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Short Communication
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Tripartite Motif Proteins - A Protein Family Strongly Linked to Cancer

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Short Communication

Cancer is a highly prevalent genetic disease and it is estimated that almost every second person will suffer from the disease during his or her life-time. Despite intensive research over the last 50 years, the development and progression of the disease is, in many cases, still incompletely understood. In the past few years, a distinctive family of proteins called the TRIM (tripartite motif), or RBCC (RING, B-box, coiled-coil region) protein family came into the focus of cancer research. The TRIM protein family is a very large family of proteins with more than 70 members in humans. All proteins of this family have a tripartite motif in their N-terminus consisting of a RING (really interesting new gene) domain, one or two B-boxes and a coiled-coil region. The RING domain within their N-terminal RBCC motif is in most cases functional and used by the individual TRIM proteins to polyubiquitinate target proteins followed by their degradation in 26S proteasomes. About half of the members of this large protein family are connected with the development, progression or metastasis of tumors (Figure 1). Many TRIM proteins are overexpressed or down regulated in the different cancers (Figure 1) and some TRIM proteins have even been postulated to be prognostic factors or potential therapeutic targets. Despite their widespread association with carcinogenesis, the individual TRIM proteins may differ in the way they exert their effects in cancer. Several TRIM proteins are part of chromosomal rearrangements. For example, TRIM19, also known as PML (promyelocytic leukemia), is fused to the retinoic acid receptor-α in acute promyelocytic leukemia [1] and TRIM24, TRIM27 or TRIM33 are fused to the RET (rearranged during transfection) protein in papillary thyroid carcinoma [2,3]. TRIM24 is also found fused to the fibroblast growth factor receptor 1 in the myeloproliferative syndrome or to the B-Raf protein in hepatocarcinomas [3]. Other chromosomal rearrangements that involve TRIM proteins are the fusion of TRIM4 to the MET kinase in melanomas and the fusion of TRIM46 to MUC1 (Mucin glycoprotein 1) and KRTCAP2 (keratinocyte associated protein 2) in high-grade serous ovarian cancer [4,5].

Other TRIM proteins are involved in carcinogenesis by controlling the abundance and/or the activity of p53, an important tumor suppressor protein [6]. Many of these TRIM proteins reduce p53 level and activity. Among them are TRIM24, TRIM32, TRIM39 and TRIM59, all of which reduce p53 activity by targeting the tumor suppressor protein for proteasomal degradation. TRIM proteins such as TRIM21, TRIM25, TRIM28, TRIM29 also reduce p53 activity but through different mechanisms. TRIM21, for instance, indirectly regulates the rapid degradation of p53 by controlling the subcellular localization of the guanine monophosphate synthase (GMPS) and the herpes virus-associated ubiquitin protease (HAUSP). Normally, TRIM21 sequesters GMPS in the cytoplasm through monoubiquitination while HAUSP is localized in the nucleus where it causes degradation of p53 by stabilizing Mdm2, the major ubiquitin ligase for p53. Upon genotoxic stress, TRIM21 is released from GMPS allowing the latter to enter the nucleus to displace Mdm2 from its interaction with p53 and HAUSP, leading to p53 stabilization [7,6]. In another case, TRIM25 suppresses p53 activity by down regulating the activity of p300, a histone acetyl transferase that acetylates p53, a post-translational modification that is mandatory for transcriptional activation of several p53 target genes [8,9]. TRIM28, on the other hand, interacts with Mdm2 and promotes Mdm2-mediated ubiquitination and degradation of p53 [10]. In addition, TRIM28 enhances the association of HDAC1 (histone deacetylase 1) and p53 to promote p53 deacetylation [6]. A different mechanism is used by TRIM29 that sequesters p53 in the cytoplasm keeping it away from the promoters of its target genes [6]. TRIM29 further promotes the proteasomal degradation of the acetyl transferase Tip60 leading to a decreased acetylation of p53 at lysine 120, a post-translational modification that is required for the transcriptional activation of the p53 target genes *bax* and *puma* and subsequent initiation of apoptosis [9,11]. TRIM66, one of the few TRIM protein with a non-functional RING

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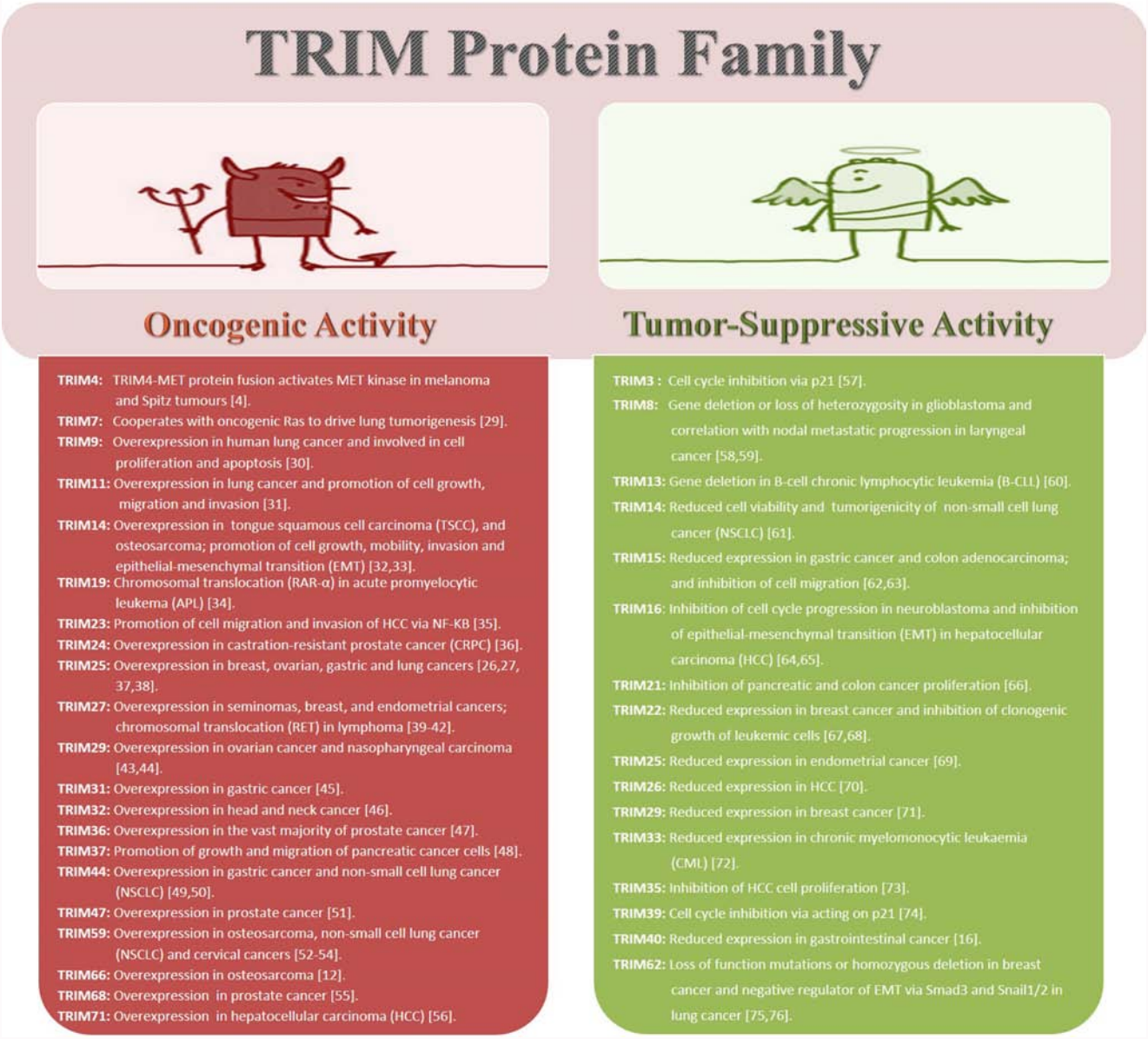

Figure 1: TRIM proteins have oncogenic and tumor suppressive activities**.** The figure shows TRIM proteins that are involved in the control of proliferation and/or are aberrantly expressed in tumors.

domain, down-regulates p53 by an as yet unknown mechanism [12].

While most TRIM proteins decrease p53 activity, there are some including TRIM8, TRIM13, TRIM19 and the TRIM-like TRIML2 that enhance p53 activity. These TRIM proteins either interfere with the interaction of MDM2 and p53, induce Mdm2 degradation or enhance p53's post-translational modifications e.g. by sequestering p53 in PML (promyelocytic leukaemia)-nuclear bodies [6].

Another important cellular node that is connected to carcinogenesis and controlled by TRIM proteins is the transcription factor NF-κB (nuclear factor kappa B), a protein that also regulates inflammation, immunological responses, cell proliferation and cell death [13]. In addition to the control of its activity by post-translational modifications, NF-κB activity is also regulated by inhibitory proteins and some of these proteins are regulated by TRIM proteins including IκK (inhibitor of nuclear factor kappa-B kinase) or PIAS (protein inhibitor of activated STAT1) proteins [14]. These inhibitory proteins, in particular PIAS3 (protein inhibitor of activated STAT1), PIASγ and IκK, are post-translationally modified by TRIM proteins such as TRIM8, TRIM32 and TRIM40. By ubiquitinating and degrading PIAS3 and PIASγ, TRIM8 and TRIM32 increase NF-κB activity while TRIM40 inhibits NF-κB activity through neddylation of IκK [15-17]. TRIM13, on the other hand, controls NF-κB activity by ubiquitinating and down regulating the activity of TRAF6 (tumor necrosis factor receptor associated factor 6) and NEMO (NF-κB essential modulator) [18,19].

Several TRIM family members (TRIM2, TRIM3, TRIM7, TRIM13, TRIM24, TRIM29, TRIM32, TRIM33, TRIM44, TRIM59 and TRIM68) control the level of other proteins that are involved in carcinogenesis. These proteins include TGF-β (transforming growth factor beta), TNFα (tumor necrosis factor alpha), β-catenin, AP1 (activator protein 1), the cell cycle inhibitor p21, Ras, Protein kinase B/AKT, Myc, mTOR (mechanistic target of Rapamycin), the androgen receptor and several proteins in the apoptotic pathway,

including BIM (Bcl-2 mediating inhibitor of cell death), Caspase 8 and XIAP (X-linked inhibitor of apoptosis). TRIM3 and TRIM32, for example, target p21 and XIAP, respectively, for degradation [20,21], and TRIM33 targets β-catenin for degradation and is furthermore involved in the regulation of TGF-β signaling and in the DNA damage response [22-24] while TRIM59 modulates Ras signaling in prostate cancer [25].

Although most TRIM proteins are restricted to the regulation of one protein or signaling cascade, some TRIM proteins regulate several pathways that are involved in carcinogenesis. TRIM25, for instance, does not only control the activity of p53, but also the abundance of 14-3-3σ, a protein that associates with cyclin/CDK (cyclin dependent kinase) complexes to inhibit CDK-activity, and TGF-β1 expression and signaling [8,26,27]. Another example of a multifunctional TRIM protein is TRIM32 that not only regulates p53 but also ubiquitinates XIAP and PIASγ to modulate NFκB and TNFα activity [17,21,28].

This brief overview over the activities of several TRIM proteins shows that more than fifty per cent of the members of the TRIM protein family that have been functionally characterized are associated with cancer. As several members of this large protein family are yet to be fully characterized, it is very likely that this percentage will increase and many more members will be shown to contribute to this disease in the years to come.

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