CHAPTER 5

TRIM INVOLVEMENT IN TRANSCRIPTIONAL REGULATION

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Abstract: Members of the tripartite motif (TRIM) protein family are found in all multicellular eukaryotes and function in a wide range of cellular processes such as cell cycle regulation, differentiation, development, oncogenesis and viral response. Over the past few years, several TRIM proteins have been reported to control gene expression through regulation of the transcriptional activity of numerous sequence-specific transcription factors. These proteins include the transcriptional intermediary factor 1 (TIF1) regulators, the promyelocytic leukemia tumor suppressor PML and the RET finger protein (RFP). In this chapter, we will consider the molecular interactions made by these TRIM proteins and will attempt to clarify some of the molecular mechanisms underlying their regulatory effect on transcription.

INTRODUCTION

Transcription factors that associate with DNA sequences in promoters and enhancers often recruit coregulators that modulate positively or negatively their activity. Many of these coregulators exist as components of large multisubunit complexes and act either through chromatin remodeling and histone modification, or at steps involving subsequent preinitiation complex formation or function (for a review see refs. 1 and 2). Recently, several tripartite motif (TRIM) proteins, also known as RBCC (N-terminal RING finger/B-box/coiled coil) proteins, have been described as dedicated coregulators in *Drosophila*, *C. elegans* and mammals.[3-7] Although the precise mechanisms by which these TRIM proteins influence transcription are still under investigation, consistent evidence

TRIM/RBCC Proteins, edited by Germana Meroni.

is accumulating for a role at the chromatin level. The activity of the transcriptional intermediary factors TIF1α/TRIM24, TIF1β/KAP1/TRIM28 and TIF1δ/TRIM66 as chromatin-related cofactors is well documented.[8-12] There is also evidence that TRIM19 and TRIM27, better known respectively as promyelocytic leukemia (PML) and RET finger (RFP) proteins, can regulate transcription through interaction with chromatin modifiers.[13,14] These findings are reviewed here and the possibility that TRIMs influence transcription by other mechanisms is also considered.

THE TIF1 FAMILY PROTEINS IN GENE-SPECIFIC REGULATION

TIF1s are members of a conserved subfamily of TRIM proteins, with orthologs present from *Drosophila* (Bonus)[3] to mammals (TIF1α to δ)[5,6,8,12,15,16] and playing crucial roles in (patho)physiological processes as diverse as organ formation and tumorigenesis (Table 1).[3,17-24] All family members have an N-terminal TRIM/RBCC motif with potential self-assembly properties[25,26] and a C-terminal bromodomain preceded by a PHD finger, two well-conserved signature motifs widely distributed among nuclear proteins acting at the chromatin level (see Chapter 2 by Micale et al).[27,28] They also have intrinsic kinase activity[9,29] and repress transcription when tethered to a promoter.[3,6,9,12,16] In the case of TIF1α, -β and -δ, a mechanistic link between repression and histone modification has been established with the demonstration that deacetylase inhibitors such as Trichostatin A can interfere with repression.[9,12] Consistent with this, TIF1β has been reported to be an intrinsic component of the histone deacetylase complex N-CoR1 and to interact both physically and functionally with the Mi2-α/CHD3 subunit of the nucleosome remodeling and deacetylase (NuRD) complex.[10,30] In addition, TIF1α, TIF1β and TIF1δ have been demonstrated to interact directly with the heterochromatin protein 1 (HP1) family proteins, a class of non-histone chromosomal proteins that serve as dose-dependent regulators of higher-order chromatin structures and contribute to the regulation of euchromatic genes (for a review see refs. 31 and 32).[8,9,12,33] It is currently assumed that the TIF1s function to target chromatin modifying complexes to specific sites in the genome through their interaction with sequence-specific DNA binding transcription factors (see Table 1).

TIF1α/TRIM24 in Nuclear Receptor-Mediated Transcription

Nuclear receptors (NRs) comprise a superfamily of transcription factors that regulate transcription in a ligand-dependent manner and play a crucial role in many aspects of vertebrate development, cell differentiation, proliferation and homeostasis.[34] Like other DNA binding transcription factors, they control transcription by recruiting different coregulator complexes.[35] TIF1α, also known as TRIM24, was among the first coregulators identified as interacting with nuclear receptors and it was shown to regulate either positively or negatively their transcriptional activity in a ligand-dependent fashion.[5,18,19,36,37] Of the four TIF1s described in mammals, TIF1α is the only member known to interact with liganded NRs.[8,12,16] Interaction is mediated through contacts with residues within the AF-2 activation domain of NRs [e.g., retinoic acid (RAR), vitamin D3 (VDR), thyroid (TR) and estrogen (ER) receptors] by means of a single LxxLL motif or NR box located in the middle region of TIF1α.[5,8] This interaction conserved in evolution is also found in *Drosophila* with the fly ortholog of the TIF1 family, Bonus

(Bon).[3] Specifically, it has been demonstrated, both biochemically and genetically, that Bonus is able to interact with the nuclear receptor βFTZ-F1 to downregulate its transcriptional activity.[3] In support of a similar effect for TIF1α in vivo, an enhanced RA induction of well-established RA target genes such as *Cyp26a1*, *Rbp1*, *Tgm2* and *Stra6* was observed in *TIF1α*-null compared to wild-type MEF cell lines.[18] Moreover, chromatin immunoprecipitation and transient transfection assays showed that, upon RA induction, TIF1α directly targets the retinoic acid (RA) responsive elements (RARE) in the *CYP26A1* promoter and can repress in a dose-dependent manner RAR-mediated transactivation on a RARE-responsive promoter.[18]

A fundamental physiological role for TIF1α in repressing a molecular pathway involving the RA receptor isotype α (RARα), which functions to prevent liver tumor formation, was recently demonstrated by genetic studies in mice lacking TIF1α.[18] In *TIF1α*-null mice, hepatocytes fail to execute proper cell cycle exit during the neonatal-to-adult transition and continue to cycle in adult livers, becoming prone to a continuum of cellular alterations that progress towards metastatic hepatocellular carcinoma (HCC). Not surprisingly, analysis of gene expression profiles revealed aberrant expression of numerous RA responsive genes in the liver tumors from *TIF1α* knockout mice. More importantly, it was shown that deletion of a single *RARα* allele in a *TIF1α*-null background was enough to suppress HCC development and to restore the wild-type expression of RA-responsive genes in the liver.[18] Altogether, these results define TIF1α as a potent liver-specific tumor suppressor in mice and provide genetic evidence that TIF1α and RARα act in opposition to each other in liver cancer.[18,38]

More recently, it has been shown that, in addition to hepatic tumors, *TIF1α* knockout mice spontaneously develop pathological calcifications in arterial vessels, lung alveoli and vibrissae.[19] Importantly, these ectopic calcifications were correlated to an increase in expression of several vitamin D receptor (VDR) direct target genes involved in calcium homeostasis (e.g., *Casr*, *Trpv5* and *Trpv6*, *Calb1* and *S100g*). Their increased expression in *TIF1α*-deficient kidneys provides evidence of the importance of TIF1α in repressing the VDR pathway in the kidney.[19] TIF1α appears therefore to act as a negative regulator of multiple NR-dependent pathways in vivo.

TIF1β/TRIM28 in KRAB-ZFP-Mediated Repression

KRAB-zinc finger proteins (ZFPs), in which a potent repressor domain called the Krüppel-associated box (KRAB) is attached to a tandem array of zinc finger motifs of the Krüppel Cys_2-His_2 type, are specific to tetrapod vertebrates and represent one of the largest family of transcriptional repressors in mammals; it has been estimated that more than 400 human loci are capable of encoding KRAB-ZFPs.[39] Their importance is inferred from their recent origin and subsequent rapid expansion in vertebrate lineages, but their role in vivo remains largely unknown. At a mechanistic level, however, it is well understood how KRAB-ZFPs operate to silence transcription; they mediate silencing through association with the corepressor protein TIF1β (also called TRIM28 or KAP1).[6,40] The tripartite motif of TIF1β binds directly to the KRAB domain of KRAB-ZFPs.[25] This binding requires integrity of all three sub-domains of the TIF1β tripartite motif with each sub-domain contributing to the formation of an oligomer that is obligatory for KRAB interaction.[25] This interaction is entirely specific for the TIF1β tripartite motif since it was not observed with the tripartite motifs from related proteins such as TIF1α, TIF1γ, TIF1δ or MID1.[12,26,40]

Table 1. The TIF1 family members in transcriptional regulation

	Transcriptional Interactor				
Family Member	DNA Binding Transcription Factor	Non DNA Binding Transcriptional Cofactor	Transcriptional Effect, Mechanism of Action	Biological Function	Refs.
Human or mouse					
TIF1α/TRIM24	Nuclear receptors	HP1, GRIP1, CARM1	Modulates ligand-dependent transactivation by nuclear receptors	Acts in liver tumor suppression and prevents arterial calcification	5, 8, 9, 18, 19, 36-38
TIF1β/TRIM28/ KAP1	KRAB-ZFPs	HP1, Mi-2α/CHD3, SETDB1/ESET	Mediates KRAB-ZFP repression through recruitment of chromatin modifiers	Regulates progression through differentiation and retrovirus silencing	8-11, 40-48
	p53*	MDM2	Inhibits p53 acetylation by interacting with MDM2 and stimulating p53-HDAC1 interaction	Regulates p53-mediated apoptosis	50
	E2F1	nd	Inhibits E2F1 activity by promoting E2F1-HDAC1 interaction	Regulates E2F1-mediated apoptosis	51
TIF1γ/TRIM33/ RFG7	Smad2/3	nd	Binds receptor-activated Smad2/3 in competition with Smad4	Stimulates TGFβ-dependent erythroid differentiation	22
TIF1δ/TRIM66	nd	HP1	Represses transcription when targeted to DNA	May regulate postmeiotic germ cell gene expression	12
Xenopus laevis Ectodermin (xTIF1γ)	Smad4	nd	Induces Smad4 ubiquitination and degradation	Acts in early embryonic development as a a general inbibitor of TGFβ and BMP signaling	23

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Table 1. Continued

Family Member	Transcriptional Interactor: DNA Binding Transcription Factor	Transcriptional Interactor: Non DNA Binding Transcriptional Cofactor	Transcriptional Effect, Mechanism of Action	Biological Function	Refs.
Danio rerio moonshine (DrTIF1γ)	nd	nd	nd	Regulates hematopoiesis	24
Drosophila melanogaster Bonus	Nuclear receptors	nd	Binds to and inhibits βFTZ-F1 transcriptional activity	Is required for viability, molting and numerous events in meta-morphosis	3

*: no direct interaction; nd: not determined; CARM1: coactivator-associated arginine methyltransferase 1; CHD3: chromodomain helicase DNA binding, protein 3; E2F1: E2F transcription factor 1; GRIP1: glucocorticoid receptor-interacting protein 1; HP1: heterochromatin protein 1; KRAB-ZFP: Krüppel, associated box-zinc finger protein; MDM2: mouse double minute 2; SETDB1/ESET: SET domain bifurcated 1/ERG-associated protein with SET domain.

To repress gene transcription by KRAB-ZFPs, TIF1β recruits HP1 proteins through a PxVxL motif located in its middle region.[9,33] Additionally, TIF1β associates with the component of the NuRD histone deacetylase complex Mi-2α/CHD3 and the histone H3 lysine 9 (H3K9) methyltransferase SETDB1/ESET via its C-terminal PHD-bromodomain unit.[10,11] The PHD domain binds to the SUMO E2 protein Ubc9 and directs SUMO conjugation of the adjacent bromodomain. Once modified by SUMO, the bromodomain of TIF1β recruits Mi-2α/CHD3 and SETDB1/ESET and their associated proteins.[41] It is currently believed that TIF1β assembles these proteins onto KRAB-ZFPs to coordinate histone deacetylation and methylation, as well as HP1 deposition, all of which cooperatively result in heritable gene silencing through the formation of condensed, transcriptionally inactive heterochromatin-like structures and/or spatial relocalization to pericentric heterochromatin domains.[42-44]

The results discussed above point to a link between TIF1β-mediated corepression and pericentric heterochromatin. Further supporting evidence for this link came from the fact that, during cell differentiation, TIF1β undergoes a dramatic redistribution, the protein moving from euchromatic nuclear compartments to heterochromatic compartments.[45] This differentiation-induced heterochromatin association of TIF1β was not observed with a PxVxL-motif mutant that fails to interact with HP1.[45] Importantly, genetically engineered F9 embryonic carcinoma cells producing this mutant form of TIF1β were able to differentiate into primitive endoderm-like cells after exposure to retinoic acid, but were unable to further differentiate into parietal endodermal cells upon addition of Bt_2cAMP, thus indicating that interaction between TIF1β and HP1 is an absolute requirement for progression through cell differentiation.[46] Importantly, interaction with HP1 was also shown to be essential in regulating TIF1β-mediated silencing of provirus in embryonic carcinoma (EC) and stem (ES) cells.[47,48]

Recently, a comprehensive study of the genomic regions bound by TIF1β in human Ntera2 cells revealed that a fourth of the TIF1β bound promoters are also enriched for trimethylated histone H3 lysine 9, indicating that many but not all TIF1β target sites are occupied by the selective histone mark for HP1.[49] This strongly suggests that HP1 may not be required for all the actions of TIF1β. In support of this, it has recently been reported that TIF1β inhibits p53 transcriptional regulation by a mechanism that is independent of its interaction with HP1.[50] This inhibitory function of TIF1β is executed in concert with MDM2, a RING domain ubiquitin E3 ligase which binds to p53, inhibits p53 acetylation and promotes p53 ubiquitination and degradation (see ref. 50 and refs. therein). TIF1β binds directly MDM2 via its coiled coil domain.[50] It cooperates with MDM2 to stimulate p53-HDAC1 complex formation, thus promoting p53 deacetylation and then p53 ubiquitination and degradation.[50] Interestingly, a similar mechanism of TIF1β transcriptional inhibition by promoting deacetylation was also described for the E2F1 transcription factor.[51]

Analyses of TIF1β deficient mice have provided evidence that TIF1β exerts cellular function(s) essential for early embryogenesis[20] and spermatogenesis.[21] An important future task will be to identify the transcriptional targets of TIF1β that mediate these functions. Recently, TIF1β was also found to be important for the maintenance of ES self-renewal.[52,53] More than 3000 genes whose promoter regions are occupied by TIF1β in mouse ES cells were identified.[53] A consensus binding motif was deduced to be GCCGCGXX and, importantly, a total of 326 target genes were found to be occupied by not only TIF1β, but also by three other pluripotency-associated transcription factors, CNOT3, C-MYC and ZFX. These common target genes are enriched for genes involved in cell cycle and cell survival, suggesting that TIF1β together with CNOT3, C-MYC and ZFX control self-renewal by regulating these processes.[53]

TIF1γ/TRIM33 in Smad-Mediated Transcription

Human TIF1γ (also known as TRIM33 and RFG7) was initially identified by virtue of its sequence homology with TIF1α[15,16] and, similarly to TIF1α, it was found in the context of a fusion oncoprotein with the tyrosine kinase domain of Ret from childhood papillary thyroid carcinomas.[17] Through their respective tripartite motifs, TIF1α and TIF1γ can hetero-oligomerize as efficiently as they homo-oligomerize, thus suggesting some possible cross-talk between the signaling pathways regulated by these two proteins.[26]

Two recent studies have implicated TIF1γ in the control of the signaling and gene responses triggered by members of the transforming growth factor-β (TGFβ) family.[22,23] TGFβ family members bind two types of membrane serine/threonine kinases, the Type I and Type II receptors, forming an heteromeric receptor complex. The Type II receptor then phosphorylates and activates the Type I receptor, which in turn phosphorylates Smad transcription factors (Smad2 and Smad3), which then form complexes with Smad4 and regulate the transcription of specific genes (see ref. 22 and refs. therein). He et al identified human TIF1γ as a protein that selectively binds receptor-activated Smads 2 and 3.[22] This binding is specific for TIF1γ and occurs via the middle region of TIF1γ. Of interest, it was shown that, in agreement with the fact that *moonshine*, the closest homolog of TIF1γ in the zebrafish, is an essential gene in hematopoiesis,[24] TIF1γ associates with Smad2/3 to stimulate erythroid differentiation in response to TGFβ.[22] These findings have been extended in an independent study by Dupont et al, who provided evidence that TIF1γ, as well as its *Xenopus* counterpart (called Ectodermin), also interfere with the Smad responses by binding to Smad4 and causing Smad4 ubiquitination and degradation.[23] This selective control of the protein level of Smad4 by TIF1γ appears to be needed to limit the TGFβ-growth arrest response in epithelial cells and was shown to play an important role in germ layer specification during the early development of *Xenopus* embryos.[23] It was demonstrated to rely on an enzymatically active TIF1γ RING finger domain and therefore provides the first evidence for a TRIM protein of the TIF1 subfamily acting as an E3 ubiquitin ligase to cause transcription factor degradation.[23]

PML/TRIM19 IN THE CONTROL OF TRANSCRIPTION

The *PML* gene was originally identified as the t(15; 17) chromosomal translocation partner of *RARα* in acute promyelocytic leukemia (APL). The PML protein acts as a negative growth regulator and tumor suppressor and as a specific regulator of hematopoietic differentiation.[54,55] Various PML isoforms have been identified that share the same N-terminal TRIM motif with variable C terminal lengths generated by alternative splicing (for a review see ref. 56). PML nuclear isoforms are typically found concentrated in discrete nuclear speckles called PML-Nuclear Bodies (PML-NBs), which recruit critical regulators of cell proliferation, apoptosis, genome stability and posttranslational modifications (see Chapter 4 by Batty et al). PML is not only the major component of PML-NBs, but also a key determinant of their formation; no PML-NB is observed in $PML^{-/-}$ cells[54] and any mutations in critical RING finger or B box cysteine residues of the PML TRIM motif disrupt PML-NB formation (see ref. 57 and refs. therein). Although the exact function(s) of PML-NBs remains still largely unknown, several lines of evidence support a role in transcriptional regulation. These include the colocalization of PML-NBs with many transcription factors and cofactors such as

CBP, HP1, Sp100, Daxx, Rb and p53, the detection of nascent RNA in the immediate periphery of PML-NBs, the association of PML-NBs with regions of high transcriptional activity and their interaction with specific genomic loci.[57-63] Moreover, PML by itself displays the properties expected for a coregulator playing a role in transcription, as either an activator or a repressor depending on the gene under consideration (see Table 2).[7]

PML as a Positive Regulator of Transcription

In agreement with a role of PML in transcriptional activation, it has been shown that PML interacts and colocalizes with the transcriptional co-activator and histone acetyltransferase CBP in the PML-NBs.[58,60] PML can potentiate the transcriptional activation function of CBP and serve as a co-activator for nuclear receptors.[36,64,65] Deletion analyses indicated that both the activation domains (AF-1 and AF-2) of the progesterone receptor (PR) as well as the tripartite motif of PML were required for the PML effect on PR-mediated transactivation.[64] These findings were supported by the analysis of *PML*$^{-/-}$ cells, showing that in the absence of PML, retinoic acid receptor-dependent transactivation was impaired as well as retinoic acid-induced myeloid differentiation and growth inhibition.[54] Moreover, PML has been reported to interact with and potentiate transcriptional activation by the p53 family members, i.e., p53, p63 and p73.[66-68] PML enhances p53 activity by several means: by recruiting p53 to PML-NBs and promoting its acetylation by CBP,[69] by interacting with p53 and MDM2 and preventing p53 ubiquitination,[70] by sequestering MDM2 to the nucleolus,[71] by promoting p53 phosphorylation by Chk2 and CK1 and blocking p53-MDM2 interaction,[72,73] or yet by promoting p53 deubiquitination by the ubiquitin protease HAUSP.[74] Similarly, PML increases p73 acetylation in a PML-NB-dependent manner, thus preventing its ubiquitinylation and subsequent degradation.[68] On the basis of a number of cotransfection and interaction data, PML was also shown to co-activate Fos and the hematopoietically expressed GATA2 transcription factor through a mechanism that requires an intact PML tripartite motif.[75,76] Moreover, a physical and functional link was described between a specific PML isoform (PMLI) and the leukemia-associated transcription factor AML-1; PMLI interacts with AML-1 through their respective C-terminal region, targets AML-1 into PML-NBs together with its co-activor p300, enhances AML-1-mediated transcription and stimulates differentiation of myeloid cells.[77] An unexpected role for a cytoplasmic isoform of PML (cPML) as an essential modulator of TGF-β-induced gene expression has recently been discovered; cPML physically interacts with Smad2/3 and SARA (Smad anchor for receptor activation) and is required for association of Smad2/3 with SARA and the accumulation of SARA and TGF-β receptor in the early endosome—a process that is crucial for TGF-β signal transduction.[78] Finally, a link between PML, higher order chromatin organization and gene regulation has been established by the demonstration that PML functionally and physically interacts with the matrix-attachment (MAR)-binding protein SATB1 to regulate chromatin-loop architecture and transcription of the major histocompatibility complex (MHC) class I locus.[79] On the other hand, PML was found to inhibit Daxx-mediated transcriptional repression by promoting recruitment of Daxx to the PML bodies,[80] while the specific isoform PMLIV can re-activate Myc-repressed target genes such as the cell cycle inhibitors *CDKN1A*/*p21* and *CDKN2B*/*p15* by mediating Myc degradation in a manner dependent on the RING domain of PML.[81]

PML as a Negative Regulator of Transcription

Evidence for a role of PML as a negative regulator of transcription is supported by the early findings that PML can inhibit transcription by itself when tethered to DNA, possibly through interaction with histone deacetylases.[13,82] In addition, PML was shown to interact through its coiled coil domain with the chromatin related-corepressors N-CoR and mSin3a and to mediate the transcriptional repression function of the tumor suppressor MAD.[83] Furthermore, a direct downregulatory effect of PML on the transcriptional activity of a variety of sequence-specific transcription activators has been described (see Table 2). It was found that PML interacts directly with the DNA binding domain of the Sp1 transcription factor through its coiled coil domain and inhibits the transactivation activity of Sp1 on the epidermal growth factor receptor (*EGFR*) gene promoter by preventing it from binding to DNA.[84] A similar mechanism of repression was described in the case of Nur77 and NF-κB, two potent transcriptional activators involved in induction of apoptosis.[85,86] Recently, PML was also shown to inhibit IFN-γ-mediated STAT-1α DNA binding and transcriptional activity, thus leading to a downregulation of numerous IFN-γ-regulated genes.[87] Finally, PML can form stable complexes with the retinoblastoma protein pRB within PML-NBs, interact with the pocket region of pRB through its B boxes and abolish activation of glucocorticoid receptor (GR)-mediated transcription by pRB.[88]

Overall, these studies define PML as a unique coregulator that in addition to interacting with various sequence-specific transcription factors, can influence their transcriptional activity by different biochemical means leading to up- or downregulation of gene expression. In the future, it will be of great importance to determine whether PML exerts all of its transcriptional activities in the PML-NBs or throughout the nucleoplasm.

RFP/TRIM27 IN THE CONTROL OF TRANSCRIPTION

The RET finger protein (RFP), also designated TRIM27, was originally identified in the context of a fusion protein with the RET tyrosine kinase that possesses transforming activity.[89] In addition to a N-terminal tripartite motif, RFP contains a specific C-terminal RFP or B30.2 domain (see Chapter 2 by Micale et al). RFP is widely expressed and, depending on the cell type or tissue, is localized either to the cytoplasm or nucleus.[90] In the nucleus, a portion of RFP associates with the nuclear matrix and localizes into the PML-NBs, where RFP binds directly to PML and Int-6.[91,92] Although no biological function has yet been ascribed to RFP, it has been shown to cause extensive apoptosis when overexpressed in human embryonic kidney 293 cells.[93] From a molecular point of view, this pro-apoptotic function of RFP may rely on its ability to control transcription. Indeed, as mentioned for PML, RFP is a protein that exhibits a potent transcriptional repressive activity when tethered to DNA through fusion to a heterologous DNA binding domain.[14] This repressor activity is regulated by sumoylation[94] and resides mainly in the coiled-coil domain, which represents a binding site for several proteins involved in chromatin-based gene silencing such as Enhancer of Polycomb 1 (EPC1), methyl-CpG binding proteins MBD2/4 and Mi-2β/CHD4, the main component of the NuRD complex (see Table 3).[95,96] Importantly, a direct inhibitory effect of RFP on the transcriptional activity of basic helix-loop-helix (bHLH) transcription factors has been described; RFP binds to the bHLH domain of

Table 2. Role of PML (TRIM19) in transcriptional regulation

PML Role	Transcription (co)Factor	Interaction Domain	Mechanism of Action	Biological Function	Refs.
Co-activation	RARα	No direct interaction	Stabilizes CBP-RAR complex	Growth inhibition, cellular differentiation	36, 54, 65
	PR	No direct interaction	nd	nd	64
	p53	DNA binding domain of p53, C-ter region of PML	Recruits p53 to the PML-NBs, promotes p53 acetylation, phosphorylation and deubiquitin-ation, sequesters MDM2 in the nucleolus	Apoptosis, senescence, growth inhibition	66, 69-74
	p63	nd	Recruits p63 to the PML-NBs	nd	67
	p73	nd	Increases p73 acetylation	nd	68
	Fos	No direct interaction	nd	nd	75
	GATA-2	Zinc finger region of GATA-2, B-box domain of PML	nd	nd	76
	AML-1	C-ter regions of AML-1 and PML I	Recruits AML-1 to the PML-NBs together with p300	Myeloid cell differentiation	77
	CBP	Aa 311-521 of CBP, coiled coil domain of PML	Recruits CBP to the PML-NBs	Cell growth control	36, 58, 60, 65
Co-repression	MAD	No direct interaction	Increases MAD-mediated repression via direct interaction with multiple corepressors (c-Ski, N-CoR and mSin3A)	Suppression of cell proliferation	83
	HDAC1	C-ter aa (447-633) of PML	nd	nd	82, 83
	c-Ski	Aa 261-330 of c-Ski, coiled coil domain of PML	Recruits c-Ski to the PML-NBs	Suppression of cell proliferation	83

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Table 2. Continued

PML Role	Transcription (co)Factor	Interaction Domain	Mechanism of Action	Biological Function	Refs.
	N-CoR	Aa 1502-1581 of N-CoR, coiled coil domain of PML	Recruits N-CoR to the PML-NBs	nd	83
De-activation	Sp1	DNA binding domain of Sp1, coiled coil domain of PML	Inhibits Sp1 transactivation activity by preventing it from binding to DNA	Repression of *EGFR* transcription	84
	Nur77/NR4A1	DNA binding domain of Nur77, coiled coil domain of PML	Interferes with Nur77 DNA binding	Cell growth, apoptosis	85
	NFκB	nd	Interferes with NFκB DNA binding	Repression of *A20* transcription, apoptosis	86
	STAT-1α	nd	Inhibits STAT-1α DNA binding	Negative regulation of IFN-γ signaling	87
	pRB	The pocket region of pRB, the RING and B1-B2 regions of PML	nd	Inhibition of glucocorticoid receptor (GR)-mediated transcription by pRB	88
De-repression	Daxx	nd	Recruits Daxx to the PML-NBs and inhibits Daxx-mediated repression	Apoptosis	80
	Myc	N- and C-ter domains of Myc, C-ter region of PML	Induces Myc destabilization	Granulocytic differentiation	81

nd: not determined; Aa: amino acids; AML-1: acute myeloid leukemia 1 protein; CBP: CREB-binding protein; c-Ski: cellular Sloan-Kettering viral oncogene homolog; Daxx: Fas death domain-associated protein; Fos: FBJ osteosarcoma oncogene; HDAC1: Histone deacetylase 1; Myc: myelocytomatosis oncogene; N-CoR: nuclear receptor corepressor; Nur77/NR4A1: nuclear receptor subfamily 4, group A, member 1; PR: progesterone receptor; pRB: retinoblastoma protein; RAR: retinoic acid receptor; STAT-1: signal transducer and activator of transcription 1.

Table 3. Role of RFP (TRIM27) in transcriptional regulation

RFP Role	Transcription (co)Factor	Interaction Domain	Cellular Function	Ref.
Co-repression	Mi-2β/CHD4	C-ter of Mi-2β, coiled coil domain of RFP	Mi-2β enhances the repressing activity of RFP	96
	EPC1	EPcA and C-ter domains of EPC1, coiled coil domain of RFP	nd	14
	MBD2/4	Aa 413-580 of MBD4, coiled coil domain of RFP	Enhances MBD2- and MBD4-dependent repression	95
Co-activation	ERα	No direct interaction	Interacts directly with the C-ter Glu/Arg-rich region of the ERα repressor SAFB1 and positively regulates a subset of ERα target genes (e.g., *CCND1* and *PR*) in MCF-7 cells	99
	Mi-2β/CHD4	C-ter of Mi-2β, coiled coil domain of RFP	Associates with Mi-2β, MCRS1 and UBF in the nucleolus and up-regulates rDNA transcription	100
De-activation	SCL	bHLH domain of SCL, B box and coiled coil motif of RFP	Inhibits transactivation by SCL and by other bHLH transcription factors (E47, MyoD, mASH-1)	97
	pRB	Coiled coil and B30.2 domains of RFP	Inhibits Rb-mediated transactivation by preventing the degradation of the EID-1 inhibitor of histone acetylation	98

nd: not determined; Aa: amino acids; CHD4: chromodomain helicase DNA binding protein 4; EPC1: enhancer of polycomb 1; ERα: estrogen receptor alpha; MBD2/4: methyl-CpG-binding domain protein 2/4; MCRS1: microspherule protein 1; pRB: retinoblastoma protein; SAFB1: scaffold attachment factor B1; SCL: stem cell leukemia protein; UBF: upstream binding transcription factor, RNA polymerase I.

the Stem Cell Leukemia gene product (SCL) through its B box and coiled coil domain and specifically inhibits transactivation by SCL and three other bHLH proteins, E47, MyoD and mASH-1, via a mechanism that requires histone deacetylation activity.[97] Recently, RFP was also shown to inhibit transcription activation by the Retinoblastoma protein pRb; RFP binds to pRB through its coiled coil and C-terminal B30.2 domain, provokes stabilization of the histone acetyltransferase inhibitor EID-1 and, through this, inhibits pRB gene-activating function.[98]

Supporting the notion that RFP could play a dual role in transcription, being involved in both repression and activation, RFP was also reported to regulate positively estrogen receptor α (ERα)-mediated transcription, through a mechanism that may involve a direct interaction with the ERα repressor SAFB1 (Scaffold attachment factor B1).[99] Moreover, RFP and Mi-2β/CHD4, known to be involved in transcriptional repression in the nucleus, have been reported to form a complex with the nucleolar protein MCRS1 (microspherule protein 1) and the rRNA transcription factor UBF in the nucleolus, where they play a direct transactivating role on ribosomal gene transcription.[100]

OTHER TRIM FAMILY MEMBERS IN TRANSCRIPTIONAL REGULATION

Besides the TIF1s, PML and RFP, a few other TRIM proteins have been associated with transcription in different organisms (see Table 4). These include RPT-1/TRIM30, Pub/TRIM14 and TRIM45 in human and mouse, Xnf7 in *X. laevis* and TAM-1 in *C. elegans*. RPT-1 (Regulatory protein, T-lymphocyte, 1) is selectively expressed by resting inducer T cells and was shown to downregulate gene expression directed by the long terminal repeat (LTR) promoter region of human immunodeficiency virus Type 1 (HIV-1) or by the promoter region of the gene encoding the α chain of the interleukin 2 receptor (*IL-2Rα*).[101] Pub, also designated TRIM14, was originally identified based on its

Table 4. Other TRIM proteins in transcriptional regulation

TRIM	Transcription Factor	Cellular Function	Refs.
Human or mouse			
RPT-1/TRIM30	nd	Downregulates *IL-2Rα* and HIV-1 transcription	101
Pub/TRIM14	Pu.1/Spi-1	Inhibits Pu.1 transcriptional activity	103
TRIM45	nd	Represses transcription by ELK-1 and AP-1	104
Other species			
Xnf7 (*X. laevis*)	nd	Regulates pre-mRNA maturation	105, 106
TAM-1* (*C. elegans*)	PHA-4/FoxA	Cooperates with PHA-4 to repress ectodermal genes in pharyngeal precursor cells	4

*: lacks the coiled coil domain; nd: not determined; PHA-4/FoxA: defective pharyngeal development protein 4/forkhead box A; Pub: PU.1 binding protein; RPT-1: Regulatory protein, T-lymphocyte, 1; Spi-1: spleen focus forming virus (SFFV) proviral integration oncogene; TAM-1: Tandem Array expression Modifier 1.

ability to interact with the human transcription factor PU.1/Spi-1, an Ets family protein which plays a central role in the differentiation and proliferation of macrophages and B cells during hematopoiesis.[102,103] In addition to a tripartite motif, Pub contains a B30.2 domain and was shown, in transient transfection assays, to inhibit PU.1 transcriptional activity in a B box integrity-dependent manner.[103] TRIM45 is a widely expressed TRIM protein, harboring in its C-terminal region a filamin-type immunoglobin (IG-FLMN) domain.[104] In forced expression studies, TRIM45 selectively inhibits the transcriptional activity of EIK-1 and AP-1, suggesting that it may act as a negative modulator of the mitogen-activated protein kinase (MAPK) signaling pathway.[104] Xnf7 is one of the first TRIM proteins described and was characterized in two amphibian species, *Xenopus laevis* and *Pleurodeles waltl*.[105] In addition to the tripartite motif, XNF7 has a chromodomain and a B30.2 domain in its N-terminal and C-terminal regions, respectively. It was found that during oogenesis, XNF7 associates through its B box and the coiled coil with the elongating RNA polymerase II transcripts on the loops of the lampbrush chromosomes, thus suggesting a role in pre-mRNA transcription and/or processing.[105,106] Biochemical and genetic studies in *C. elegans* have identified TAM-1, a RING finger/B box protein lacking the coiled coil domain, as a corepressor interacting with and mediating via association with the NuRD complex the repressive activity of the PHA-4/FoxA transcription factor.[4] It was found that TAM-1 and NuRD cooperate with PHA-4 to repress ectodermal genes in pharyngeal precursor cells and thereby promote specification to pharyngeal fate.[4]

CONCLUSION

Although up to now only a relatively small subset of TRIM proteins has demonstrated transcriptional regulatory activity, it appears that these TRIMs control transcription by means of a wide and varied range of activities and play critical roles in a plethora of cellular processes such as apoptosis, cell cycle regulation, differentiation and retrovirus restriction. This functional diversity relies on the intrinsic properties of the concerned proteins and their ability to interact with distinct classes of sequence-specific transcription factors and cofactors. Through these interactions, they can either positively or negatively regulate target gene expression. Prominent among the mechanisms of action is the potential to cooperate with chromatin modifiers, to recruit transcription factors and cofactors to specialized nuclear compartments and to regulate directly or indirectly their posttranslational modification. Exactly how TRIMs operate in these alternative mechanisms and how they are regulated should receive great deal of attention in the coming years.

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