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The role of ribosomal proteins in the regulation of cell proliferation, tumorigenesis, and genomic integrity

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Ribosomal proteins (RPs), the essential components of the ribosome, are a family of RNA-binding proteins, which play prime roles in ribosome biogenesis and protein translation. Recent studies revealed that RPs have additional extra-ribosomal functions, independent of protein biosynthesis, in regulation of diverse cellular processes. Here, we review recent advances in our understanding of how RPs regulate apoptosis, cell cycle arrest, cell proliferation, neoplastic transformation, cell migration and invasion, and tumorigenesis through both MDM2/p53-dependent and p53-independent mechanisms. We also discuss the roles of RPs in the maintenance of genome integrity via modulating DNA damage response and repair. We further discuss mutations or deletions at the somatic or germline levels of some RPs in human cancers as well as in patients of Diamond-Blackfan anemia and 5q- syndrome with high susceptibility to cancer development. Moreover, we discuss the potential clinical application, based upon abnormal levels of RPs, in biomarker development for early diagnosis and/or prognosis of certain human cancers. Finally, we discuss the pressing issues in the field as future perspectives for better understanding the roles of RPs in human cancers to eventually benefit human health.

ribosomal protein, tumorigenesis, genomic integrity, ribosomal stress, p53, MDM2

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INTRODUCTION

Ribosomes, consisting of RNAs and proteins, are intracellular translational machinery responsible for protein biosynthesis. In eukaryotic cells, the ribosome, termed 80S ribosome, is composed of two subunits: a 40S small subunit, which has the decoding function, and a 60S large subunit, which catalyzes the formation of peptide bonds. Eukaryotic 80S ribosomes contain four ribosomal RNA (rRNA) species (5S, 5.8S, and 28S rRNAs in the large subunits and 18S rRNA in the small subunits) and 80 (79 in yeast) ribosomal proteins (RPs) (Wilson and Doudna Cate, 2012). RPs not only are components of ribosomes but also play fundamental roles in ribosome biogenesis in which RPs, functioning as RNA chaperones, stabilize rRNAs and promote their correct folding for the assembly of ribosomal subunits. Ribosome biogenesis is an essential process in the life cycle of a cell and is required for cellular activity and function (Fromont-Racine et al., 2003). Increasing evidence has demonstrated that the biological mechanisms that regulate cell proliferation also control ribosome biogenesis. Perturbation of any step in the process of ribosome biogenesis triggers nucleolar stress, as characterized by a loss of nucleolar integrity, and results in a halt to cell proliferation (Boulon et al., 2010). It is conceivable that either impairment or hyperactivation of ribosome biogenesis is associated with deregulation of cell growth, which could eventually

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result in either tumorigenesis or suppression of tumorigenesis (Barna et al., 2008).

Over last decades, accumulating studies indicate that RPs, independent to their prime roles in ribosomal assembly and protein translation, perform multiple extraribosomal functions, including regulation of apoptosis, cell cycle arrest, cell proliferation, cell migration and invasion, and DNA damage repair (Anderson et al., 2007; Da Costa et al., 2003; Du et al., 2005; He and Sun, 2007; Hegde et al., 2004; Jang et al., 2004; Kim et al., 1995, 2004; Lindstrom and Zhang, 2008; Shen et al., 2006; Volarevic et al., 2000; Yang et al., 2013b; Zhan et al., 2010). The extraribosomal functions are mainly mediated and regulated by the p53-MDM2 axis (for review, see (Zhou et al., 2012)). Specifically, several RPs were successively found to activate the p53-dependent cell cycle arrest and apoptosis by directly interacting with MDM2 and inhibiting its E3 ubiquitin ligase activity towards p53 (Miliani de Marval and Zhang, 2011; Wu et al., 1993). On the other hand, extraribosomal functions can also be regulated in a p53-independent manner through the binding of RPs to other critical partners, such as transcription factors c-Myc and SP1, and NPM (nucleophosmin) (Donati et al., 2012; Russo et al., 2013; Wanzel et al., 2008).

In addition to responding to nucleolar stress, some RPs also serve as sensors in response to DNA damage or directly participate in the process of DNA repair, thus playing some roles in the maintenance of genomic stability. The roles of RPs as tumor suppressors are underscored by detection of somatic or germline mutations in some RP genes in various human cancers (De Keersmaecker et al., 2013; Nieminen et al., 2014). Furthermore, patients with two human congenital disorders, Diamond-Blackfan anemia (DBA) and 5q- syndrome, both of which are characterized by deletions or mutations in multiple RP genes, are at higher risk of developing cancers. Taken together, these data strongly suggest a close association of dysfunction of RPs with human tumorigenesis (for recent comprehensive reviews, see (de las Heras-Rubio et al., 2014; Kim et al., 2014; Wang et al., 2015a; Zhou et al., 2012)). In this review, we will focus on the roles of RPs in regulation of cell growth, tumorigenesis and genome integrity, and discuss RPs as potential cancer biomarkers for early diagnosis and prognosis.

RIBOSOME BIOGENESIS

Ribosome biogenesis is a critical process to provide translational machinery in the life cycle of a cell in which RPs not only are structural components of the ribosome but also play essential roles in regulating the assembly of ribosome particles (Fromont-Racine et al., 2003; Wilson and Doudna Cate, 2012). Ribosome biogenesis begins in the nucleolus and requires four different species of rRNAs, 80 RPs and three RNA polymerases (Pol I, Pol II, and Pol III) along with a large number of accessory factors (Fromont-Racine et al., 2003; Sollner-Webb and Mougey, 1991; Uechi et al., 2001). There are three key steps during ribosomal synthesis: rDNA transcription into precursor rRNAs (pre-rRNAs); post-transcriptional processing to generate mature rRNAs from pre-rRNAs; and the assembly of rRNAs with RPs into subunits (Fatica and Tollervey, 2002; Fromont-Racine et al., 2003; Lafontaine and Tollervey, 2001).

In eukaryotes, ribosomes are preassembled in the nucleolus before being transferred to the cytoplasm. The process of ribosome synthesis includes the formation of preribosomal particles in the nucleolus and the assembly of two subunits in the cytoplasm. The rate of rRNA transcription is a limiting factor in the production of ribosomes, and the mature rRNAs are generated from pre-rRNAs undergoing post-transcriptional processing. During pre-rRNA transcription and processing, many RPs, such as S15, S19, S24, assemble onto the mature rRNA regions of pre-RNA and are involved at various stages of rRNA processing (Choesmel et al., 2008; Flygare et al., 2007; Idol et al., 2007; Rouquette et al., 2005). In addition, some RPs, such as L22, L24, and L29, are involved in the interaction between the small and large subunits and the stabilization of the ribosome by surrounding the polypeptide exit channel, whereas other RPs, such as S7, S9, S12, S13, L1, and L5, are responsible for direct contact with tRNAs (de las Heras-Rubio et al., 2014; Wilson and Doudna Cate, 2012). Thus, RPs play significant roles during the assembly of ribosome particles and the regulation of ribosome biogenesis. Perturbation of any step in the process of ribosome biogenesis by, for example, DNA damage, RP mutations, drug insults, nutrient deprivation, or oncogenic activation, would trigger nucleolar stress (Figure 1A), also known as ribosomal stress to cause RPs release from the nucleolus and trigger many biological changes, mainly through p53 activation but also through p53-independent events, which will be discussed in detail below (Boulon et al., 2010).

THE EXTRARIBOSOMAL FUNCTIONS OF RPS

In addition to their primary function in ribosome biogenesis, many RPs have extraribosomal functions (Warner and McIntosh, 2009; Zhou et al., 2015). As suggested by Warner and McIntosh (Warner and McIntosh, 2009), the following criteria must be met to define extraribosomal functions of RPs: (i) interaction with some nonribosomal components of the cell; (ii) the interaction has physiological effects on cellular functions; (iii) the effects occur away from ribosomes; (iv) the effects do not influence protein synthesis. This section will mainly focus on extraribosomal functions of RPs related to a few key cellular processes whose abnormal regulation would lead to tumorigenesis, including apoptosis, cell cycle arrest, cell proliferation, neoplastic transformation, and cell migration and invasion (de las Heras-Rubio et al., 2014; Takada and Kurisaki, 2015; Wang et al., 2015a) (Table 1).

Apoptosis

Apoptosis is one of the major defensive mechanisms against non-repairable damage from intrinsic and extrinsic stresses. Increasing data suggest that a few RPs are involved in regulation of apoptosis (Warner and McIntosh, 2009). Interestingly, some are positive regulators, whereas others are negative regulators in response to cellular stress. For example, S3 induced apoptosis in response to extracellular stress by activating JNKs (c-Jun N-terminal kinases) in a caspase-dependent manner (Jang et al., 2012a). S6, especially in its unphosphorylated form, exhibited pro-apoptotic activity by inducing DR4 expression in TRAIL-induced cell death

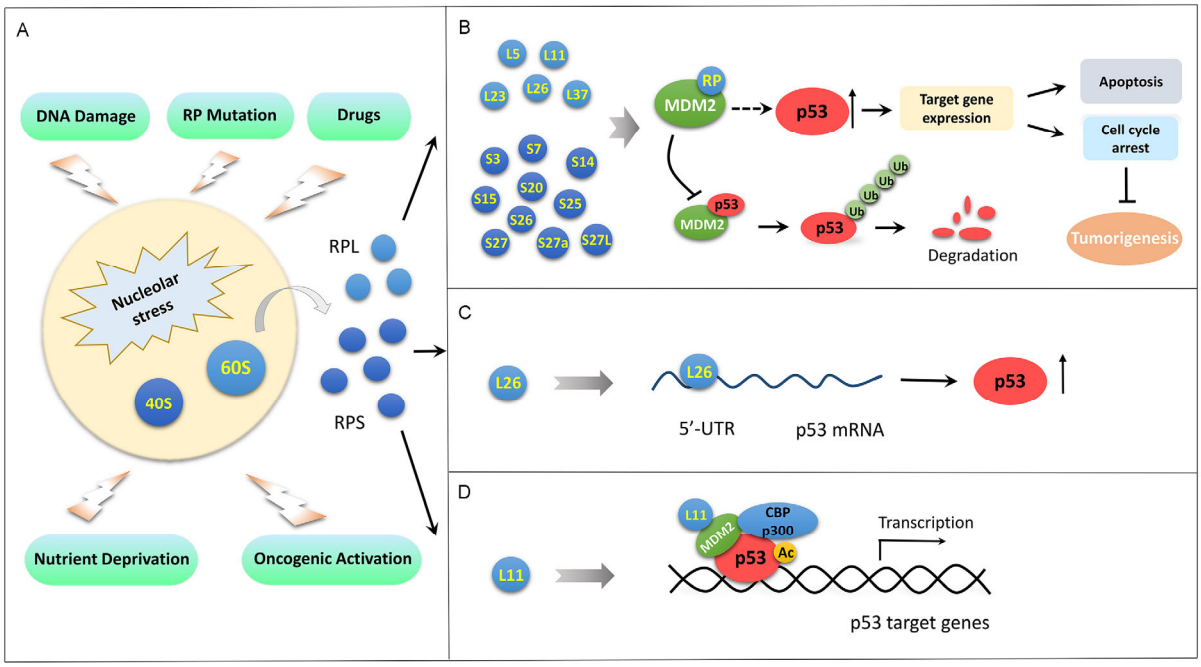

Figure 1 RPs regulate tumorigenesis in a p53 dependent manner. Upon nucleolar stress, including DNA damage, RP mutation, nutrient deprivation, drug insults, and oncogenic activation, ribosomal proteins (RPs), including those from the 60S large subunit (RPL) and those from the 40S small subunit (RPS), were released from nucleoli (A) to activate p53 by the following mechanisms: RPs bind to MDM2 and suppress its E3 ligase activity against p53, resulting in p53 accumulation (B); RPL26 binds to the 5′ untranslated region (5′-UTR) of p53 mRNA to enhance its translation (C); RPL11 recruits p53 transcriptional co-activators p300/CBP to facilitate p53 acetylation on K382, leading to p53 activation. Also L11 binding to MDM2 at the promoters of p53 target genes results in a relief from MDM2-mediated repression of p53 transactivation (D). Activated p53 then transactivates its downstream targets to induce growth arrest and apoptosis to block tumorigenesis.

Table 1 Extraribosomal functions of RPs in growth regulation and tumorigenesis

Extraribosomal functions	RPs	References
Apoptosis	S3, S3a, S6, S7, S14, S25, S27, S27L, S29, L3, L6, L7, L8, L23, L26	(Adilakshmi and Laine, 2002; Bai et al., 2014; Barlow et al., 2010a; He and Sun, 2007; Jang et al., 2012a; Jeon et al., 2008; Khanna et al., 2003; Li et al., 2010; Naora et al., 1998; Neumann and Krawinkel, 1997; Russo et al., 2013; Takagi et al., 2005; Wu et al., 2012; Yang et al., 2012; Zhu et al., 2009)
Cell cycle	S3, S5, S6, S7, S14, S15, S19, S20, S25, S26, S27, S27L, S27a, L3, L5, L6, L7, L11, L13, L23, L26, L31, L34, L37, L41	(Cui et al., 2014; Daftuar et al., 2013; Dai and Lu, 2004; Dai et al., 2004, 2007b; Gao et al., 2013; Gou et al., 2010; Iadevaia et al., 2010; Kobayashi et al., 2006; Maruyama et al., 2014; Matragkou et al., 2008; Moorthamer and Chaudhuri, 1999; Neumann and Krawinkel, 1997; Russo et al., 2013; Sun et al., 2011; Takagi et al., 2005; Wang et al., 2011a; Wanzel et al., 2008; Xiong et al., 2011; Yoon et al., 2011; Zhang et al., 2013, 2015; Zhou et al., 2013a)
Cell proliferation	S6, S9, S13, S14, S15a, S24, S27, L6, L8, L11, L15, L17, L26, L29, L31, L34, L36a	(Dai et al., 2007a; Gou et al., 2010, 2011; Kim et al., 2004; Li et al., 2010, 2012; Lindstrom and Zhang, 2008; Maruyama et al., 2014; Smolock et al., 2012; Volarevic et al., 2000; Wang et al., 2015b, 2006; Xiong et al., 2011; Yao et al., 2015; Zhou et al., 2013b)
Neoplastic transformation	P1, S3a, S14, L5, L22, L41	(Artero-Castro et al., 2009; Naora et al., 1998; Rao et al., 2012; Wang et al., 2010, 2014; Wool, 1996)
Cell migration and invasion	S3, p-S6, S7, S15a, S24, S27, L15	(McDonald et al., 2008; Nagao-Kitamoto et al., 2015; Wang et al., 2013, 2015b; Yan et al., 2015; Yang et al., 2013b; Yao et al., 2015)

(Jeon et al., 2008). S29 is another positive regulator that induced apoptosis by activating mitochondria-mediated caspase-dependent death pathways via decreasing expression of Bcl-2, Bcl-X_L, survivin, and NF-κB (Khanna et al., 2003). Both L3 and L7 were also reported to induce apoptosis (Neumann and Krawinkel, 1997; Russo et al., 2013). In contrast, some RPs, such as S27 and L23, exhibit anti-apoptotic activity (Wu et al., 2012; Yang et al., 2012). S27 (also known as metallopanstimulin-1, MPS-1) was highly expressed in many human cancers and its knock-down induced apoptosis through the inhibition of NF-κB activity by reducing phosphorylation of p65 at Ser536 and IκBα at Ser32 (Yang et al., 2012). L23 was also shown to be a negative regulator of apoptosis. In higher-risk myelodysplastic syndrome (MDS) patients, L23 was overexpressed at the mRNA levels and elevated L23 expression was inversely associated with apoptosis in $CD34^+$ marrow cells (Wu et al., 2012). L23 expression also promotes primary multidrug resistance (MDR) in gastric cancer cells by suppressing drug-induced apoptosis (Shi et al., 2004). Thus, RPs play either promoting or inhibiting roles in apoptosis which are dependent on the individual RPs and stress conditions. A better mechanistic understanding of RPs should provide new insights into how certain RPs could be selectively targeted for clinical applications.

Cell cycle arrest vs. cell proliferation

In addition to regulating apoptosis, RPs are extensively involved in the regulation of cell cycle progression via p53-dependent and independent mechanisms. Remarkably, many RPs, including S3, S7, S14, S15, S20, S25, S26, S27, S27a, S27L, L5, L6, L11, L23, L26, and L37, were reported to activate p53 and to induce p53-dependent cell cycle arrest as well as apoptosis upon ribosomal stress (Cui et al., 2014; Daftuar et al., 2013; Dai and Lu, 2004; Dai et al., 2007b, 2004; Gou et al., 2010; Jang et al., 2012b; Sun et al., 2011; Takagi et al., 2005; Xiong et al., 2011; Yoon et al., 2011; Zhang et al., 2013; Zhou et al., 2013a; Zhu et al., 2009). This is mainly achieved by the binding of RPs to MDM2, which inhibits MDM2-mediated p53 ubiquitylation and degradation, leading to p53 activation (Cui et al., 2014; Daftuar et al., 2013; Dai and Lu, 2004; Dai et al., 2007b, 2004; Sun et al., 2011; Takagi et al., 2005; Xiong et al., 2011; Zhang et al., 2013; Zhu et al., 2009) (Figure 1B). In addition, RPs, such as S6 (Zhang et al., 2015), S19 (Iadevaia et al., 2010; Morishita et al., 2008) and L7 (Neumann and Krawinkel, 1997), also induce cell cycle arrest in a p53-independent manner (Donati et al., 2012).

On the other hand, quite a few RPs, including S6, S15A, L15, L26, L29, L34, and L36A, were reported to promote cell proliferation (Kim et al., 2004; Li et al., 2012; Volarevic et al., 2000; Wang et al., 2006; Yang et al., 2016; Yao et al., 2015). For example, S15A is overexpressed in human glioblastoma tumor tissues and its knockdown in glioblastoma cells reduces the levels of phosphorylated Akt and triggers cell cycle arrest at G0/G1 phase, leading to inhibition of proliferation and migration (Yao et al., 2015). Similarly, silencing of L26 and L29 in human PANC-1 pancreatic cancer cells also suppresses cell proliferation (Li et al., 2012). In contrast, some RPs serve as negative regulators of cell proliferation. For instance, L17 siRNA when delivered using pluronic gels to C3H/F carotid arteries, caused an 8-fold increase in the number of proliferating cells (Smolock et al., 2012), whereas S14 was found to suppress cell proliferation induced by c-Myc (Zhou et al., 2013b). It is conceivable that the regulatory effects of RPs in cell proliferation are likely associated with tumorigenesis and tumor progression, suggesting some RPs may serve as potential biomarkers and therapeutic targets in the management of human cancers.

Neoplastic transformation

Numerous reports suggest that dysregulation or mutation of RPs predisposes cells to neoplastic transformation. For instance, Rpl22 inactivation by induction of stemness factor Lin28B, which was increased in late-stage aggressive cancers (Viswanathan et al., 2009), not only predisposes T-lineage progenitors to transformation, but also promotes transformation of both primary and immortalized MEFs (Rao et al., 2012). Consistently, Rpl22 haploinsufficiency accelerates the development of T-cell lymphoma in a mouse model (Rao et al., 2012). Rplp1, a member of the P group of ribosomal proteins, activates E2F-1 transcriptional activity and subsequent transcription of its downstream target cyclin E in MEFs (Artero-Castro et al., 2009). Moreover, the overexpression of Rplp1 alone bypasses replicative senescence in murine cells and cooperates with oncogenic Ras to transform NIH3T3 cells and immortalize MEFs. Additionally, S3A, S14, L5, and L41 were reported to regulate malignant transformation (Naora et al., 1998; Wang et al., 2010, 2014; Wool, 1996). All of these studies suggest that aberration of RP expression contributes to neoplastic transformation and cancer progression, although detailed mechanisms remain to be elucidated.

Cell migration and invasion

Increasing evidence from cell-based studies, *in vivo* mouse models and metastatic tumors from cancer patients indicates that some of RPs play indispensable roles in the regulation of cell migration and invasion. For instance, silencing of S27 inhibits the migration and invasion of gastric cancer cells *in vitro* and in an *in vivo* xenograft model (Yang et al., 2013b). Integrin β4 (ITGB4) appears to be responsible for S27-regulated cell migration and invasion. Overexpression of ITGB4 restored migration and invasion in S27 knockdown cells. More importantly, S27 expression is significantly correlated with the tumor-node-metastasis stage in human gastric carcinomas, and high expression of S27 and/or ITGB4 predicts poor survival of patients with gastric cancers. Consistent with these findings, elevated expression

of phosphorylated S6 is associated with metastatic tumors and with shorter metastasis-free survival in patients with lung adenocarcinomas (McDonald et al., 2008). Moreover, S3, S15A, and S24 were identified to positively regulate migration of osteosarcoma cells, glioma cells, and colorectal cancer cells *in vitro*, respectively (Nagao-Kitamoto et al., 2015; Wang et al., 2015b; Yao et al., 2015). Conversely, L15 and S7 were reported to negatively regulate cell invasion and migration *in vitro* and *in vivo* through repressing epithelial-mesenchymal transition (EMT) (Wang et al., 2013; Yan et al., 2015). Overexpression of L15 induced the expression of epithelial markers (E-cadherin and zonula occludens-1) and decreased the expression of mesenchymal markers (N-cadherin and fibronectin-1), thus significantly inhibiting the invasion of pancreatic cancer cells (Yan et al., 2015). Silencing of S7 promotes cell migration and invasion by up-regulating matrix metalloproteinase family proteins, MMP2, MMP9, and MMP13, but by down-regulating E-cadherin and β-catenin in ovarian cancer cell lines and in xenograft tumor tissues derived from ovarian cancer cells (Wang et al., 2013). Thus, RPs play a role not only in the initiation and progression stage, but also in the late metastasis stage of tumorigenesis.

MAJOR MECHANISMS THAT MEDIATE EXTRA-RIBOSOMAL FUNCTIONS OF RPS

The p53-dependent pathways

Inactivation of the p53 tumor suppressor is the most frequent genetic alteration found in human cancers. More than 50% of human cancers harbor mutations in *TP53*, and in most of the remaining cancers, the p53 pathway is also inactivated through multiple mechanisms, including overexpression of MDM2, the main E3 ubiquitin ligase responsible for p53 ubiquitylation and degradation (Toledo and Wahl, 2006). RPs activate p53 at several levels, including (i) blocking its degradation by inhibiting MDM2; (ii) promoting its translation, and (iii) facilitating transcription of its downstream target genes, leading to growth arrest and apoptosis to block tumorigenesis (Figure 1).

Under normal unstressed conditions, p53 protein is maintained at very low levels due to targeted ubiquitylation by MDM2 E3 ubiquitin ligase for subsequent degradation by 26S proteasome (Haupt et al., 1997; Wu et al., 1993). MDM2 also binds to p53 and inhibits its transcriptional activity (Eischen and Lozano, 2014; Kruse and Gu, 2009). On the other hand, MDM2 is a p53 downstream target gene and subjected to p53 transactivation, thus forming a negative feedback loop to keep p53 levels under control (Wu et al., 1993). Emerging evidence revealed that in response to ribosomal stress, a long list of RPs, including S3, S7, S14, S15, S20, S25, S26, S27, S27a, S27L, L5, L11, L23, L26, and L37, regulate the MDM2-p53 axis by directly binding with MDM2 and inhibiting its ligase activity towards p53, leading to p53 activation, followed by p53-dependent cell cycle arrest and apoptosis (Miliani de Marval and Zhang, 2011; Yadavilli et al., 2009; Zhang et al., 2013; Zhang and Lu, 2009) (Figure 1B). Based upon the mode of MDM2 interaction and p53 activation, RPs can be further categorized into a few groups: (i) "direct effectors", such as L5, and L11. This group of RPs directly binds to MDM2 and are required for p53 activation; knockdown of either one fails to induce p53 under ribosome stressed conditions (Dai and Lu, 2004; Zhang et al., 2003). (ii) "Indirect activators", including S6, S9, S19, S23, L7A, L24, L29, L30, and L37. This group of RPs do not bind to MDM2, nor inhibit MDM2 ligase activity, but rather enhance the interaction of MDM2 with L11 and L5 to activate p53, which is significantly attenuated by their knockdown simultaneously (Barkic et al., 2009; Daftuar et al., 2010; Fumagalli et al., 2009; Lindstrom and Nister, 2010; Llanos and Serrano, 2010; Sun et al., 2010; Zhou et al., 2013a). A special case is S14, which appears not only to bind with MDM2, but also to activate p53 via an L11- and L5-dependent pathway (Zhou et al., 2013a). (iii) "Direct substrates", such as S7, S27a, S27L, and L26. This group of RPs bind directly to MDM2, but are also direct substrates of MDM2 E3 ligase for targeted degradation, thus establishing yet another auto-regulatory feedback loop (Ofir-Rosenfeld et al., 2008; Sun et al., 2011; Xiong et al., 2011; Zhu et al., 2009). (iv) "Direct p53 targets", such as S27a and S27L, which are transcriptionally activated by p53, whereas S27 and S25 are transcriptionally suppressed by p53 (Sun et al., 2011; Xiong et al., 2011; Zhang et al., 2013). Thus, the RPs-MDM2-p53 axis is subjected to inter-regulation at both transcriptional and post-translational levels to accommodate complicated responses to ribosomal stress. A key question facing the entire RPs field is why so many RPs are needed to regulate the MDM2/p53 axis upon ribosomal stress? In addition, it is not clear whether some RPs are more critical than others or whether these cells-based observations can be extended to the *in vivo* situation? Our recent *in vivo* knockout study begins to address these questions. We found that total *Rps27l* KO causes postnatal death under Rps27-wild type background (Xiong et al., 2014), indicating these two family members are not functionally redundant during development. The facts that increased levels of Mdm2 are detected in *Rps27l*-null MEF cells and multiple organs and that death phenotype of *Rps27l* KO mice can be rescued by simultaneous deletion of one p53 allele (Xiong et al., 2014) indicate that Rps27l indeed regulates the Mdm2/p53 axis *in vivo*. The potential importance of other RPs in regulation of the MDM2/p53 axis needs to be vigorously tested under *in vivo* physiological conditions using mouse models.

The next obvious question is whether the RPs-MDM2-p53 axis indeed regulates *in vivo* tumorigenesis. Using a knockin mouse model to address this question, it was found that expression of the cancer-associated missense mutant $Mdm2^{C305F}$, which lost its binding capacity to L5

and L11 and thereby lacked a p53 response to perturbations in ribosome biogenesis, but retained normal p53 response to DNA damage, had significantly accelerated formation of lymphoma induced by Eμ-Myc overexpression (Macias et al., 2010). Our recent study also showed that mice with *Rps27l*$^{-/-}$; *p53*$^{+/-}$ background have an accelerated rate of lymphomagenesis (Xiong et al., 2014). Thus, the RPs-MDM2-p53 axis indeed plays a role in tumorigenesis, particularly lymphomagenesis.

In addition to inducing p53 accumulation and activation via inhibiting MDM2 E3 ligase activity, RPs also activate p53 by other manners. For example, p53 translation can be enhanced by L26, which binds to the 5′ untranslated region of p53 mRNA and leads to a rapid increase in p53 synthesis (Ofir-Rosenfeld et al., 2008) (Figure 1C). On the other hand, L26 itself is a substrate of MDM2 for targeted degradation, thus suppressing L26-mediated augmentation of p53 protein synthesis (Ofir-Rosenfeld et al., 2008). Under non-stressed conditions, MDM2 not only inhibits the stabilization and the transcriptional activity of p53 by itself, but also keeps low cellular p53 levels by constitutively reducing p53 translation by inhibiting L26.

Furthermore, L11 is required for p53 transcriptional activity upon nucleolar stress. Upon actinomycin D treatment, a rapid decrease in L11 NEDDylation allows rapid but transient recruitment of L11 at the promoter of p53 target genes. L11 is required for the recruitment of p53 transcriptional co-activators p300/CBP and p53 K382 acetylation, thus activating the transcriptional activity of p53 (Mahata et al., 2012) (Figure 1D). Therefore, RPs participate in the regulation of p53 activation by diverse mechanisms. Given the importance of the tumor suppressor p53 in tumorigenesis, further studies should be directed to elucidate how multiple RPs coordinate and cooperate with each other to regulate the synthesis, stability and activity of p53 in response to diverse stresses, which may provide a clear picture of RPs-mediated p53 regulation in tumor suppression.

The p53-independent pathways

In addition to regulating p53 activation at several levels in response to nucleolar stress, accumulating data support that RPs also regulate tumorigenesis by affecting cell proliferation related processes through p53-independent pathways (Figure 2).

The first example is through the regulation of c-Myc, an oncoprotein which is frequently overexpressed in various human cancers (Adhikary and Eilers, 2005). c-Myc is a general inducer of protein synthesis, which upregulates ribosome biogenesis via promoting RNA Pol I-and Pol III-mediated transcription of rRNAs and tRNAs, respectively, and activating RNA Pol II-mediated RP expression. Intriguingly, c-Myc itself is also subjected to RP regulation. It has been reported that L5, L11, and S14 interact with c-Myc and inhibit c-Myc-induced transcription, thus suppressing c-Myc- mediated cell proliferation. L11 regulates c-Myc function via a negative feedback mechanism (Dai et al., 2007b). Specifically, L11, a transcriptional target of c-Myc, competes with the transcriptional co-activator transformation/transcription domain-associated protein (TRRAP) for binding to Myc box II (MB II), one of two conserved segments in the N-terminal transcriptional activation domain of c-Myc, leading to inhibition of TRRAP recruitment to c-Myc target gene promoters. As a result, the transcription of c-Myc- mediated rRNAs and downstream genes (such as E2F-2, nucleolin, and eIF-4E genes) is decreased, leading to cell growth inhibition (Dai et al., 2007a, 2010). S14, on one hand, inhibits c-Myc transcriptional activity by preventing the recruitment of TRRAP to the promoter of c-Myc target genes, and on the other hand, induces c-Myc mRNA degradation, thus resulting in inhibition of c-Myc-induced cell proliferation (Zhou et al., 2013b). Furthermore, L11 controls c-Myc mRNA turnover by recruiting micro-RNA-induced silencing complex (miRISC) with miR-24 or miR-130a to c-Myc mRNA at its 3′ untranslated region (3′-UTR), leading to c-Myc mRNA degradation (Challagundla et al., 2011; Li et al., 2015). Finally, L5 was found to co-reside on c-Myc mRNA with L11 and miRISC, suggesting that L5 cooperates with L11 to regulate the stability of c-Myc mRNA (Liao et al., 2014) (Figure 2A).

The second example is through the regulation of E2F, a transcription factor that promotes S phase entry and progression (Dimova and Dyson, 2005). Ribosomal proteins, such as L11 or other free RPs that released upon inhibition of rRNA synthesis, were found to reduce E2F-1 levels through binding with MDM2 to release its binding with E2F-1. Unlike MDM2-p53 binding for targeted p53 degradation, MDM2-E2F-1 binding stabilizes E2F-1 by preventing its ubiquitylation (Donati et al., 2011; Zhang et al., 2005). Reduction in E2F-1 levels causes a decrease in the transcription of its target genes which are drivers for both entry into and progression through S phase, leading to the inhibition of cell proliferation (Dimova and Dyson, 2005). Furthermore, depletion of S19 causes a drastic destabilization of PIM1, a constitutively active serine/threonine kinase regulated by cytokines, growth factors and hormones (Iadevaia et al., 2010), resulting in p27 accumulation (Morishita et al., 2008) to inhibit CDK2 and subsequent E2F-1 inactivation (Figure 2B).

The third example is through the regulation of ATF4 (activating transcription factor 4), a transcription factor, which is commonly overexpressed in tumors and a major coordinator of tumor cell survival in stress (Ameri et al., 2004; Ye et al., 2010). It was reported that L41 induces the proteasomal degradation of ATF4 by promoting ATF4 phosphorylation and its translocation from the nuclei to the cytoplasm (Wang et al., 2011a) (Figure 2C).

The fourth example is through NF-κB, a transcriptional factor that protects cells from apoptosis (Wang et al., 1998).

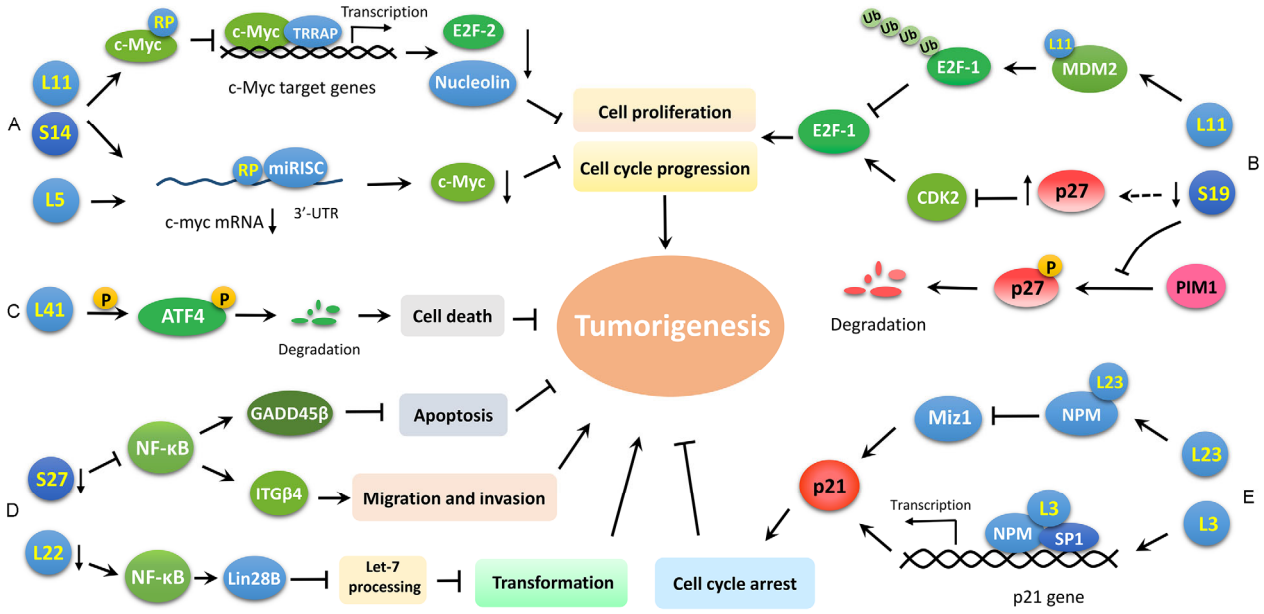

Figure 2 RPs regulate tumorigenesis in a p53-independent manner. A, Through c-Myc: RPS14 and RPL11 affect c-Myc transcription activity by interacting with the Myc box II domain to prevent the recruitment of c-Myc and its co-activator, TRRAP, to c-Myc target gene promoters, resulting in the suppression of c-Myc-induced transactivation and subsequent cell proliferation; RPS14, L5, and L11 are localized to the 3′-UTR of c-myc mRNA to facilitate the recruitment of miRNA-induced silencing complex (miRISC), leading to c-myc mRNA degradation and suppression of cell cycle progression. B, Through E2F-1: RPL11 binds to MDM2 to release its stabilization of E2F-1, leading to reduced E2F-1 levels; Depletion of RPS19 causes a drastic destabilization of PIM1 kinase, which is responsible for the phosphorylation and subsequent degradation of cell cycle inhibitor $p27^{Kip}$. The stabilized $p27^{Kip1}$ then inactivates CDK2 to block E2F-1, leading to the inhibition of cell cycle progression. C, Through ATF4: L41 induces the phosphorylation of ATF4 and promotes its translocation from the nucleus to the cytoplasm for proteasomal degradation to trigger cell death. D, Through NF-κB: RPS27 knockdown inhibits transactivation activity of NF-κB to reduce the levels of GADD45β and ITGβ4, thus regulating apoptosis, and migration and invasion; On the other hand, RPL22 deficiency induces NF-κB-mediated Lin28B expression to inhibit Let-7 processing, thus regulating transformation. E, Through NPM and SP1: L23 interacts with nucleophosmin (NPM) to suppress Miz1-dependent expression of p21, leading to cell cycle progression and cell growth; RPL3, when binding with SP1 and NPM, transactivates p21 transcription to induce cell cycle arrest. Tumorigenesis is controlled and regulated by a combination of these effects.

It was demonstrated that S27 knockdown suppresses NF-κB activity by blocking its nuclear translocation and inhibiting its DNA binding activity (Yang et al., 2012). The inhibition of NF-κB activity reduced the expression of its target gene GADD45β (growth arrest DNA damage inducible gene 45β), an anti-apoptosis factor (De Smaele et al., 2001; Zazzeroni et al., 2003), leading to spontaneous apoptosis and repressed proliferation of gastric cancer cells (Yang et al., 2012). Furthermore, S27 knockdown inhibits migration and invasion of gastric cancer cells *in vivo* partially via downregulation of NF-κB-mediated expression of integrin β4 (ITGB4) at both mRNA and protein levels (Yang et al., 2013b). On the other hand, L22 silencing was reported to activate NF-κB, leading to activation of Lin28B to inhibit Let-7 processing and accelerate transformation (Rao et al., 2012) (Figure 2D).

Other examples include the regulation of NPM and SP1. L23 forms a complex with NPM to block Miz1, leading to p21 inhibition to promote cell growth (Wanzel et al., 2008), whereas L3 forms a complex with NPM to activate SP1, leading to transactivatioin of p21 expression to induce growth arrest (Russo et al., 2013) (Figure 2E). It is anticipated that more RPs will be found to regulate cell proliferation and tumorigenesis via a mechanism independent of p53.

RPS IN MAINTENANCE OF GENOMIC STABILITY

The genome of a cell is constantly damaged due to internal metabolites such as reactive oxygen species as well as environmental insults, including ultraviolet light, ionizing radiation (IR), drug exposure, and oxidative stress. Therefore, organisms have evolved complex mechanisms to maintain genomic integrity in response to DNA damage insults (Ermolaeva and Schumacher, 2014; Marechal and Zou, 2013; Zhou and Elledge, 2000). More data show that RPs might play an important role in maintaining genomic stability through multiple mechanisms (Cui et al., 2014; Hegde et al., 2004; Kim et al., 2014).

Given the role of p53 as a guardian of the genome (Vogelstein et al., 2000), RPs could maintain the genomic integrity via inhibiting MDM2 to activate p53. Specifically, RPs serve as novel DNA damage sensors to directly increase p53 levels and transcriptional activity, or to indirectly activate p53 by MDM2 suppression (Figure 3A). Among all MDM2-binding RPs released from nucleolus upon DNA

damage, L11 appears to be the most important for p53 activation as it not only directly binds with MDM2, but also is required for the involvement of many RPs in regulating p53 activation through the MDM2-p53 axis (Daftuar et al., 2010; Sun et al., 2010). It has been reported that DNA damage-induced proteasomal degradation of L37 also leads to the L11-dependent stabilization of p53 by increasing the association of MDM2 with L11, whereas ectopic expression of L37 attenuates p53-mediated DNA damage responses (Llanos and Serrano, 2010). S7 and L26, two MDM2-binding RPs and MDM2 substrates, also emerge as novel regulators of the MDM2-p53 feedback loop in response to DNA damage. S7 induces p53 activation by binding to MDM2 and inhibiting its activity upon genotoxic stress (Zhu et al., 2009). However, L26 not only acts as the regulator of p53 activation via an L11- and MDM2-dependent mechanism, but also promotes p53 translation after DNA damage. Under unstressed conditions, MDM2 inhibits L26 interaction with p53 mRNA and targets it for degradation. Upon genotoxic stress, the inhibitory effects of MDM2 on L26 are attenuated, enabling L26 binding to the 5′UTR of p53 mRNA, leading to a rapid increase in p53 synthesis (Ofir-Rosenfeld et al., 2008; Takagi et al., 2005). Furthermore, S26 directly interacts with p53 (independent of MDM2) and p300 in response to DNA damage and promotes p300-induced p53 acetylation and subsequent p53 transactivation of its target genes (Cui et al., 2014) (Figure 3A).

We recently found using a knockout mouse model that S27L regulates genomic stability and lymphomagenesis in a p53 dependent manner (Xiong et al., 2014). In a *Trp53*$^{+/+}$ background, *S27l* deletion triggers ribosomal stress to stabilize Mdm2 for targeted Mdm4 degradation, leading to reduced Mdm2/Mdm4 E3 ligase activity, increased p53 levels, and consequently postnatal death due to p53-dependent apoptosis in hematopoietic stem cells. In a *Trp53*$^{+/-}$ background, *S27l* deletion causes genomic instability with selection pressure for deletion of the wt p53 allele, eventually leading to enhanced lymphomagenesis. In a *Trp53*$^{-/-}$ background, *S27l* deletion has no effects on lymphomagenesis nor mouse survival (Xiong et al., 2014) (Figure 3A).

Emerging evidence revealed that RPs may also function as regulators of the DNA damage response and DNA repair in a p53-independent manner (Figure 3B). For instance, L3 is involved in p21-dependent and p21-independent DNA repair (Esposito et al., 2014). The level of ribosome-free L3 increased after treatment with 5-FU, a DNA damaging agent. Increased L3 alters p21 expression and prevents DNA repair via homologous recombination and non-homologous end joining (Esposito et al., 2014). Moreover, the ectopic expression of L3 was found to increase DNA repair through mechanisms independent of p21 status, which need further investigation (Esposito et al., 2014) (Figure 3B, top).

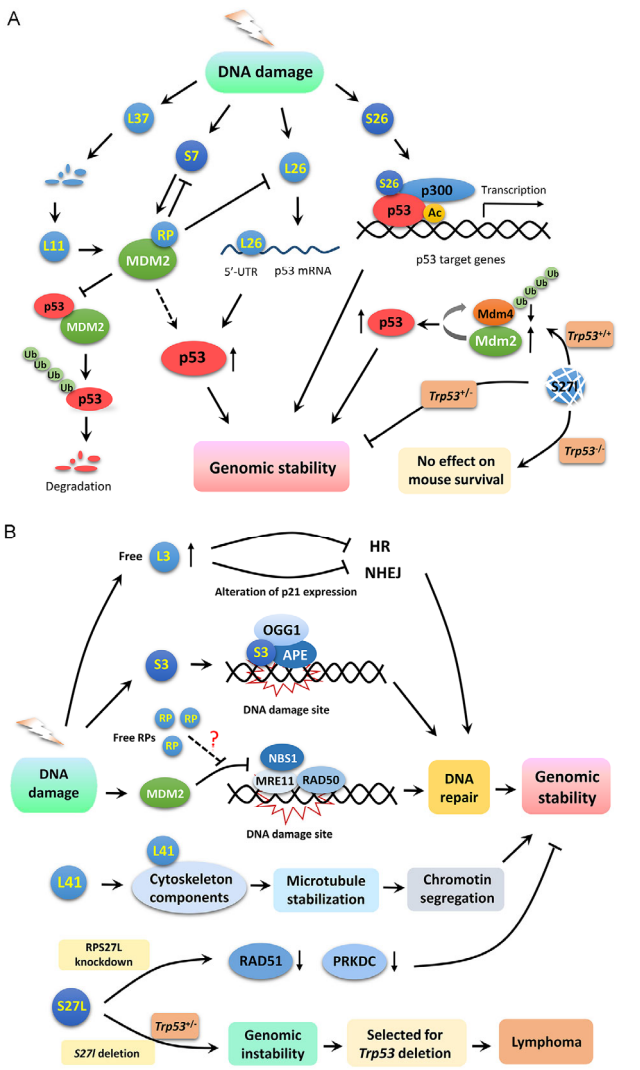

Figure 3 RPs regulate genomic integrity. A, p53-dependent: in response to DNA damage, several RPs were released from nucleoli to bind to and inhibit MDM2 ligase activity, leading to p53 accumulation; RPL26 also binds to 5′UTR of p53 to enhance p53 translation; whereas RPS26 recruits p300 to acetylate p53 to increase its activity. p53 acts as a guardian of genome to keep genomic instability. On the other hand, RPS27L regulates genomic stability only when p53 is at the heterozygous status in which *Rps27l* deletion triggers genomic stability via an unknown mechanism. B, p53 independent: Upon DNA damage, elevated free RPL3 inhibits both homologous recombination (HR) and non-homologous end joining (NHEJ) repair, directly or by alteration of p21 expression (top); RPS3 has a high binding affinity to 7,8-dihydro-8-oxoguanine (8-oxoG) and AP sites in DNA, and also positively interacts with the human BER enzymes N-glycosylase/AP lyase OGG1 (OGG1) and APE/Ref-1 (APE) to influence their repair activities at sites of DNA damage (2nd panel). MDM2 associates with the MRE11/RAD50/NBS1 DNA repair complex by specifically binding to NBS1. The NBS1-binding region on MDM2 overlaps with the binding site for at least eight RPs, suggesting that RPs may be involved in regulating DNA repair by competing with NBS1 for MDM2 binding (3rd panel). RPL41 is also a microtubule-associated protein, which binds to cytoskeleton components and alters microtubule stabilization and chromatin segregation (4th panel). RPS27L knockdown reduces transcription of RAD51 and PRKDC to inhibit DNA repair; *S27l* deletion also significantly increases the rate of aneuploidy in primary *Trp53*$^{+/-}$ MEFs to confer selection pressure for p53 gene deletion, leading to spontaneous lymphomagenesis (bottom).

Another ribosomal protein S3 was found to perform dual functions as a DNA repair endonuclease and a signaling mediator of apoptosis (Hegde et al., 2004; Jang et al., 2004). Specifically, S3 binds to the sites of DNA damage and physically interacts with proteins known to be involved in DNA repair. S3 was also shown to have high-affinity binding to the 7,8-dihydro-8-oxoguanine (8-oxoG) and apurinic/apyrimidinic (AP) sites in DNA (Hegde et al., 2004). Moreover, S3 positively affects the catalytic N-glycosylase activity of hOGG1 in removing 8-oxoG from a synthetic DNA oligonucleotide (Hegde et al., 2004). Thus, S3 may influence repair activities at DNA damage sites (Figure 3B, second panel).

Furthermore, it has been reported that MDM2 specifically binds to NBS1 to inhibit the activity of the MRE/RAD50/NBS1 DNA repair complex, leading to genomic instability (Alt et al., 2005; Bouska and Eischen, 2009; Wang et al., 2008). The NBS1-binding region on MDM2 (amino acid 198-228) overlaps with the binding site for at least eight RPs (L5, L23, L26, S14, S25, S26, and S27/27L) (Kim et al., 2014), which implies that these MDM2-binding RPs may facilitate the maintenance of genomic stability by attenuating the binding of MDM2 to NBS1 (Figure 3B, third panel).

In addition to acting as the "effector" in response to DNA damage or as a DNA repair enzyme, some of RPs appear to maintain chromosome stability and centrosome integrity during mitosis. L41, also a microtubule-associated protein, binds to several cytoskeleton components and increases their acetylation for microtubule stabilization (Wang et al., 2010). Cells with down-regulated L41 showed abnormal microtubule spindle, which is essential for chromosome segregation during mitosis, leading to premature centrosome splitting and likely contributing to malignant transformation (Wang et al., 2010). Indeed, down-regulation of L41 induces malignant transformation of NIH3T3 cells (Wang et al., 2010) (Figure 3B, forth panel).

Recent studies showed that S27L plays a role in maintenance of genomic stability. In cell-based assays, knockdown of S27L resulted in a deficiency in DNA damage checkpoints, leading to conversion of the DNA damage-induced p53 response from cell cycle arrest to apoptosis (Li et al., 2007). The decreased transcription of two DNA DSB (double-strand break) repair genes, RAD51 and PRKDC, was found to coincide with S27L knockdown upon DNA damage response, suggesting a role of S27L in DNA repair (Huang et al., 2013). Consistently, the analysis of S27L protein expression in the feces and colonic tissues of patients with colorectal cancer showed elevated S27L levels were associated with better patient survival (Huang et al., 2013). Finally, we found that the rate of aneuploidy in primary *Trp53*$^{+/-}$ MEFs is significantly increased upon disruption of Rps27l, which happens prior to the deletion of the remaining wt p53 allele, seen in lymphoma tissues, suggesting that Rps27l disruption triggers genomic instability and confers selection pressure for p53 gene deletion, leading to spontaneous lymphomagenesis *in vivo* (Xiong et al., 2014) (Figure 3B, bottom).

RPS DEFICIENCY AND HUMAN MALIGNANCIES

Deletions or mutations in RP encoding genes are seen in human congenital disorders, such as Diamond-Blackfan anemia (DBA) and 5q- syndrome. Both disorders belong to a group of diseases called ribosomopathies with defects in ribosome biogenesis and increased risk of cancer development (Barlow et al., 2010a, b; Doherty et al., 2010; Draptchinskaia et al., 1999; Ebert et al., 2008; Farrar et al., 2008; Gazda et al., 2006, 2008; Narla and Ebert, 2010). Specifically, mutations in a number of RP genes have been identified in up to 50% of patients with DBA. Approximately 25% of DBA-affected individuals carry mutations, insertions, or deletions in the S19 encoding gene, while mutations or deletions in other RP genes have also been identified (Table 2) (Danilova and Gazda, 2015). Haploinsufficiency of certain RPs in DBA, such as S19, S24, and S17, leads to impaired pre-rRNA processing and abnormalities in ribosome biogenesis, which may be the main cause of DBA pathogenesis (Choesmel et al., 2008; Cmejla et al., 2007; Flygare et al., 2007). Importantly, in addition to anemia and birth defects, DBA is associated with predisposition to cancer, in particular acute myeloid leukemia (AML), colon cancer, and osteogenic sarcoma (Janov et al., 1996; Vlachos et al., 2001). It was reported that 6 of 354 patients who met the diagnostic criteria for DBA had malignancies with three being osteogenic sarcoma, suggesting their association (Lipton et al., 2001). The 5q- syndrome, another disorder of aberrant ribosome biogenesis, was identified to have mutations or haploinsufficiency in *RPS14*. The patients with this disease also appear to have an increased incidence of AML (Pellagatti et al., 2008). However, the causal association of ribosome defects with elevated cancer risks needs to be established.

Recently, somatic or germline mutations in some RP genes were found in various human cancers (Table 2). For instance, acquired somatic mutations in *L5* and *L10* were detected in T-cell acute lymphoblastic leukemia (T-ALL) by using whole-exome sequencing (De Keersmaecker et al., 2013). Moreover, heterozygous deletion in the region of chromosome 1p that contains *RPL22* has been also identified in the patients with T-ALL (Rao et al., 2012). In both *in vivo* mouse model of T-cell malignancy and *in vitro* assays, monoallelic loss of *Rpl22* enhances transformation potential through induction of stemness factor, Lin28B, to accelerate development of thymic lymphoma. Interestingly, RP genes have also been identified as haploinsufficient suppressors of tumorigenesis in zebrafish, in which a high frequency of malignant peripheral nerve sheath tumors was observed (Amsterdam et al., 2004). It is worth noting that a truncating

Table 2 Deletions or mutations of RPs in human disorders and malignancies

RP gene(s)	Cancer susceptibility or Tumors	p53 function	References
S19, L5, S26, L11, L35A, S10, S24, S17, S7, L26, L15, S29, S28, L31, S27, L27 (Diamond-Blackfan anemia)	Acute myeloid leukemia; Osteosarcoma; Colon carcinoma	Activation	(Doherty et al., 2010; Draptchinskaia et al., 1999; Farrar et al., 2008; Gazda et al., 2006, 2008)
S14 (5q- syndrome)	High risk of acute myeloid leukemia (Drug insensitive patients); Low risk of acute myeloid leukemia (Drug sensitive patients)	Activation	(Barlow et al., 2010a, b; Ebert et al., 2008; Pellagatti et al., 2008)
L22	T-acute lymphoblastic leukemia; Microsatellite-unstable endometrial tumors; Colorectal cancer; Gastric cancer	Unclear	(Anderson et al., 2007; De Keersmaecker et al., 2013; Ferreira et al., 2014; Rao et al., 2012; Wang et al., 2011b)
L5, L10	T-acute lymphoblastic leukemia	Unclear	(De Keersmaecker et al., 2013; Sulima et al., 2014)
S20	Familial colorectal cancer type X	Activation	(Nieminen et al., 2014)
L39	Breast cancer lung metastasis	Unclear	(Dave et al., 2014)

germline mutation in *RPS20* has been identified in familial colorectal cancer type X (FCCX) by genetic linkage analysis, exome sequencing, tumor studies, and functional investigations of 4 generations of an FCCX family (Nieminen et al., 2014). S20 mutation affects the balance between different pre-rRNA species and maturation of 18S rRNA, thus disturbing ribosome biogenesis, which is associated with a dominant predisposition to colorectal cancer. Knockdown of L39 and myeloid leukemia factor 2 (MLF2) in patient-derived and human cancer xenografts reduced tumor volume and lung metastases with a concomitant decrease in breast cancer stem cells. The mutations in both L39 and MLF2 were found in a significant number of patient lung metastases (n=53). These mutations were statistically associated with shorter median time to pulmonary metastasis (Dave et al., 2014). All these studies suggest that RP mutation or deficiency may be closely associated with human malignancies. The large-scale cancer sequencing should unveil a spectrum of RP mutations in an array of human cancers and uncover the link between aberrant ribosome biogenesis and tumorigenesis.

RPS AS POTENTIAL CANCER BIOMARKERS

Given that RPs are actively involved in cell proliferation, and their dysregulation is associated with human tumorigenesis, alterations in the levels of RPs are being used as potential cancer biomarkers. Indeed, some RPs have been found to be up-regulated in human cancer tissues, as compared to adjacent normal tissues (Table 3). For example, up-regulation of L13 mRNA expression was observed in 10 of 36 (28%) gastric, 19 of 46 (41%) colorectal and 5 of 25 (20%) liver cancer tissues compared to their corresponding adjacent normal tissues (Kobayashi et al., 2006). Moreover, high expression of L13 is correlated with later staging of gastric cancers (Kobayashi et al., 2006). The elevated expression of L19 is associated with prostatic malignancy, and more importantly, poor survival of prostate cancer patients (Bee et al., 2006). Up-regulation of L19 was observed in colorectal cancer tissues as well as in the feces of late-stage patients (Huang et al., 2008), whereas elevated S27L expression, in either feces or tissues, was related to a better prognosis (Huang et al., 2013).

On the other hand, some RPs were found to be down-regulated in some cancer tissues. A typical example is L22, which was found to be substantially down-regulated at its mRNA levels in invasive breast carcinoma compared with normal breast (Finak et al., 2008), as well as in lung adenocarcinoma, small squamous cell lung carcinoma, and adult T-cell leukemia (Bhattacharjee et al., 2001; Choi et al., 2007). Moreover, L41 allelic loss was detected in 59% of tumor cell lines and L41 down-regulation was detected in 75% of primary breast cancers (Wang et al., 2010). Decreased expression and loss of heterozygosity (LOH) of L14 were detected in 63% and 43% of esophageal squamous cell carcinomas, respectively (Huang et al., 2006). In dysplasia samples in which their corresponding tumors have LOH, 47% lost the same allele of L14 and only 11% retained both L14 alleles, suggesting that allelic loss of L14 might occur in an early stage of esophageal tumorigenesis and can be served as a diagnostic biomarker for early detection (Huang et al., 2006).

Finally, although no RP has been used as a direct cancer target, CX-5461, a small-molecule inhibitor of RNA polymerase I (for ribosomal RNA synthesis), which distinctly produces nucleolar disruption, but not genotoxic damage, is currently undergoing a Phase I/II clinical trial in patients with hematologic malignancies (Hannan et al., 2013). It has been shown that CX-5461 selectively induces the death of Eμ-Myc malignant cells *in vivo*, while allowing normal B cells to grow and proliferate, and potently induces p53-dependent apoptosis of non-MYC driven tumor cells as well (Bywater et al., 2012). Mechanistically, inhibition of rRNA synthesis in cancer cells would likely cause acute perturbation of ribosome biogenesis, resulting in accumulation of free RPs and subsequent activation of p53 and induction of apoptotic cell death. Thus, selective disruption of ribosome biogenesis in cancer cells, if applicable, could

Table 3 Dysregulation of RPs in human cancers

Cancer Type	RPs	Alteration	Implications for disease	References
Prostate cancer	S2, S14, S15a, S27, L7a, L19, L23a, L31, L37	Upregulation	L19 expression is correlated with Gleason scores of patients with prostate cancer. Increased L19 expression is highly predictive of shorter patient survival.	(Bee et al., 2006; Coleman et al., 2006; Fernandez-Pol et al., 1997; Maruyama et al., 2014; Vaarala et al., 1998; Wang et al., 2009)
Gastric cancer	S13, S27, L6, L13, L15, L23	Upregulation	Increased L6 expression in human gastric tissues is associated with poor prognosis.	(Kobayashi et al., 2006; Shi et al., 2004; Wang et al., 2006; Wu et al., 2011; Yang et al., 2013b)
Colorectal cancer	S3, S11, S19, S27, S27a, L7, L10a, L13, L19, L29, L36a (L44)	Upregulation	High level of S27L in faeces or cancer tissues is associated with a better prognosis of CRC patients.	(Chien et al., 2012; Ganger et al., 1997; Huang et al., 2008, 2013; Kasai et al., 2003; Kobayashi et al., 2006; Lai and Xu, 2007; Liu et al., 2006; Ojala et al., 2002)
	Sa, S8, S12, S18, S24, S27L, L13a, L18, L28, L32, L35a	Downregulation		
Lung cancer	p-S6, S27, S15a, L34	Upregulation	The expression of p-S6 is a negative independent predictor of metastasis-free survival after adjustment for tumor stage.	(Fernandez-Pol, 1996; McDonald et al., 2008; Yang et al., 2013a, 2016; Zhao et al., 2015)
	L22	Downregulation		
Liver cancer	p-S6, S8, S27, S27a, L12, L13, L23a, L27, L30, L36, L36a (L44)	Upregulation	L36 is involved in the early stage of hepatocellular carcinoma, and its expression indicates better overall survival in patients.	(Fatima et al., 2012; Ganger et al., 2001; Kim et al., 2004; Masuda et al., 2014; Song et al., 2011)
Esophageal cancer	p-S6, L15	Upregulation	Downregulation of L14 occurs frequently in ESCC and is an early event in the tumorigenesis of the esophagus.	(Huang et al., 2006; Kim et al., 2013; Wang et al., 2001)
	L14	Downregulation		
Breast cancer	S15a, S27, S27a, L19, L24	Upregulation	L41 is down-regulated in breast cancer and related to malignant transformation.	(Adams et al., 1992; Finak et al., 2008; Atsuta et al., 2002; Hannemann et al., 2006; Hong et al., 2014; Wang et al., 2010; Wilson-Edell et al., 2014)
	L22, L41	Downregulation		
Osteosarcoma	S3, S15a	Upregulation	Low expression of L7a predicts poor survival of osteosarcoma patients with lung metastasis.	(Nagao-Kitamoto et al., 2015; Zhang et al., 2014; Zheng et al., 2009)
	L7a	Downregulation		
Renal cell carcinoma	S6, p-S6, S27a	Upregulation	High levels of both S6 and p-S6 predict shorter survival of patients with renal cell carcinoma.	(Kanayama et al., 1991; Knoll et al., 2015; Lee et al., 2015)
Melanoma	S3	Upregulation	Overexpression of S3 predicts poor prognosis of melanoma patients.	(Tian et al., 2015)
Glioblastoma	S11, S15a, S20	Upregulation	Overexpression of S11 and S20 is associated with shorter patient survival.	(Yao et al., 2015; Yong et al., 2015)
Pancreatic cancer	L15	Downregulation	Low expression of L15 is associated with tumor progression and predicts poor overall survival.	(Yan et al., 2015)
Ovarian cancer	L13a, L29	Upregulation	Low level of S4X in human serous epithelial ovarian cancer is associated with poor prognosis.	(Bian et al., 2015; Li et al., 2009; Tsofack et al., 2013; Wang et al., 2013)
	S4X, S7	Downregulation		

have therapeutic utility for anticancer therapy.

CONCLUSIONS AND FUTURE PERSPECTIVES

In summary, ribosomal proteins not only play seminal roles in ribosomal biogenesis and protein synthesis, but also contribute to abnormal cell growth and tumorigenesis, if dysregulated. It is well established that the major extraribosomal function of RPs is mediated through the MDM2-p53 axis. To date, fifteen RPs have been shown to bind MDM2, leading to p53 accumulation and activation in response to stress. It is still an open question as to why so many RPs are needed to have the same MDM2-binding function to activate p53. Are they released from nucleolus in response to different stresses on an individual basis? Do they coordinately regulate and cooperate with each other? Our recent *S27l* KO study began to address these questions. We showed that depletion of S27l alone in the presence of all other Mdm2-binding RPs is sufficient to trigger p53 activation, leading to postnatal death (Xiong et al., 2014), suggesting an individual RP can be quite unique in modulating the MDM2/p53 axis. However, the precise role of each individual MDM2-binding RPs in regulation of the MDM2-p53 axis will have to await for *in vivo* evidence derived from mouse KO models. Intercrossing these genetically modified mice will help to elucidate their potential interaction under physiological conditions.

The involvement of RPs in the maintenance of genomic integrity is of particular interest, given that the acquisition of genomic instability is a hallmark of cancer (Hanahan and Weinberg, 2011). Indeed, in response to DNA damage, several RPs are involved in regulating DNA repair in p53-dependent or -independent manners. However, how the signaling cascade induced by DNA damage transmits to RPs is not well-understood, nor the detailed mechanisms by which RPs participate in the process of DNA repair, which

deserve extensive future investigation.

Finally, the contribution of RP gene mutations to human tumorigenesis is unknown. Are these mutations drivers or merely passengers of tumorigenesis? Furthermore, the mechanisms by which the RP deficiency seen in patients with human congenital diseases causes cancer predisposition are not clear. Future studies should be directed to answer these questions, leading to a better use of RPs as biomarkers or even therapeutic targets for cancer management.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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