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REVIEW

Multiple crosstalks between mRNA biogenesis and SUMO

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Abstract mRNA metabolism involves the orchestration of multiple nuclear events, including transcription, processing (e.g., capping, splicing, polyadenylation), and quality control. This leads to the accurate formation of messenger ribonucleoparticles (mRNPs) that are finally exported to the cytoplasm for translation. The production of defined sets of mRNAs in given environmental or physiological situations relies on multiple regulatory mechanisms that target the mRNA biogenesis machineries. Among other regulations, post-translational modification by the small ubiquitin-like modifier SUMO, whose prominence in several cellular processes has been largely demonstrated, also plays a key role in mRNA biogenesis. Analysis of the multiple available SUMO proteomes and functional validations of an increasing number of sumoylated targets have revealed the key contribution of SUMO-dependent regulation in nuclear mRNA metabolism. While sumoylation of transcriptional activators and repressors is so far best documented, SUMO contribution to other stages of mRNA biogenesis is also emerging. Modification of mRNA metabolism factors by SUMO determine their subnuclear targeting and biological activity, notably by regulating their molecular interactions with nucleic acids or protein partners. In particular, sumoylation of DNA-bound transcriptional regulators interfere with their association to target sequences or chromatin modifiers. In addition, the recent identification of enzymes of the SUMO pathway within specialized mRNA biogenesis machineries may provide a further level of regulation to their specificity. These multiple crosstalks between mRNA metabolism and SUMO appear therefore as important players in cellular regulatory networks.

Keywords Sumoylation · mRNA transcription · mRNA processing · Messenger ribonucleoparticle (mRNP)

Abbreviations

hnRNP	Heterogenous nuclear ribonucleoprotein
mRNA	Messenger RNA
mRNP	Messenger ribonucleoparticle
NPC	Nuclear pore complex
RNAP II	RNA polymerase II
SIM	SUMO-interacting motif
STUbL	SUMO-targeted ubiquitin ligase
SUMO	Small ubiquitin-like modifier

Introduction

mRNA biogenesis is a regulated process that allows the tight adaptation of protein synthesis and cellular metabolism to environmental and physiological changes. Accurate and efficient formation of export-competent messenger ribonucleoparticles (mRNPs) involves the coordination of several distinct biochemical events in the nucleus (Fig. 1, reviewed in Luna et al. 2008). DNA-bound transcriptional activators, together with co-activators, direct the formation of RNA polymerase II (RNAP II) pre-initiation complexes on gene promoters. Pre-mRNAs synthesized by RNAP II subsequently interact with several RNA-binding complexes in a dynamic manner: mRNA processing machineries catalyze 5′ capping, intron splicing, and 3′ end processing (e.g., cleavage/polyadenylation), while other mRNA-associated proteins serve as adaptors for the mRNA export machinery. These multiple events are associated with quality control mechanisms ensuring that only mature, exportable mRNPs are ultimately brought to nuclear pore complexes

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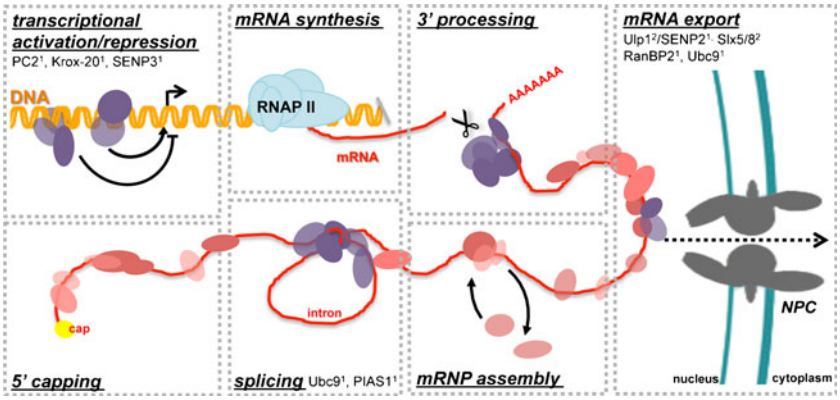

Fig. 1 The mRNA biogenesis pathway. The different processes contributing to nuclear mRNA biogenesis are represented: transcriptional activation/repression, mRNA synthesis, 5′ capping, splicing, 3′ processing, mRNP assembly, and mRNA export. Enzymes of the SUMO pathway in association with specific machineries are indicated (*1*, in mammalian cells; *2*, in yeast). *RNAP II*, RNA polymerase II; *NPC*, nuclear pore complex

(NPCs) for translocation (reviewed in Oeffinger and Zenklusen 2012). The different steps of mRNA biogenesis are tightly coupled, for instance through the carboxy-terminal domain of the RNAP II largest subunit that allows the co-transcriptional recruitment of the mRNA processing machinery. In addition, mRNA biogenesis, from transcription to export, is regulated through post-translational modifications (reviewed in Tutucci and Stutz 2011 ; Babour et al. 2012), including methylation, phosphorylation, ubiquitinylation but also sumoylation by which SUMO is covalently conjugated to target proteins.

SUMO (small ubiquitin-like modifier), a member of the ubiquitin-like post-translational modifiers, is well conserved among eukaryotes (reviewed in Geiss-Friedlander and Melchior 2007 ; Wilkinson and Henley 2010). Invertebrate and fungi only express one isoform of SUMO, called Smt3 in budding yeast, whereas multiple conjugatable paralogues of SUMO are found in plants and vertebrates (Table 1). More precisely, the three mammalian isoforms of SUMO differ in sequence as SUMO-1 shares 48 % identity with SUMO-2 and -3 that are 97 % identical and are thus most frequently referred to as SUMO-2/3. Like ubiquitin, SUMO is conjugated to its targets by an isopeptide bond between its C-terminal glycine and the ε-NH_2 group of a lysine residue in the target protein. SUMO modification most frequently targets the consensus modification site Ψ-K-X-D/E of a protein, where Ψ is a hydrophobic residue. Sumoylation requires an enzymatic cascade involving an E1 SUMO-activating enzyme, an E2 SUMO-conjugating enzyme, and in most cases, an E3 SUMO ligase (Fig. 2 and Table 1). In addition, SUMO-specific proteases are also required to process SUMO precursors and to deconjugate SUMO from the substrates (Fig. 2 and Table 1; reviewed in Hickey et al. 2012). SUMO modification can occur either at a single or at multiple lysine residues in the target protein, leading to mono- or multisumoylation, respectively. In addition, SUMO can also be

Table 1 List of SUMO pathway components in budding yeast, mammals, and plants

	Budding yeast	Mammals	Plants[a]
SUMO isoforms	Smt3	SUMO-1–SUMO-2–SUMO-3[b]	SUM1–SUM2–SUM3–SUM4–SUM5–SUM6–SUM7–SUM8
E1	Aos1/Uba2[c]	SAE1/SAE2[c]	SAE1a-b/SAE2[c]
E2	Ubc9	Ubc9 (UBE2I)	SCE1
E3	Siz1–Siz2 (Nfi1)–Mms21–Zip3 (Cst9)	PIAS1–PIASxα–PIASxβ–PIASy–PIAS3–HDAC4–MMS21–PC2–RanBP2–Topors–TRAF7–Krox20[d]–SRSF1 (SF2/ASF)[d]	SIZ1–MMS21 (HPY2)
SUMO proteases[e]	Ulp1–Ulp2–Wss1[f]	SENP1–SENP2–SENP3–SENP5–SENP6–SENP7–DESI1–DESI2–USPL1	Ulp1a (ELS1)–Ulp1b–Ulp1c (OTS2)–Ulp1d (OTS1)–ESD4–Ulp2a–Ulp2b
STUBls	Slx5 (Hex3)/Slx8[c]	RNF4	?

Alternative names are in brackets

[a] The names of the proteins of the SUMO pathway in plants are from *Arabidopsis thaliana* (Miura and Hasegawa 2010)

[b] A SUMO-4 paralog has been identified but lacks a proper conjugatable C terminus and may not be conjugated to targets

[c] The subunits of the dimeric enzymes (Aos1/Uba2, SAE1/SAE2 and Slx5/Slx8) are separated by a slash

[d] See text for details

[e] The contribution of distinct SUMO proteases to processing, deconjugation, and chain editing has been previously reviewed (Palancade and Doye 2008 ; Hickey et al. 2012)

[f] Wss1 has SUMO editing activity but can also cleave ubiquitin from the end of a poly-SUMO chain (Mullen et al. 2010)

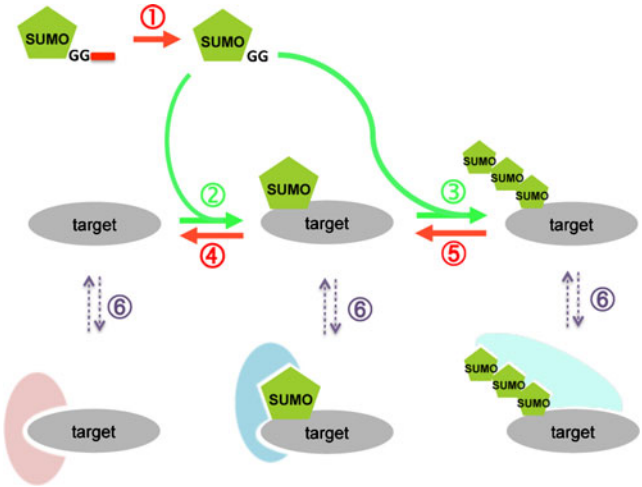

Fig. 2 The SUMO pathway. SUMO is translated as an immature precursor with a short C-terminal extension (*in red*) that must be cleaved by specific SUMO proteases to reveal the C-terminal GG motif (step 1). An enzymatic cascade allows the conjugation of the mature SUMO to a single lysine residue in the target protein (monosumoylation, step 2). Multiple SUMO additions can further occur on distinct lysine residues in the same target protein (multisumoylation, not depicted). SUMO-2/3 in mammals or Smt3 in *S. cerevisiae* can also be conjugated to one or several internal lysine residues within SUMO itself leading to the formation of SUMO chains (polysumoylation, step 3). All these processes are highly regulated by SUMO proteases that either deconjugate SUMO from the substrate (step 4) and/or depolymerize SUMO chains (step 5), according to their specificity for the SUMO isoforms. In most cases, sumoylation triggers changes in the intermolecular interactions involving the SUMO target (step 6). SUMO addition can prevent the recognition by specific partners (*in pink*), or allow the recruitment of SUMO or poly-SUMO binding factors (*in blue*). Among poly-SUMO binding proteins, STUbLs allow the transfer of ubiquitin entities on SUMO chains or on the substrate that in turn is targeted for proteasomal degradation

conjugated to an internal lysine residue within another SUMO polypeptide, leading to the formation of poly-SUMO chains, usually in response to cellular stress (Fig. 2). Most frequently, SUMO addition regulates intra- or inter-molecular interactions, by altering either the conformation of the targeted protein or the recruitment of its partners (reviewed in Gareau and Lima 2010). In several cases, these effects can be mediated by non-covalent interaction of SUMO with proteins harboring SUMO-interaction motifs (SIMs). These SUMO–SIM interactions have important consequences on protein dynamics, ranging from structural rearrangements, as reported for thymine DNA glycosylase, to multiprotein complex assembly as described for nuclear PML bodies (reviewed in Geiss-Friedlander and Melchior 2007). Finally, sumoylation can also interfere with protein stability by triggering ubiquitinylation of poly-SUMO-modified proteins through the recruitment of SUMO-targeted ubiquitin ligases (STUbL). This novel class of enzymes exhibit a RING domain involved in ubiquinitylation and several repetitive SIMs which bind poly-SUMO chains (reviewed in Geoffroy and Hay 2009).

The importance of sumoylation in protein biological function was further highlighted by reports showing that inactivation of SUMO in *Saccharomyces cerevisiae* or of the unique E2 SUMO-conjugating enzyme Ubc9 in mice is lethal (Johnson et al. 1997 ; Nacerddine et al. 2005). Consistently, multiple studies have shown that sumoylation regulates a wide range of cellular functions including intracellular transport, maintenance of genome integrity, formation of nuclear subdomains (reviewed in Geiss-Friedlander and Melchior 2007), but also some aspects of rRNA or snoRNA metabolism (Panse et al. 2006 ; Westman et al. 2010 ; Finkbeiner et al. 2011). Here, we will review the implication of sumoylated factors at each stage of nuclear mRNA biogenesis, from transcription to export of mature mRNPs. We will then highlight the multiple facets of the SUMO-dependent regulation of mRNA biogenesis, notably the molecular impacts of sumoylation on the biological activity of proteins. Finally, we will discuss some recent data suggesting that beyond being regulated by sumoylation, mRNP metabolism machineries may provide spatial regulations by recruiting specific sumoylating or desumoylating enzymes.

SUMO targets all stages of mRNA biogenesis

Multiple factors of the mRNA metabolism machinery are sumoylated

The role of SUMO at distinct steps of mRNA metabolism is first supported by the identification of several sumoylated targets in proteomic analyses. Indeed, multiple factors involved in transcription or mRNA-related processes were shown to be modified by SUMO in yeast (Zhou et al. 2004; Wohlschlegel et al. 2004; Panse et al. 2004; Hannich et al. 2005; Denison et al. 2005; Wykoff and O'Shea 2005), mammalian cells (Li et al. 2004; Zhao et al. 2004; Vertegaal et al. 2004; Gocke et al. 2005; Rosas-Acosta et al. 2005; Vertegaal et al. 2006; Ganesan et al. 2007; Schimmel et al. 2008; Golebiowski et al. 2009; Tatham et al. 2011), and plants (Budhiraja et al. 2009; Elrouby and Coupland 2010; Miller et al. 2010). A significant overrepresentation of factors involved in mRNA metabolism was notably observed among proteins modified by SUMO-2/3 (Blomster et al. 2009 ; Golebiowski et al. 2009; Bruderer et al. 2011). In addition, the specific targets identified for the E3 SUMO-ligase TOPORS or for the STUbL RNF4 encompass an important number of transcriptional regulators and proteins involved in mRNA processing (Pungaliya et al. 2007 ; Bruderer et al. 2011). Functional analysis of a subset of these sumoylated proteins, in particular transcriptional regulators, has confirmed the key function of SUMO-dependent regulations in mRNA biogenesis processes, as described below.

Different effects of SUMO on mRNA transcription

Among the different stages of mRNA biogenesis, transcription activation is the process whose regulation by sumoylation is best documented. Several studies in mammalian cells have notably reported that sumoylation of a wide range of transcription factors, including p300, Elk1, Sp3, or c-Jun, either counteracts transcriptional activation or mediates transcriptional repression (Table 2, reviewed in Seeler and Dejean 2003 ; Girdwood et al. 2004 ; Gill 2005 ; Garcia-Dominguez and Reyes 2009). Interestingly, sumoylation often occurs within previously characterized repression domains, providing further mechanistic insights into their repression mechanism (Girdwood et al. 2004). For instance, the transcriptional activity of p300, a co-activator for several DNA-binding transcription factors such as p53, NF-κB, or myoD, was found to be inhibited by sumoylation within its cell cycle-regulatory domain (Girdwood et al. 2003). When sumoylated, this region, previously reported to be critical for repression, allows the recruitment of the histone deacetylase HDAC6 that in turn generates a transcriptionally repressive chromatin environment (Girdwood et al. 2003). In agreement with a negative impact of sumoylation in transcriptional activation, artificial tethering of SUMO (Holmstrom et al. 2003) or of the SUMO-conjugating enzyme Ubc9 (Shiio and Eisenman 2003) to the promoters of reporter genes is sufficient to repress their transcription.

A repressive effect of SUMO on transcription is however not systematic. An early demonstration of a role of SUMO in mRNA biogenesis indeed came from studies revealing that sumoylation of the transcription factor p53 stimulates its ability to activate target genes (Rodriguez et al. 1999; Gostissa et al. 1999), an effect that varies depending on the promoter (Table 2). Since then, several studies have reported that SUMO modification of transcription factors can be required for their transcriptional activity, or can counteract their repressing properties (Table 2, reviewed in Lyst and Stancheva 2007). Moreover, sumoylation can have both activating and repressing effects on the same target depending on the conjugated SUMO isoform: sumoylation of the transcriptional repressor MBD1 by SUMO-1 counteracts its repressing activity whereas its sumoylation by SUMO-2/3 contributes to repression (Uchimura et al. 2006; Lyst et al. 2006).

Interestingly, this dual function of SUMO in mediating transcriptional activation or repression is conserved in budding yeast. Inactivation of the E2 SUMO-conjugating enzyme Ubc9 indeed results in increased transcription from regulated promoters and delayed transcriptional shut-off of the *ARG1* repressible gene but also leads to a reduction of RNAP II levels on constitutive genes (Rosonina et al. 2010). Consistently, several transcription factors have also been confirmed to be sumoylated in yeast (Table 3).

Besides transcription initiation, SUMO probably also controls later stages of transcription, as suggested by the report of sumoylation of the largest subunit of RNAP II upon impairment of transcription elongation (Chen et al. 2009). Further investigations will be required to address the functional implication of this observation and the relationships between sumoylation and other post-translational modifications targeting RNAP II and the transcription apparatus.

Other steps in mRNA metabolism are regulated by sumoylation

SUMO-mediated regulation is also well established for other steps of nuclear mRNA biogenesis, although much fewer targets have so far been identified in these processes (Tables 2 and 3). The importance of sumoylation has notably been established for the processing of the 3′ end of mRNAs in mammalian cells. mRNA cleavage and polyadenylation activities are both reduced in cell extracts obtained either upon in vivo depletion of Ubc9, or following in vitro treatment with the purified SUMO-protease SENP2 (Vethantham et al. 2007). This regulatory effect could be mediated by CPSF73 and symplekin, two components of the 3′ processing complex that have been shown to be modified by SUMO-2/3 and to interact with the SUMO protease SENP2 (Vethantham et al. 2007). In addition, sumoylation of the poly-A polymerase PAP by SUMO-2/3 regulates the in vitro enzymatic activity, stability, and subcellular localization of the polymerase (Vethantham et al. 2008). This impact of SUMO on 3′ processing may be conserved in budding yeast as suggested by the identification of the E1 SUMO-activating enzyme Uba2 as a partner of poly-A-polymerase Pap1 (del Olmo et al. 1997) and by the sumoylation of several subunits of the cleavage–polyadenylation factor uncovered by proteomic screens (Wohlschlegel et al. 2004; Panse et al. 2004; Hannich et al. 2005).

Several factors of the 5′ capping and splicing machineries have also been identified in SUMO-proteomes. However, the outcome of SUMO on their function awaits further characterization (reviewed in Vethantham and Manley 2009). Likewise, proteins involved in mRNP assembly or export, such as hnRNPs, were found to be sumoylated in yeast or human cells (Tables 2 and 3, reviewed in Vethantham and Manley 2009). However, the global impact of SUMO on mRNA export appears to vary among species. In plants, mRNA export out of the nucleus requires a proper balance in SUMO homeostasis since mutants of the SUMO-ligase SIZ1 or the SUMO-protease ESD4 exhibit nuclear poly-A+mRNA retention (reviewed in Meier 2012). On the contrary, in budding yeast, sumoylation does not appear to be critical for mRNA export since *ubc9* or *ulp1* mutants exhibit neither nuclear poly-A+mRNA retention nor major

Table 2 Mammalian sumoylated proteins involved in mRNA biogenesis

Transcriptional activation / repression				
AhR	(1)	●		*Xing 2012*
AhRR	(1)	●		*Oshima 2009*
AIB1	(1)	●		*Wu 2006*
AP-2γ	(1)	●		*Eloranta 2002*
APA1	(1)			*Benanti 2002*
AR	(1),(2)	●		*Rytinki 2012*
ARNT/HIF1 β	(1)	●		*Tojo 2002; Oshima 2009*
ATF1	(1)			*Iwasaki 2007*
ATF3	(2)	●		*Wang 2012*
ATF7	(1)			*Hamard 2007*
Bach2	(1)			*Tashiro 2004*
BASP1	(2)	●		*Green 2009*
Bcl11b/Ctip2	(1),(2)	●		*Zhang 2012*
BEND3	(1),(2)	●		*Sathyan 2011*
BKLF	(1)	●		*Perdomo 2005*
Blimp-1	(1)	●		*Shimshon 2011; Ying 2012*
BMAL-1	(1),(2)			*Cardone 2005; Lee 2008*
BRCA1	(1)	●		*Park 2008*
Bright/ARID3A/DRIL1	(1)			*Prieur 2009*
Brightlike/ARID3	(1)			*Tidwell 2011*
c-Fos	(1),(2)	●		*Bossis 2005*
c-Jun	(1),(2)	●		*Muller 2000*
c-Maf	(1)	●		*Leavenworth 2009; Lin 2010*
c-Myb	(1)	●		*Bies 2002*
C/EBPα	(1),(2)	●		*Kim 2002; Sato 2006*
C/EBPβ	(1),(2)	●		*Kim 2002; Eaton 2003; Wang 2008*
C/EBPδ/NF-IL6β	(1)	●		*Kim 2002 ; Wang 2006*
C/EBPε	(1)			*Kim 2002*
CBP	(1)	●		*Kuo 2005*
CoCoA	(1)	● ● a		*Yang 2008*
CoREST	(1)	●		*Muraoka 2008*
CRTR-1	(1)	●		*To 2010*
CtBP1	(1)	●		*Lin 2003*
CTCF	(1),(2)	●		*MacPherson 2009*
Daxx	(1)	●		*Muromoto 2006*
DDX21/RHII/Gu	(2)			*Blomster 2009*
DEC1	(1),(2)	●		*Hong 2011*
DJ1	(1)	●		*Fan 2008*
DLX3	(1)	●		*Duverger 2011*
Dnmt3a	(1)	●		*Ling 2004*
Dnmt3b	(1)			*Kang 2001*
DREAM	(1)	●		*Palczewska 2011*
Duplin	(1)			*Yamashina 2006*
E12	(1)			*Torikoshi 2012*
E2F1	(1)	●		*Yang 2011*
E2F6	(1)			*Yang 2011*
EBP1/p42	(1)	●		*Oh 2010*
EGR1	(1)	●		*Yu 2009*
Elk1	(1)	●		*Yang 2004 ; Salinas 2004*
Elk3	(1)	●		*Wasylyk 2005*
Elk4	(1)	●		*Kaikkonen 2010*
ERK5	(2)	●		*Woo 2008*
ERRα	(2)	●		*Tremblay 2008*
ERRγ	(2)	●		*Tremblay 2008*
ETS1	(1)	●		*Macauley 2006 ; Nishida 2006*
ETV1/ER81	(1)	●		*Bojovic 2008*
ETV4/E1AF/PEA3	(1),(2)	●		*Nishida 2007 ; Bojovic 2008; Guo 2011*
ETV5/ERM	(1)	●		*Degerny 2005*
ETV6/Tel	(1),(2)	●		*Chakrabarti 2000; Wood 2003; Roukens 2008*
FLASH	(1)	●		*Alm-Kristiansen 2009*
FLI1	(1),(2)			*Van den Akker 2005*
FOG1	(1)	●		*Snow 2010*
FOXC1	(2)	●		*Danciu 2012*
FOXC2	(2)	●		*Danciu 2012*
FOXL2	(1)	● ● b		*Marongiu 2010; Georges 2011*
FXR		●		*Vavassori 2009*
GATA1	(1)	●		*Collavin 2004 ; Lee 2009*
GATA2	(1),(2)			*Chun 2003*
GATA4	(1)	●		*Wang 2004*
GCM1	(1)	●		*Chou 2007*
GLI1	(1)			*Cox 2010*
GLI2	(1)	●		*Cox 2010 ; Han 2012*
GLI3	(1)			*Cox 2010*
GR	(1),(2)	●		*Tian 2002; Le Drean 2002; Davies 2008*
GRIP1	(1)	●		*Kotaja 2002*
GSC	(1),(2)	●		*Izzi 2008*
HDAC1	(1)	●		*David 2002*
HDAC4	(1)	●		*Kirsh 2002*
HDGF	(1)			*Thakar 2008*
HIC1	(1)	●		*Stankovic-Valentin 2007*
HIF1 α	(1)	●		*Tojo 2002*
HIPK2	(1)			*Gresko 2005*
HIPK3	(1)			*Gresko 2005*
Histone H4	(1),(2)	●		*Shiio 2003*
HNF4 α	(1),(2)			*Zhou 2012*
hnRNP K	(1),(2)	●		*Pelisch 2012; Lee 2012*
HSF1	(1)			*Hietakangas 2003*
	(2)	●		*Brunet-Simioni 2009*
HSF2	(1)	●		*Hietakangas 2006*
HSF4b	(1)	●		*Hietakangas 2006*
IKAROS	(1)	●		*Gomez-del Arco 2005*
ING2	(1)	●		*Yhhier 2010*
IRF1	(1)	●		*Kim 2008*
IRF2	(1)	●		*Han 2008*
IRF3	(1),(2)	●		*Kubota 2008*
IRF7	(1),(2)	●		*Kubota 2008*
IRF8	(2)	●		*Chang 2012*
JunB	(1),(2)	●		*Garaude 2008*
KLF4	(1)			*Du 2010*
KLF5	(1)	●		*Oishi 2008; Du 2008*
KLF8	(1),(2)	●		*Wei 2006*
Kyo T2	(1)	●		*Wang 2007*
LEDGF/p75/p52	(1),(2)	●		*Bueno 2010*
Lef1	(2)			*Sachdev 2001*
Lipin 1 α	(1),(2)	●		*Liu 2009*
Lipin 1 β	(1),(2)			*Liu 2009*
LRH1	(1)	●		*Venteclef 2010*
LXR α	(2)	●		*Lee 2009*
LXR β	(1),(2)	●		*Ghisletti, 2007; Lee 2009*

SUMO isoform
(1) : *SUMO-1*
(2) : *SUMO-2/3*

Biological effect of SUMO
● *negative*
● *positive*

Molecular effect of SUMO
change in interactions with proteins
change in interactions with nucleic acids
change in subcellular localization
change in enzymatic activity
change in ubiquitinylation and/or stability
other consequences

defects in the overall composition of their mRNPs (Bretes et al., unpublished results; Panse et al. 2006). However, a few proteins playing key functions in mRNP assembly and export, notably the Yra1, Sub2, and Hpr1 subunits of the TREX (Transcription and Export) complex are sumoylated (Bretes et al., unpublished results; Wohlschlegel et al. 2004; Hannich et al. 2005). In addition, the growth defects of a *yra1* mutant are suppressed upon *ULP1* overexpression (Kashyap et al. 2005). Although not affecting bulk mRNA export in yeast, sumoylation could either control TREX-dependent export of a limited subset of mRNAs or regulate other reported functions of the TREX complex in mRNA elongation and genetic stability (Luna et al. 2008).

Besides constituents of the TREX complex, a few multifunctional proteins contributing to different stages of mRNA biogenesis have also been shown to be sumoylated (highlighted in bold in Table 2). This is the case of the transcriptional regulators SAFB (Garee et al. 2011) and

Table 2 (continued)

Maf A	(1),(2)	●		*Shao 2009*
Maf B	(1)	●		*Tillmanns 2007*
Maf G	(2)	●		*Motohashi 2006*
MAML1	(1)	●		*Lindberg 2010*
MBD1	(1)	●		*Lyst 2006*
	(2)	●		*Uchimura 2006*
MEF/Elf4	(1),(2)	●		*Suico 2006*
MEF2A	(1)	●		*Shalizi 2006*
MEF2C	(2)	●		*Grégoire 2005*
MEF2D	(2)	●		*Grégoire 2005*
MEL1S	(1)	●		*Nishikata 2011*
MITF	(1)	●		*Miller 2005*
MKL1	(1)	●		*Nakagawa 2005*
MR	(1)	●		*Tallec 2003*
Msx1	(1)			*Gupta 2006*
MTA1	(2)	●		*Cong 2011*
MTF-1	(1)	●		*Liu 2011*
MZF1	(1)			*Noll 2008*
N-CoR	(1)	●		*Tiefenbach 2006*
Nab	(1)	●		*Garcia-Gutierrez 2011*
NF-E2/p45	(1)	●		*Shyu 2005*
NF-κB/RelA	(2)	●		*Liu 2012*
NF-κB2/p100	(1)	●		*Vatsyayan 2008*
NFAT1	(1)	●		*Terui 2004*
NFATc1/C	(1)	●		*Nayak 2009*
Nkx2-5	(1)	●		*Wang 2008*
NRL	(1)	●		*Roger 2010*
Oct-4	(1)	●		*Wei 2007*
OZF/ZNF146	(1)			*Antoine 2005*
p300	(1)	●		*Girdwood 2003*
p53	(1),(2)	●●c		*Rodriguez 1999; Gostissa 1999; Schmidt 2002; Wu 2009; Stindt 2011*
p63α	(1)	●		*Huang 2004; Ghioni 2005*
p66α	(1)	●		*Gong 2006*
p66β	(1)	●		*Gong 2006*
p68/DDX5	(1),(2)	●●c		*Jacobs 2007; Mooney 2010*
p72/DDX17	(1),(2)	●		*Mooney 2010*
p73 α	(1)			*Minty 2000*
PARP1	(1),(2)	●●c		*Messner 2009; Martin 2009*
Pax6	(1)	●		*Yan 2010*
Pax8	(1)			*de Cristofaro 2009*
PLAG1	(1)	●		*Van Dyck 2004; Zheng 2005*
PLAGL2	(1)	●		*Zheng 2005*
PLZF	(1)	●		*Kang 2008*
Pokemon1/ZBTB7	(1)	●		*Roh 2007*
Pontin	(1)	●		*Kim 2007*
PPAR α	(1),(2)	●		*Leuenberger 2009*
PPAR γ 1/2	(1)	●		*Ohshima 2004; Pascual 2005*
PPARGC1α/PGC-1α	(1)	●		*Rytinki 2009*
PR-Set7/Set 8	(1)	●		*Spektor 2011*
PROX1	(1)	●		*Shan 2008; Pan 2009*
PR	(1)	●		*Abdel-Hafiz 2002*
PSF	(1)	●		*Zhong 2008*
RBP1	(1),(2)	●		*Binda 2006*
RIP140/NRIP1	(1),(2)	●		*Rytink 2008*
Ror α	(1),(2)	●		*Hwang 2009*
RXR	(1)			*Burrage 2008*
RXR α	(1)	●		*Choi 2006*
SAFB1	(1),(2)	●		*Garee 2011*
Sall 1	(1)			*Netzer 2002*
Sall 4 B	(1),(2)	●●c		*Yang 2012*
Sam68	(1),(2)	●		*Babic 2006; Pelich 2010*
SAP130	(1)			*Gocke 2005*
SATB1	(1),(2)			*Tan 2008*
SATB2	(1),(2)	●		*Dogreva 2003*
SF-1	(1),(2)	●		*Komatsu 2004; Chen 2004*
Sip1	(1)	●		*Long 2005*
SIZN1	(1)			*Cho 2009*
Smad4	(1)	●●c		*Lin 2003; Lee 2003; Chang 2005*
SnoN	(1)	●		*Hsu 2006*
Sox10	(1)	●		*Taylor 2005; Lee 2012*
Sox2	(1)	●		*Tsuruzoe 2006*
Sox3	(1),(2)	●		*Savare 2005*
Sox6	(1),(2)	●		*Fernandez-Lloris 2006*
Sox8	(1)			*Lee 2012*
Sox9	(1)	●		*Taylor 2005; Lee 2012*
Sp1	(1)	●		*Spengler 2006*
Sp3	(1),(2)	●		*Sapetsching 2002; Ross 2002*
SRC-1	(1)			*Chauchereau 2003; Abdel-Hafiz 2009*
SREBPs	(1)	●		*Hirano 2003*
SRF	(1)	●		*Matsuzaki 2003*
STAT 1	(1),(2)	●		*Rogers 2003; Ungureanu 2003*
Stra 13	(1)	●		*Wang 2012*
SUPT7L/STAF65γ	(1)			*Gocke 2005*
SUZ12	(1)			*Rising 2008*
TBL1	(1)			*Choi 2011*
TBLR1	(1)	●		*Choi 2011*
TBX22	(1)	●		*Andreou 2007*
TCF4	(1)	●		*Yamamoto 2003*
TFE3	(1)			*Miller 2005*
TFEB	(1)			*Miller 2005*
TFII-I	(1)			*Zhao 2004 ; Gocke 2005*
TIF1α	(1)			*Seeler 2001*
TIF1β/KAP1/TRIM28	(1),(2)	●		*Mascle 2007 ; Lee 2007*
TR2	(1)	●		*Park 2007*
TRPS1		●		*Kaiser 2007*
Uhrf1	(2)			*Gocke 2005*
WT1	(1)			*Smolen 2004*
XBP1	(1),(2)	●		*Chen 2010*
YY1	(1),(2)			*Deng 2007*
ZBP-89/ZFP148	(1),(2)	●		*Chupreta 2007*
ZBTB1	(2)	●		*Matic 2010*
ZFP282	(1)	●		*Yu 2012*
ZNF131	(1)	●		*Oh 2012*
ZNF198	(1)			*Kunapuli 2006*
ZNF24	(1)			*Gocke 2005*
ZNF451	(1)	●		*Karvonen 2008*
ZNF76	(1)	●		*Zheng 2004*
ZXDC	(1),(2)	●		*Jambunathan 2007*
mRNA synthesis (initiation, elongation)				
TAF5 (TFIID)	(1)			*Boyer-Guittaut 2005*
TAF12 (TFIID)	(1)			*Boyer-Guittaut 2005*
TCERG1	(1),(2)	●		*Sanchez-Alvarez 2010*
Splicing				
SART1	(2)			*Vertegaal 2004*
S164/RBM25	(1)			*Gocke 2005*
3' processing				
Symplekin	(1),(2)			*Gocke 2005 ; Vethantham 2007*
CPSF73	(2)			*Vethantham 2007*
PAP	(2)	● d		*Vethantham 2008*
mRNP assembly / export				
hnRNP C1	(1)			*Vassileva 2004*
hnRNP M	(1),(2)			*Vassileva 2004 ; Vertegaal 2004*
hnRNP A1	(1)			*Li 2004*
hnRNP F	(1)			*Li 2004*
Other				
ADAR	(1)	●		*Desterro 2005*

The names of the proteins involved in mRNA biogenesis and confirmed to be sumoylated in mammalian cells are displayed. Proteins are ranked depending on the stage of nuclear mRNA metabolism to which they contribute. Proteins reported to be involved at distinct steps of mRNA biogenesis appear in bold

The SUMO isoform demonstrated to modify each target protein is indicated : (1), SUMO-1; (2), SUMO-2/3. The final outcome of sumoylation on the biological activity of the protein is illustrated by green or red filled circles, indicating respectively a positive or a negative effect of SUMO on mRNA synthesis/processing. When available, molecular consequences of sumoylation on the protein are indicated: change in interactions with proteins (yellow square) or nucleic acids (DNA or RNA, purple square); change in subcellular localization (blue square); change in enzymatic activity (black square); change in ubiquitinylation and/or stability (orange square), or other consequences (gray square)

References appear as *First Author*, *Year of publication* and are not further listed in the References section due to space limitation

[a] Opposite effects of sumoylation were reported for the different activation domains of the protein

[b] Sumoylation enhances both activating and repressing properties of the protein

[c] Opposite effects of sumoylation were reported on distinct target genes of the protein

[d] Effect of sumoylation on the activity of the protein was analyzed in vitro only

Table 3 Yeast sumoylated proteins involved in mRNA biogenesis

Transcriptional activation / repression			
Abf1			*Hannich 2005*
Gcn4	●		*Rosonina 2012*
Gcn5	●		*Sterner 2006*
H2A	●		*Nathan D 2006*
H2B	●		*Nathan D 2006*
H4	●		*Nathan D 2006*
Isw1			*Hannich 2005*
Mot1		■	*Wang 2009*
Nut1			*Wykoff 2005*
Pdr1			*Panse 2004*
Pob3			*Wohlschlegel 2004*
Reb1			*Denison 2005*
Rsc2			*Wohlschlegel 2004; Denison 2005*
Rsc58			*Wohlschlegel 2004; Wykoff 2005*
Rsc8			*Panse 2004 ; Wykoff 2005*
Spt7			*Denison 2005*
Ssn6			*Panse 2004*
Stb3			*Hannich 2005*
Ste12			*Wang 2006*
Swc1			*Wohlschlegel 2004*
Tec1		■	*Wang 2009*
Tup1			*Panse 2004 ; Denison 2005 ; Wykoff 2005*
Vps72			*Wohlschlegel 2004*
mRNA synthesis (initiation / elongation)			
Rpb1 (RNAP II)			*Chen 2009*
Rpb4 (RNAP II)			*Wohlschlegel 2004*
Taf8 (TFIID)			*Wykoff 2005*
Tfa2 (TFIIE)			*Hannich 2005*
Splicing			
Prp45			*Wohlschlegel 2004*
3' processing			
Ysh1			*Wykoff 2005*
mRNP assembly/export			
Hpr1			*a*

The names of the proteins involved in mRNA biogenesis and confirmed to be sumoylated in *S. cerevisiae* are displayed. Proteins are ranked depending on the stage of nuclear mRNA metabolism to which they contribute

A red filled circle indicates a negative outcome of sumoylation on the biological activity of the protein. To date, positive effects of SUMO on the activity of proteins involved in mRNA metabolism have not been reported in yeast

Change in ubiquitinylation and/or stability of the target protein upon sumoylation is indicated by an orange square. Other effects have not been reported

References appear as *First Author*, *Year of publication* and are not further listed in the References section due to space limitation

[a] Bretes et al., unpublished results

hnRNP-K (Lee et al. 2012; Pelisch et al. 2012) in mammals, for which functions in transcription and splicing have been reported. SUMO was demonstrated to regulate their transcriptional activity (Garee et al. 2011; Lee et al. 2012; Pelisch et al. 2012); it will now be interesting to examine the effect of sumoylation on their splicing function and its potential impact on the coupling between different aspects of mRNA biogenesis.

Molecular impact of sumoylation on mRNA biogenesis factors

The consequences of sumoylation on mRNA biogenesis are frequently inferred from in vivo and in vitro analysis of the biological activity of non-sumoylatable or constitutively sumoylated versions of target proteins. These studies have illustrated the various mechanistic impacts of sumoylation on the function of these targets (Fig. 3).

Sumoylation and nucleic acid binding

At virtually every stage, mRNA metabolism requires nucleic acid–protein interactions: transcription factors selectively recognize target DNA sequences, while processing and export factors associate with mRNAs. Several reports have indicated that sumoylation can interfere with the nucleic acid-binding properties of proteins (Fig. 3a, b). For instance, sumoylation of the mammalian transcription activator Hsf2 prevents its interaction with the heat-shock responsive element in the promoter of its target genes, presumably due to steric interference (Tateishi et al. 2009; Anckar et al. 2006). Sumoylation of RNA-binding proteins such as mammalian hnRNP C or hnRNP M also decreases their affinity for ssDNA in vitro, suggesting that it could regulate their association with mRNAs in vivo (Vassileva and Matunis 2004). This functional impact of sumoylation is intuitively expected since the lysine residues targeted by SUMO can be part of basic DNA- or RNA-recognition domains. However, in some cases, sumoylation can favor protein–DNA interaction, as established for the transcriptional activator Oct-4 (Wei et al. 2007). In this case, DNA-binding could be facilitated by SUMO presumably through a conformational change in the target protein.

Sumoylation and protein–protein interactions

During mRNA biogenesis, numerous macromolecular complexes are assembled in a stepwise fashion to allow mRNA synthesis and processing. In this respect, the well-documented impact of sumoylation on protein–protein interactions (Geiss-Friedlander and Melchior 2007) is expected to impinge on the activity of protein complexes involved in mRNA metabolism. Sumoylation can indeed disrupt protein–protein interactions critical for mRNA synthesis (Fig. 3c, d). For instance, SUMO-1 modification of the DNA-bound transcriptional repressor MBD1 prevents the interaction of the repressor with the histone methyltransferase SETDB1 without altering its interaction with DNA, leading to derepressed transcription of its target gene *p53BP2* (Lyst et al. 2006).

However, addition of the SUMO moiety on target proteins can create in many cases new interaction surfaces that favor the non-covalent recruitment of specific SIM-containing

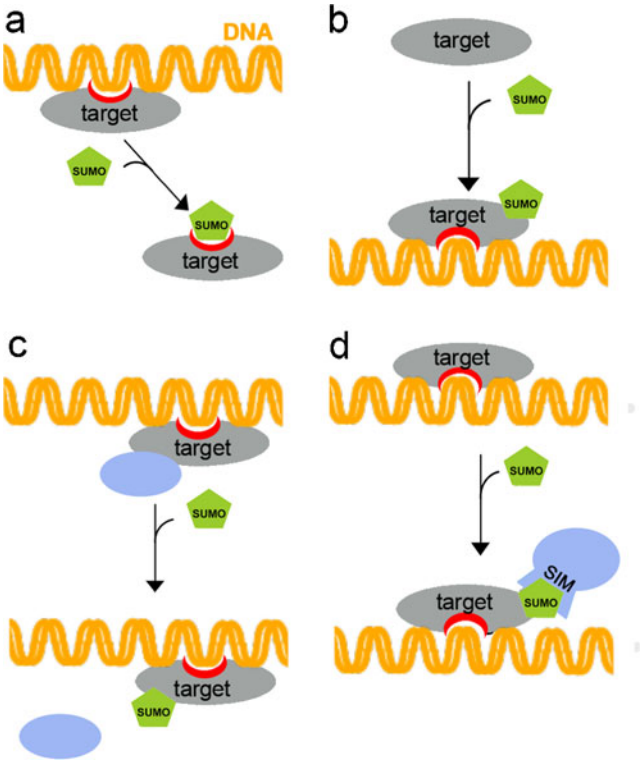

Fig. 3 Multiple effects of sumoylation on intermolecular protein interactions in mRNA biogenesis. The scheme depicts changes in intermolecular interactions occurring in proteins associated (either directly or indirectly) with DNA but the same principles could apply for RNA-associated proteins. Nucleic acid recognition domains appear in *red*. **a**, **b** Modulation of direct protein-nucleic acid association. Sumoylation can either inhibit (**a**) or enhance (**b**) direct DNA recognition by the sumoylated target, as described for Hsf2 and Oct-4, respectively (Anckar et al. 2006; Wei et al. 2007). **c**, **d** Modulation of protein–protein interactions. Sumoylation can disrupt protein–protein interactions without changing their association with nucleic acids (**c**), as reported for MBD1 (Lyst et al. 2006). Alternatively, sumoylation can favor the recruitment of SIM domain-harboring partners (**d**), as described for multiple transcriptional repressors (Garcia-Dominguez and Reyes 2009)

protein partners (Fig. 3b). As described for several transcription regulators, sumoylation enhances binding to histone deacetylases or co-repressor complexes that possess SIM domains (reviewed in Garcia-Dominguez and Reyes 2009). This function of SUMO in the regulation of protein–protein interactions required for mRNP metabolism may even be more widespread, as suggested by the recent in silico identification of SIMs in multiple cellular proteins, including putative RNA processing factors (Sun and Hunter 2012). Interestingly, sumoylation has been shown to target SART1, a factor required for tethering the U4-5-6 snRNP to the spliceosome (Vertegaal et al. 2006; Schimmel et al. 2010). Whether SART1 sumoylation controls spliceosome assembly in a SIM-dependent manner will require further investigations, in particular through the systematic search of SIMs within these protein complexes.

Sumoylation and subcellular localization

SUMO-mediated changes in protein–protein interactions can also affect their subcellular localization, for example by interfering with recognition by a transport receptor or retention in defined subnuclear domains. Sumoylation has indeed been shown to control the subcellular partitioning of a subset of factors contributing to mRNA biogenesis (Table 2), such as the poly-A-polymerase PAP (Vethantham et al. 2008) or the transcriptional repressor Daxx (Muromoto et al. 2006). PAP sumoylation is required for its nuclear targeting (Vethantham et al. 2008) while Daxx sumoylation favors its recruitment to PML nuclear bodies, possibly enhancing its transcriptional repressive activity (Muromoto et al. 2006). These nuclear subdomains may similarly modulate the activity of several other transcription factors (Bernardi and Pandolfi 2007).

Sumoylation and enzymatic activity

In some cases, sumoylation could also induce a conformational change in the target protein impacting on its enzymatic activity. This has been proposed to account for the SUMO-dependent inhibition of the activity of PAP (Vethantham et al. 2008) and of the RNA-editing enzyme ADAR-1 (Desterro et al. 2005). In the latter case, the SUMO-1 acceptor site was mapped in the dimerization domain of ADAR-1, leading to the hypothesis that sumoylation could impair dimer formation that regulates its enzymatic activity (Desterro et al. 2005).

Interplay between sumoylation and other post-translational modifications

Sumoylation was first described to compete with alternative post-translational modifications targeting lysine residues such as ubiquitinylation and acetylation (reviewed in Gareau and Lima 2010). For instance, acetylation of the p300 transcriptional co-activator at SUMO acceptor sites prevents SUMO-dependent repression (Bouras et al. 2005).

In addition, recent studies have revealed a new role for SUMO-dependent ubiquitinylation in the regulation of transcription factors. STUbLs were shown to control the ubiquitin-mediated proteolysis of a few proteins involved in mRNA metabolism such as the TBP (TATA-binding protein) regulator Mot1 in budding yeast (Wang and Prelich 2009). Consistently, proteomic analysis of sumoylated proteins accumulating upon proteasome inhibition in mammalian cells has revealed enrichment in mRNA metabolism-related factors (Tatham et al. 2011). Surprisingly, STUbLs could also target specific substrates for proteasomal degradation independent of their sumoylation, as demonstrated for the transcription factor MATα2 in budding yeast (Xie et al. 2010). However, protein degradation does not represent the only mechanism by which STUbLs affect mRNA biogenesis. Indeed, studies in flies have

shown that STUbLs can regulate protein–protein interactions without targeting their substrate for degradation (Abed et al. 2011). Ubiquitinylation of the transcription repressor Hairy by the STUbL Dgrn does not impact on the stability of Hairy, but rather reduces its affinity for its co-repressor Groucho, thus regulating co-repressor choice and gene-expression selectivity during development (Abed et al. 2011).

Notably, SUMO–SIM interactions can also be regulated by post-translational modifications targeting either SUMO itself or the SIM domain. On one hand, acetylation of SUMO prevents its binding to specific SIM domains and attenuates SUMO-dependent transcriptional repression (Ullmann et al. 2012). On the other hand, CK2-mediated phosphorylation of serine residues adjacent to the SIM domains in PIAS E3 SUMO ligases is required for SUMO recognition and contributes to PIAS transcriptional regulatory activity (Stehmeier and Muller 2009). These examples further illustrate how additional post-translational modifications cooperate with sumoylation to modulate protein–protein interactions and ensure a fine tuning of mRNA transcription.

Sumoylating and desumoylating enzymes in the mRNP metabolism machinery

While an ever-growing number of proteins involved in mRNA biogenesis appear to be regulated by SUMO, a series of recent findings suggests that, conversely, localization and activity of enzymes of the SUMO pathway are controlled by multiprotein complexes involved in mRNA metabolism (Fig. 1).

Transcription regulatory complexes contain SUMO-modifying enzymes

The first example of such an association was provided by PC2, a vertebrate-specific E3 SUMO ligase associated with polycomb repressive complexes (PRC1/2). PRC1/2 are chromatin-bound multiprotein assemblies involved in the repression of a large cohort of developmental genes and clustered into subnuclear structures termed PcG bodies (reviewed in Wotton and Merrill 2007). PC2 can modify a subset of transcriptional corepressors such as CtBP and SIP1, most likely within PcG bodies, and modulate their repressing activity on specific target genes (Lin et al. 2003; Long et al. 2005).

More recently, two reports identified enzymes of the sumoylation pathway as part of transcription regulatory complexes. Garcia-Gutierrez et al. (2011) demonstrated that Krox-20, a key transcription regulator of brain development, exhibits E3 SUMO ligase activity both in vitro and in vivo. Krox-20 functions as an E3 for sumoylation of its coregulator Nab2, which in turn mediates repression of Krox-20-responsive genes (Garcia-Gutierrez et al. 2011). In another report, the chromatin-bound transcription regulator Chtop was shown to associate with 5FMC (5 Friends of Methylated Chtop), a recently characterized nuclear multiprotein complex encompassing the SUMO-protease SENP3 in mammalian cells (Fanis et al. 2012). In the context of this complex, SENP3 desumoylates Zbp89, a Chtop-associated transcription factor, and contributes to the regulation of its target genes (Fanis et al. 2012). In these distinct cases, the association of the SUMO ligase or of the SUMO protease with defined partners, loci, or subnuclear domains probably favors their activity towards defined substrates.

A spliceosome component regulates sumoylating activities

A potential connection between splicing and the sumoylation machinery was initially suggested by the identification of the E3 SUMO ligase PIAS1 in a proteomic analysis of the spliceosome (Rappsilber et al. 2002). Moreover, nuclear bodies enriched in splicing factors were found to contain components of the SUMO pathway: Ubc9 is present in nuclear SC35-positive speckles in mouse ovocytes (Ihara et al. 2008) while the SUMO protease USPL1 is found in Cajal bodies (Schulz et al. 2012), a localization also shared by SUMO-1 in neurons (Navascues et al. 2008). More recently, the serine-/arginine-rich (SR) protein SRSF1 (SF2/ASF), a splicing factor with various functions in mRNA metabolism, was shown to regulate sumoylation in mammalian cells (Pelisch et al. 2010). SRSF1 directly interacts with Ubc9 and stimulates the transfer of SUMO-1 or SUMO-2/3 to specific substrates such as topoisomerase-1 or p53 in both in vitro and in vivo assays. In this respect, SRSF1 could be defined as a new type of E3 SUMO ligase. Interestingly, SRSF1 also interacts with PIAS1 regulating its E3 activity, leading to a synergistic effect on overall protein sumoylation (Pelisch et al. 2010). These data strongly suggest that SRSF1 could act as a coregulator of the SUMO pathway to modulate the specificity and efficiency of sumoylation of some splicesome components. Consistently, overexpression of SRSF1 in living cells stimulates sumoylation of the RNA-binding protein Sam68 that belongs to the hnRNP K family (Babic et al. 2006; Pelisch et al. 2010). Whether some of the splicing factors so far identified in SUMO-proteomes are similarly regulated by SRSF1 remains to be investigated.

Nuclear pore complexes encompass several enzymes of the SUMO pathway

The last step of the nuclear life of mRNAs is their export through NPCs that includes mRNP docking at the nuclear face of NPCs, translocation through the NPC channel, and

remodeling on the cytosolic side (Oeffinger and Zenklusen 2012). Interestingly, several enzymes of the SUMO pathway have been shown to associate with NPCs. The E2 SUMO-conjugating enzyme Ubc9 and the E3 SUMO ligase RanBP2/Nup358 are associated with the cytosolic filaments of NPCs in vertebrates, while the SUMO protease Ulp1/SENP2 is found at NPCs in all eukaryotes (reviewed in Palancade and Doye 2008). More recently, the STUbL Slx5/8 was reported to associate with NPCs in budding yeast (Nagai et al. 2008).

In mammals, RanBP2 acts as a SUMO E3 ligase for hnRNP C and M (Vassileva and Matunis 2004). Since SUMO modification hinders the association of these two mRNA-binding proteins with nucleic acids, it is tempting to speculate that sumoylation at the cytoplasmic face of NPCs could contribute to the mRNP remodeling process (Vassileva and Matunis 2004). The SUMO protease Ulp1/SENP2 is anchored to NPCs through a network of proteins including components of the inner nuclear basket such as Mlp1 and Mlp2 in yeast (reviewed in Palancade and Doye 2008; Goeres et al. 2011). Of note, Mlp1 and Mlp2 are also involved in the docking of mRNPs to the nuclear side of NPCs prior to export (Green et al. 2003 ; Vinciguerra et al. 2005). In addition, Mlp1 was demonstrated to play a role in the transient association of activated genes to the nuclear pores (Dieppois et al. 2006; Tan-Wong et al. 2009). Nuclear pore complexes could therefore bring potential chromatin and/or mRNP-associated sumoylated proteins at the vicinity of the SUMO protease, thus contributing to its specificity. Systematic identification of such targets will be required to unravel the role of these NPC-associated enzymes of the SUMO pathway in mRNP metabolism.

Concluding remarks and future perspectives

Sumoylation has been demonstrated to regulate the different stages of mRNA biogenesis in yeast, mammalian cells, and plants. While a prominent role of SUMO was first reported in the control of transcription activation, all the other steps of nuclear mRNA metabolism were recently shown to be regulated by the sumoylation machinery. Spatio-temporal regulation and specificity may be provided during the course of mRNA biogenesis by the association of enzymes of the SUMO pathway with transcription, splicing, or nuclear pore complexes. To which extent such mechanisms can apply to other protein complexes involved in mRNA metabolism (Fig. 1) remains an open and exciting question.

A tight control of mRNA metabolism is crucial to allow the cell to respond to environmental, physiological, or developmental cues. Proteomic studies have revealed that heat-shock or oxidative stress remodels the cellular SUMO-proteome in mammalian and plant cells, with extensive SUMO conjugation or deconjugation events targeting mRNA biogenesis factors (Manza et al. 2004; Blomster et al. 2009; Golebiowski et al. 2009; Bruderer et al. 2011; Miller et al. 2012). Chemically induced DNA damage has been shown to trigger phosphorylation of the SUMO E3 ligase PC2, hence stimulating the sumoylation of hnRNP K and its role in the p53-dependent transcriptional response (Pelisch et al. 2012). Several signaling pathways have also been shown to modulate mRNA metabolism through SUMO-dependent processes: for example, type I-interferon induces sumoylation of Daxx, impacting on the expression of its target genes (Muromoto et al. 2006) and ligand binding to LXRs or PPARγ nuclear receptors triggers their sumoylation, potentiating their transrepression activities (Liu and Shuai 2009). Developmentally regulated sumoylation of a great number of transcription factors has also been demonstrated to play a role in defining cell- or organ-specific gene-expression programs (Lomeli and Vazquez 2011). Further studies will be required to understand how such stress or signaling events are transduced to the mRNA biogenesis machinery through SUMO-dependent regulations.

Despite our expanding knowledge of the crosstalks between SUMO and mRNA biogenesis, an ever-increasing number of sumoylated factors remain to be functionally validated. The presence of SUMO targets and enzymes of the SUMO pathway in the mRNA metabolism machineries is reminiscent of the case of DNA repair, for which regulation by SUMO has been extensively studied. Importantly, the effect of SUMO on the final accuracy of the repair process has been recently shown to rely on the simultaneous sumoylation of several proteins that belong to the same pathway (Psakhye and Jentsch 2012). Whether this novel concept will also apply to mRNA biogenesis regulations will require exhaustive functional analysis of both sumoylated and SIM-containing proteins in this process.

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