TRIM

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The tripartite motif (TRIM) gene family is a large group of E3 ubiquitin ligase proteins that can also have proteasome-independent functions. TRIM/RBCC are a large family of proteins that include more than 80 proteins, most of which act as E3 ligases and catalyze the direct transfer of Ubiquitin, SUMO and ISG15 on specific protein substrates. They are involved in oncogenesis processes and in cellular immunity.

TRIM proteins TRIM8 p53 cancer

1. TRIM Proteins Biological Functions

TRIM proteins are involved in distinct cellular processes, despite showing a similar structure: regulation of cellular homeostasis, cell cycle, senescence, apoptosis, differentiation, specific metabolic pathways, meiosis and protein quality control [1][2][3]. They exert their actions on transcriptional regulation, cytoskeletal remodeling, intracellular trafficking, membrane repair and oncogenesis [4][5][6][7]. Moreover, these proteins are implicated in the development and regulation of the immune system [8][9][10].

Most TRIM molecules act as E3 ligases and directly catalyze the transfer of Ub, SUMO and ISG15 on specific protein substrates [11][12][13][14]. The conjugation reaction of ubiquitin to a substrate is catalyzed by E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzymes and E3 ubiquitin ligases [15]. The E3 ubiquitin ligases can be divided into two major classes: the homologous to E6-AP COOH terminus (HECT) E3 ubiquitin ligase family and the RING-finger-containing E3 ubiquitin ligase family [16][17]. The high number of E3 ligases is associated with their specificity in selectively targeting protein substrates [1]. Mostly, the enzymatic activity exerted by the E3 ligases on ubiquitin and Ubiquitin-like molecules (UBL) depends on the presence in the protein structure of the RING domain [18][19]. E3 ligases transfer the ubiquitin or UBLs from E2 conjugating enzymes to the substrates, and thus they are responsible for recognizing the substrates and are determinants of target specificity [20]. In order for ubiquitination to take place, however, it is not sufficient for the RING domain to recognize the specific substrate, but specific functional protein dimers must be formed [21][22][23]. The B-box and coiled-coil domains are responsible for the dimerization of TRIM proteins [24][25].

Many TRIM proteins play a pivotal role during mitosis and cell-cycle progression. Specifically, TRIM19, TRIM22, TRIM28, TRIM37 and TRIM6 are important during prophase; TRIM19, TRIM32 and TRIM69 in prometaphase; TRIM17, TRIM36 and TRIM69 in metaphase; and TRIM17, TRIM21, TRIM47 and TRIM76 in cytokinesis. Furthermore, in the course of the bipolar spindle assembly during all phases of mitosis, TRIM8 is involved in the

mitotic spindle formation through interaction with two important regulators of mitotic spindle machinery and cytoskeleton reorganization, KIF11 and KIFC1, and through localization at the mitotic spindle [26]. TRIM8 colocalizes on centrosomes with Plk1 and straight reacts to CEP170-like protein. This interaction, suppressing TRIM8 function, induces a delay of the mitosis progression with a cell accumulation in the G2/M phase. TRIM8 is also necessary for chromosomal stability. As a matter of fact, the suppressing of TRIM8 induced an increased rate of chromosomal instability leading to a significant rise of cells with less than 46 chromosomes [1][16].

TRIM proteins have the distinctive feature of exerting a large variety of different roles and activities because of their ubiquitination or ubiquitin-like function that labels the target proteins to be degraded at the proteasome level, as well as stabilize or dislocate them in various cellular compartments through such modifications. Ubiquitination is a post-transductional modification of protein substrates necessary for different biological mechanisms, such as:

- Regulation of the activity and stability of oncogenes and tumor suppressors [27][28];
- Degradation of toxic protein aggregates [29];
- Activation of specific inflammatory pathways [4][30].

The alteration of the post-transduction mechanism of ubiquitination affects the functionality of protein substrates, with consequent alteration of the biological mechanisms in which they are involved. At a macroscopic level, these alterations can lead to the development of various pathological conditions, including tumor pathologies [24][31][32]. TRIM proteins are involved in carcinogenesis. In particular, these proteins are implicated in several biological functions: DNA repair, metastasis, tumor-suppressive and oncogenic regulation [4]. Furthermore, some of the TRIM family proteins play a pivotal role in autophagy and innate immunity and regulate important cellular processes, such as intracellular signaling and transcription [16]. The down-regulation or overexpression of TRIM proteins has long been investigated in the study of oncogenesis. However, many reports showed that TRIM alterations were observed in lung cancer, breast cancer, liver cancer, colorectal cancer and prostate cancer [33][34]. Indeed, reduced expression of these proteins could reflect the suppressive role of the tumor, whereas their over-expression could reflect their contribution to the disease development and/or progression. Therefore, some TRIMs could be considered biomarkers for some kind of cancer. In particular, TRIM11, TRIM14, TRIM24, TRIM25, TRIM27, TIM28, TRIM29, TRIM33, TRIM37, TRIM44 and TRIM59 are the most associated with cancer [33].

2. TRIM Proteins and Cancer Pathogenesis

TRIM proteins could influence cancer pathogenesis through the following mechanisms:

- Chromosomal translocation [35]. It could generate a fusion protein without activity or with a different activity that could dysregulate some signaling pathways, leading to the generation of some tumor shapes. An example is a translocation between the TRIM19 gene (PML) on chromosome 15 and the retinoic acid receptor α (RARa) gene on chromosome 17. This translocation leads to the formation of a fusion protein that represses acid

signaling retinoic and is associated with Acute Promyelocytic Leukemia [36]. Such similar examples are the following: TRIM24, TRIM27 and TRIM33 were found in translocations with the RET gene and are involved in papillary thyroid cancer, lymphoma and non-small cell lung carcinoma, respectively. Similarly, TRIM24 was found translocated with the BRAF gene in melanoma and lung cancer and with the FGFR1 gene in myeloproliferative syndrome [33];

- Modulation of the activity and stability of p53. TRIM11, TRIM13, TRIM21, TRIM24, TRIM25, TRIM28, TRIM29, TRIM31, TRIM32, TRIM39 and TRIM59 can ubiquitinate the p53 protein, a fundamental macromolecule in cell development whose purpose is to promote genomic stability and induce cell cycle arrest and apoptosis if extensive DNA damage is found in the cell. The ubiquitination of this protein leads to its direct degradation or to its sequestration in the cytoplasm: since it can no longer penetrate the nucleus, the ubiquitinated protein is no longer able to detect any damage to the DNA; consequently, the cell replicates itself by transmitting the same error in the nucleic acid sequence, resulting in the possible onset of tumor forms [37];

- Regulation of pathways to cancer stemness, including STAT signaling, AKT signaling, NANOGSox2-Oct-3/4 networks. Specifically, through these pathways, TRIM28 is involved in breast cancer, TRIM24 in glioblastoma and colorectal cancer, TRIMs 14 in gastric cancer and TRIM16 has been associated as a negative regulator of stemness in breast and ovarian cancer cells [33].

Stem cells (SCs) are cells with no signs of differentiation, capable of self-renewing and generating progeny capable of differentiating into different cell types. They constitute the reserve elements of human tissues; in fact, they are activated only to restore tissue damage or to ensure normal cell turnover. SCs are capable of self-renewal, are multi-potent and immortal, and are highly resistant to chemical and physical agents, all characteristics also possessed by cancer cells. Furthermore, SCs tend to maintain the ability to de-differentiate in order to return to a primitive state of development. Such cells cannot survive outside their environment or in case of deficiency of specific cytokines and growth factors. Mutated stem cells, however, despite having all the aspects of stem cells, are unable to support tissue homeostasis, favoring, instead, the onset and progression of tumor diseases. The stem characteristics common to HF and cancer cells provide the building blocks for cancer maintenance and survival, from the potential for self-renewal and differentiation to the organization of microenvironments that support stemness. Thus, cancer stem cells (CSCs) are defined as the small population of cells within tumors that possess stem properties that support cancer development, such as advanced capabilities for cloning, growth, metastasis, re-proliferation and self-renewal. CSCs exhibit remarkable organizational skills. In fact, they can educate neighboring cells to provide nutrients and collaborate in evading the immune system, thus creating an environment favorable for tumor progression [38]. CSCs give rise to heterogeneous cell populations, often with a high potential for plasticity, high resistance to stressors, such as low oxygen or nutrient levels, or the initiation of cell death by chemotherapeutic agents, and the capability for quiescence as a typical response to these factors [39]. Among the possible pathways by which TRIM proteins act on tumor stemness are the signaling of STAT, AKT (**Figure 1**) and the NANOGSox2-Oct-3/4 networks [40]. In fact, TRIM proteins control stem cell characteristics mostly positively by enhancing the activity of core transcription factors, induction of specific signaling pathways, epigenetic silencing of pro-differentiation genes, metabolic reprogramming and activation of the epithelium-mesenchymal transition pathway. Several members, such as TRIM24 and TRIM28, negatively regulate stem cell self-renewal, presumably

by ubiquitin-mediated degradation of stem cell transcription factors or inhibition of specific signaling pathways. Furthermore, several TRIM proteins, such as TRIM8, modulate the stem cell phenotype both positively and negatively [38]. In addition, the role of TRIM proteins on autophagic processes may represent a not-well investigated mechanism involved in cancer stemness [33].

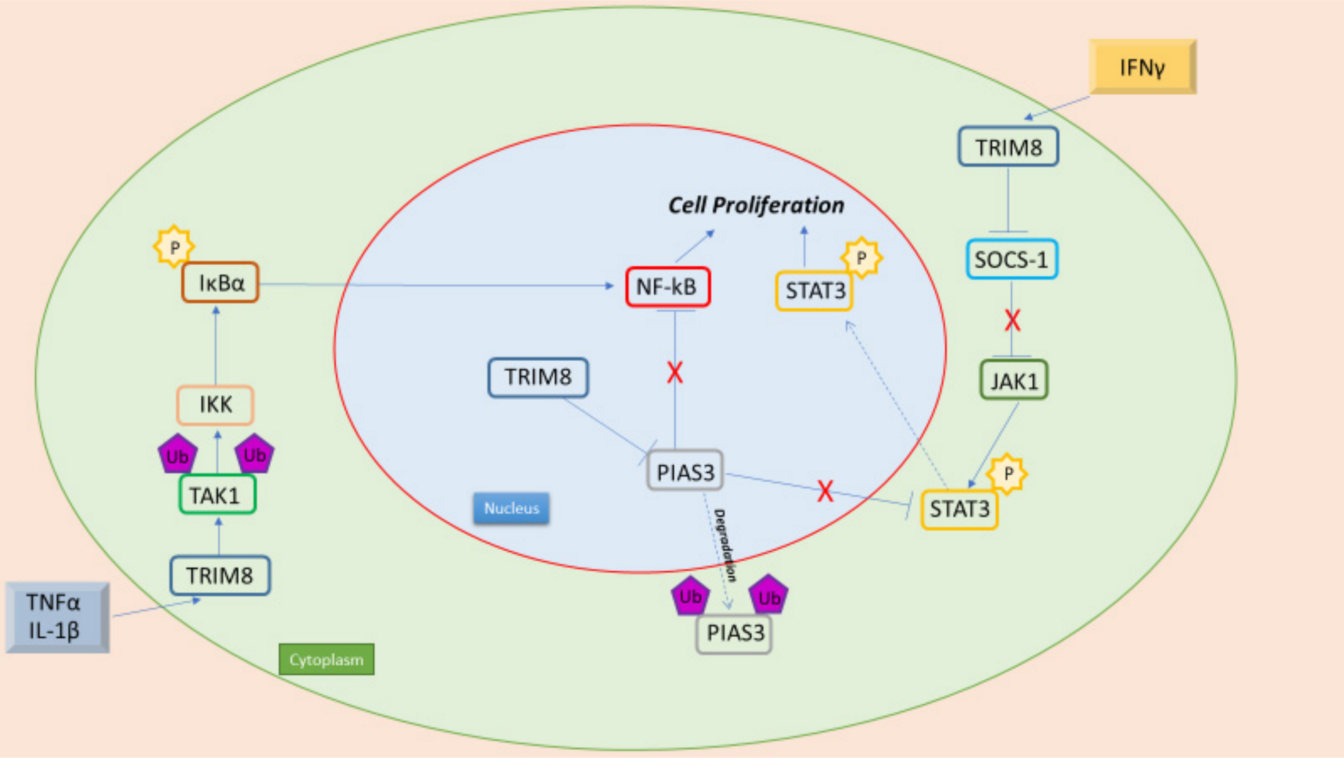

Figure 1. TRIM8 is an oncogenic protein, with its interaction with NF-kB and STAT3 leading to cell proliferation. Pro-inflammatory cytokines (TNFα e IL-1β) promote NF-kB activation through TRIM8. In fact, TRIM8 promotes TAK1 Lys63- linked polyubiquitination, leading to IKK kinase activation. Moreover, in the nucleus, TRIM8 promotes the translocation of PIAS3 in the cytoplasm, where it is then degraded. PIAS3 in the nucleus interacts with NF-kB preventing its activation. Furthermore, TRIM8 induces the activation of the JAK-STAT pathway promoted by IFN-γ through the degradation of two STAT protein inhibitors, PIAS3 and SOCS-1.

- Regulation of pathways related to epithelial-mesenchymal transition (EMT) [33][41].

The epithelium-mesenchymal transition (EMT) is a biological process that allows a polarized epithelial cell, which normally reacts with the basement membrane through its basal surface, to suffer several biochemical changes that permit it to acquire a mesenchymal cell phenotype, which includes a prominent migratory ability, invasiveness, significant opposition to apoptosis and considerably raised production of components of the extracellular matrix. The achievement of an EMT is signaled by the degradation of the underlying basement membrane and the development of a mesenchymal cell that can move away from the epithelial layer where it arises [42].

The biological processes that initiate an EMT include activation of specific transcription factors, expression of cell surface proteins, reorganization and expression of cytoskeletal proteins, production of degradative enzymes and

changes in the expression of specific microRNAs. Some of these factors can be used as biomarkers to establish the switch of a cell through an EMT [43].

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