrates [1][2].

Each ubiquitin molecule contains seven lysine residues: Lys6, Lys11, Lys27, Lys29, Lys33, Lys48 and Lys63; additional ubiquitins can be attached to each of these lysines to form chains of various lengths with different functions. Proteasome-dependent degradation is related to Lys48-linked chains while nonproteolytic roles of ubiquitin Lys63-linked chains function as signaling scaffolds for Nuclear Factor-κB (NF-κB) activity, DNA repair and intracellular trafficking [3][4][5]. Moreover, Lys63 polyubiquitin chains are involved in autophagy, recruiting several

ubiquitin-binding proteins such as p62, Neighbor of BRCA1 gene 1 (NBR1) or Histone DeACetylase 6 (HDAC6), triggering the formation of inclusion bodies within the autophagic pathway. On the other hand, Lys6-linked ubiquitin chains function within a nondegradative route and have been linked to physiological roles in DNA damage repair. Proteasome signaling has been linked to Lys11, Lys27, Lys29 and Lys33 ubiquitin chains. Lys11 polyubiquitination increases at the end of mitosis, connecting polyubiquitination to cell cycle regulation. Lys27 ubiquitination has been observed in conjunction with mitochondrial damage.

In addition to the aforementioned seven internal lysine residues, N-terminal methionine ubiquitination has been identified by Iwai and colleagues as the action site for a novel RING E3 ligase complex capable of connecting ubiquitin molecules in a head-to-tail fashion [6][7]. Met1-linked linear chains are formed by the Linear Ubiquitin Assembly Complex (LUBAC): a 600-κD E3 ligase complex composed of two RBR ligases, the Heme-Oxidized Iron-responsive element-binding protein 2 ubiquitin Ligase-1L (HOIL-1L) and the HOIL-1L-interacting Protein (HOIP), in addition to SHank-Associated Rh domain-interacting ProteIN (SHARPIN). Linear ubiquitination is a new atypical nondegradative ubiquitin modification [1][2]. It has been shown that the RBR ligase domain of HOIL-1L is able to add Lys48 polyubiquitin chains to target proteins regardless of LUBAC.

The importance of the ubiquitin signaling system is highlighted by the fact that misregulation of ubiquitin signaling or functional impairment of the proteasome has been associated with several pathological conditions.

It is interesting to note that autosomal defects in LUBAC are associated with atypical autoinflammation and immunodeficiency.

Significant progress has been recently made regarding the discovery of different roles of polyubiquitination chains in different signaling pathways and how dysfunctions in these processes are involved in cancer, inflammatory disorders, autoimmunity, neurodegeneration, infection and other diseases.

Most tumors are prone to develop upon alterations in ubiquitination-mediated events. Furthermore, the analysis of the transcriptional profile of patients affected by lung adenocarcinoma and glioblastoma showed differential expression of HOIL-1L with higher levels being associated with decreased survival [1][2].

2. TRIM8, a Double-Edged Weapon

In recent years, there has been growing interest in TRIM8 protein research. The TRIM8 gene is located on the 10q24.3 chromosome and transcribes an mRNA of about 3.0 κb that is translated into a protein of 551 a.a. with a molecular weight of 61.5 κDa.

The protein structure consists of a RING finger domain at the N-terminal, two B-box domains, a Coiled-Coil domain and an RFL-like domain at the C-terminal (Figure 1) [8]. Moreover, TRIM8 protein contains a Nuclear Localization Signal (NLS), which allows translocation and functioning in the nucleus. The Coiled-Coil domain of TRIM8 permits the formation of Nuclear Bodies (NBs) similar to TRIM19/PML, regulating the activity of important cellular proteins

through protein–protein interactions [9]. Recently, an important role in the mitotic spindle machinery has been described for TRIM8. From the analysis of the TRIM8 interactome in primary mouse embryonic neural stem cells, it was found that TRIM8 interacts with KIFC1 and KIF11/Eg5 kinesins, two master regulators of mitotic spindle assembly and cytoskeleton reorganization. In particular, during mitosis TRIM8 localizes at the mitotic spindle playing a role in centrosome separation. TRIM8 knock-down slows centrosome separation at the prometaphase resulting in chromosome instability as aneuploidic cells and micronuclei formation [10].

TRIM8 is involved in many cell reactions in response to different stimuli such as genotoxic stress and attacks by viruses or bacteria, playing a central role in the immune response and orchestrating various fundamental biological processes such as cell survival, innate immune response, carcinogenesis, autophagy, apoptosis, differentiation and inflammation. Its dysfunction is linked to cancer, inflammatory processes and autoimmune disorders. The involvement of TRIM8 in such a plethora of cellular functions is fundamentally linked to its involvement in the regulation of three pivotal cellular signaling pathways: the p53 tumor suppressor signaling pathway, the NF-κB pathway (Nuclear Factor kappa-light-chain-enhancer of activated B cells) and STAT3 (Signal Transducer and Activator of Transcription 3) of the JAK-STAT pathway. The TRIM8 liaison with these three pathways determines its dual role in cancer as oncogene or tumor suppressor functions [11].

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