



HAL
open science

The role of LARP1 in translation and beyond

Jean-Marc Deragon, Cécile Bousquet-Antonelli

► **To cite this version:**

Jean-Marc Deragon, Cécile Bousquet-Antonelli. The role of LARP1 in translation and beyond. Wiley Interdisciplinary Reviews-RNA, 2015, Topics in Current Genetics, 6 (4), pp.399-417. 10.1002/wrna.1282 . hal-04823904

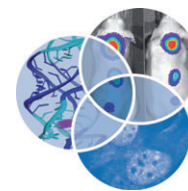
HAL Id: hal-04823904

<https://hal.science/hal-04823904v1>

Submitted on 18 Dec 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



The role of LARP1 in translation and beyond

Jean-Marc Deragon^{1,2} and Cécile Bousquet-Antonelli^{1,2,*}

The LARP1 proteins form an evolutionarily homogeneous subgroup of the eukaryotic superfamily of La-Motif (LAM) containing factors. Members of the LARP1 family are found in most protists, fungi, plants, and animals. We review here evidence suggesting that LARP1 are key versatile messenger RNA (mRNA)-binding proteins involved in regulating important biological processes such as gametogenesis, embryogenesis, sex determination, and cell division in animals, as well as acclimation to stress in yeasts and plants. LARP1 proteins perform all these essential tasks likely by binding to key mRNAs and regulating their stability and/or translation. In human, the impact of LARP1 over cell division and proliferation is potentially under the control of the TORC1 complex. We review data suggesting that LARP1 is a direct target of this master signaling hub. TOR-dependent LARP1 phosphorylation could specifically enhance the translation of TOP mRNAs providing a way to promote translation, growth, and proliferation. Consequently, LARP1 is found to be significantly upregulated in many malignant cell types. In plants, LARP1 was found to act as a cofactor of the heat-induced mRNA degradation process, an essential acclimation strategy leading to the degradation of more than 4500 mRNAs coding for growth and development housekeeping functions. In *Saccharomyces cerevisiae*, the LARP1 proteins (Slf1p and Sro9p) are important, among other things, for copper resistance and oxidative stress survival. LARP1 proteins are therefore emerging as critical ancient mRNA-binding factors that evolved common as well as specific targets and regulatory functions in all eukaryotic lineages. © 2015 John Wiley & Sons, Ltd.

How to cite this article:

WIREs RNA 2015, 6:399–417. doi: 10.1002/wrna.1282

INTRODUCTION

Coordinate and precisely regulate the expression of large gene sets are key cellular processes that allow organisms to grow, develop, differentiate but also acclimate and survive. The regulation and reprogramming of gene expression is a higher order function exerted throughout the various steps of messenger RNA (mRNA) biology: transcription, processing, export, translation, and stabilization.

mRNA fate is dictated by the dynamic remodeling of their mRNP structures. During or shortly

after transcription, an mRNA is associated to an array of RNA-binding proteins (RBPs) to form a dynamic ribonucleoprotein complex (mRNP). Remodeling its mRNP structure through quantitative and qualitative alteration of its RBP composition, allows a given transcript to proceed through the various steps of maturation and export. It is also by modifying its protein composition that mRNP translation rate, stability, and cytoplasmic localization can be reprogrammed. Eukaryotic cells contain between one hundred (yeast¹) to several hundreds (higher plants and animal cells^{2–4}) mRNA-RBPs. By binding mRNA arrays, these proteins allow the coordinate regulation of sets of functionally related genes. This permits the rapid and massive alteration of cellular functions necessary for developmental transitions or stress acclimation. Pools of such commonly post-transcriptionally regulated transcripts are called ‘RNA-operons’.⁵

*Correspondence to: cecile.antonelli@univ-perp.fr

¹CNRS, LGDP-UMR5096, Perpignan, France

²University of Perpignan, LGDP-UMR5096, Perpignan, France

Conflict of interest: The authors have declared no conflicts of interest for this article.

In the cytoplasm, mRNAs are in balance between active translation, degradation, and storage. Alteration in this equilibrium is essential to the efficient and immediate reprogramming of gene expression.⁶ Canonical mRNAs bear an m⁷Gppp structure (cap) at their 5'-end and a polyadenylate (poly(A)) tail at their 3'-extremity. These structures are respectively bound by the eIF4E-eIF4G heterodimer and the Poly(A) binding protein (PABP) and play a crucial role in mRNA stabilization and translation efficiency. Translation is an iterative process, generally coupled to slow deadenylation. When mRNAs reach the end of their translatable life, they enter the general turnover process and are decayed in a 5'- or 3'-directed manner.^{7,8} In somatic cells mRNA degradation occurs in the cytosolic fraction, but also in processing bodies (p-bodies), which consist in mRNP aggregates that concentrate actors of the degradative machinery but also their cofactors, translation repressors, and various RNA-RBPs. P-bodies formation and translation activity are inversely correlated and only mRNAs fully disengaged from polysomes can associate into such RNP granules. Stress exposure is one of the cues triggering reprogramming of mRNA stability and translation. One of the first cellular responses to stress is the general repression of translation initiation and selective expression of stress responsive factors.⁹ Translation inhibition drives the disengagement of mRNAs from polysomes and appearance of another type of mRNP granules, the Stress Granules (SG), which generally concentrate translation initiation factors, the PABP and the 43S subunit.¹⁰ Stress granules and p-bodies are mRNP remodeling centres proposed to act as sorting entities involved in protection but also degradation of translationally silent mRNAs.⁶ Stress also induces the massive downregulation, through accelerated turnover of thousand of transcripts.¹¹ Cytoplasmic post-transcriptional regulations of gene expression exerted through translation reprogramming and/or mRNA degradation are also key determinants of oocyte maturation, maternal-zygote transition, or sex determination in animals.^{12,13}

The La and Related Proteins (La and LARPs) constitute a super family of eukaryotic RNA-binding factors that have in common the highly conserved La-Motif (LAM).^{14–16} These proteins classify into five evolutionary distinct subgroups, which members share functional properties.¹⁵ Recent publications support that members of subfamilies 1, 4, and 6 are mRNA-binding factors involved in the post-transcriptional control of gene expression (see Ref 14 for a general review on LARPs). We will review here the current knowledge of the physiological,

cellular, and molecular roles of proteins of the LARP1 type which are emerging as important regulators of mRNA stability and translation at developmental or environmental transitions.

FEATURES OF THE LARP1 PROTEINS

In contrast to other LARP subfamilies (Box 1), the LARP1 subgroup has members in most if not all eukaryotes¹⁵ (Figure 1, Box 2). The LARP1 proteins display two main organizations (Figures 1 and 2(a)): (1) they are either long (up to 1400 amino acids in fly for example) and display a La-Module at their centre and a highly conserved C-terminus named DM15 or (2) they are relatively short (300–500 amino acids) and only bear a LAM located at their very C-terminal end. In either configuration, the LAM is very well conserved and retains all six residues (Q₂₀(F/Y/W)₂₃(F/Y/W)₂₄D₃₃(F/Y)₃₅F₅₅) found to be present in most La and LARP proteins (except for the LARP4 and higher plant LARP6 proteins)^{14,15,24} and directly involved in UUU-3'OH recognition by the genuine La protein.^{25,28,29} LARP1 proteins have a peculiar La-module as its RRM1 moiety (named RRM_{1.5}) is not conserved at the primary sequence level and was solely found through secondary structure prediction programs which recognized the typical $\alpha\beta$ sandwich fold of an RRM in the region located immediately downstream to the LAM.¹⁵ The actual functional importance of this RRM1 remains so far an unaddressed question. The LARP1 DM15 region is a structured domain composed of three tandemly arranged related boxes (denoted A, B, C) bordered by two short folded motifs (denoted 1 and 2 in Figure 2(a)) (A. Berman's unpublished data; Lahr et al., manuscript in preparation). All eukaryotes except for some fungi lineage (Box 2), possess such tandem (ABC) arrangement bordered at the N-terminus by the conserved box 1 and the more divergent C-terminal box 2 (Ref 15; Lahr et al., manuscript in preparation). The DM15 region, which is only found on LARP1 proteins,¹⁵ is hence extremely specific and highly conserved at the primary sequence level and most likely at the structural level, which supports a high functional significance. The role of the DM15 region remains mostly unknown but it has RNA-binding ability *in vitro* (Ref 32; Lahr et al., manuscript in preparation) and was found to be necessary for LARP1a association to the human poly(A) binding protein *in vivo*.³³

Genomes can encode 1–3 LARP1 proteins.¹⁵ *Drosophila melanogaster* and *Caenorhabditis elegans* contain a single type 1 LARP1 protein: Dlarp1³⁴ and CeLARP-1 (Figure 2(b)), while *Homo sapiens* and

BOX 1

THE LA-MOTIF AND LA-MODULE (LAM-RRM1): COMMON THEMES TO GENUINE LA AND RELATED PROTEINS

Some 40 years ago the serum 'La' from patients suffering from the rheumatic autoimmune disease systemic lupus erythematosus was shown to react against a broad spectrum RNA-RBP^{17,18} targeting pol III primary transcripts.^{19,20} The sequence of the human La autoantigen, now called the La protein, was reported in 1988,²¹ but it was not until the characterization of the drosophila and yeast orthologues by the Wolin's lab that the LAM was identified.^{22,23} The LAM is an ancestral domain that emerged early after the archaea-eukarya radiation¹⁵ and is shared by several hundred proteins^{15,16,24} that are either genuine (or authentic) La or non-orthologous **La-Related Proteins (LARPs)**. The LAM from genuine La adopts a winged-helix like fold²⁵ conserved, although with minor variations, in the human LARP6.²⁶ Although absolutely necessary, the LAM is not able to bind RNA alone and cooperates with an adjacent RNA recognition motif (RRM1) and the interdomain linker to form the RNA-binding pocket known as the La-Module.^{26–29} La and related proteins form a superfamily of eukaryotic factors, which classify into five clusters: the genuine La and four LARP subfamilies: LARP1, 4, 6 and 7¹⁵ (Figure 1). Most LARPs retained a La-module organization, but unlike the LAM which diverged very little, the RRM1 and interdomain linker are specific to each subfamily.^{15,26} The genuine La and LARP7 proteins share a related canonical RRM1 (adopting the typical $\alpha\beta$ sandwich fold and bearing the RNP1 and RNP2 aromatic patches³⁰), while the other LARP families have specific non-canonical RRM1¹⁵ (Figure 1). Members of a subfamily share additional motifs likely to be key actors of the proteins' functions. This convergence of unique evolutionary and structural characteristics supports the idea that proteins belonging to a subfamily have conserved functional properties whether working in the same biological process and binding to homologous targets or adopting a similar molecular mode of action on different targets (see Ref 14 for a general review on LARPs).

Arabidopsis thaliana contain three LARP1 proteins; denoted a, b and c.¹⁵ While the human a and b proteins are long type 1 proteins, HsLARP1c is a

short type 2 LARP1 (Figure 2(b)). In HeLa cells, the HsLARP1b mRNA is much less abundant than that of HsLARP1a,³⁵ which is so far the only human LARP1 protein functionally studied.^{33,35,36} *A. thaliana* contains a single type 1 (AtLARP1a) and two type 2 LARP1 proteins (Figure 2(b)). AtLARP1a and c mRNAs are ubiquitously expressed at similar levels in all plant organs while AtLARP1b mRNA is ubiquitously expressed but at very low levels. In male tissues, before fecundation (i.e., in immature and mature but not germinated pollen), the AtLARP1c transcript is ten times more abundant than in other tissues while the AtLARP1a is no longer detected in mature and germinated pollen (data from the Gene Expression Map of Arabidopsis development at Arabidopsis eFP browser <http://bar.utoronto.ca/efp/cgi-bin/efpWeb.cgi>³⁷). In the following sections of this review we will refer to the Human and Arabidopsis LARP1a proteins as 'HsLARP1' and 'AtLARP1' and to the *C. elegans* and *D. melanogaster* proteins as CeLARP1 and DmLARP1.

LARP1 IS AN MRNP PROTEIN INVOLVED IN THE CYTOPLASMIC POST-TRANSCRIPTIONAL CONTROL OF GENE EXPRESSION

Several data support that type 1 LARP1 proteins have RNA-binding abilities and are involved in mRNA biology and mRNP structures. As part of the LAM superfamily, the LARP1 proteins were readily categorized as 'RNA-binding'. The first preliminary evidence of LARP1's RNA-binding ability was for CeLARP1. Nykamp et al. showed with RNA-binding assays that an *in vitro* translated CeLARP1 protein binds poly(G) and to a lesser extent poly(U) (but not poly(C) nor poly(A)) RNA homopolymers.³² They also demonstrated that the DM15 domain alone and a CeLARP1 Δ DM15 mutant binds poly(G) and poly(U) RNAs.³² Work by Aoki et al. suggests that the human LARP1 protein preferentially binds to 3'-terminally located poly(A) tail of at least nine adenylates long.³⁸ In this article the authors used an RNA-based affinity column to purify poly(A) RBPs out of a crude cell extract, a protocol that does not formally prove that HsLARP1 retention is the consequence of its direct binding to RNA. A. Berman's team challenged the DM15 domain ability to bind *in vitro* an A₁₆ RNA homopolymer or several TOP (Terminal OligoPyrimidine) sequences. Their results suggest that the DM15 region is not by itself able to bind poly(A) while it shows binding to TOP sequences in presence of non specific competitor (Lahr et al., manuscript in preparation). Altogether, these analyses constitute an initial

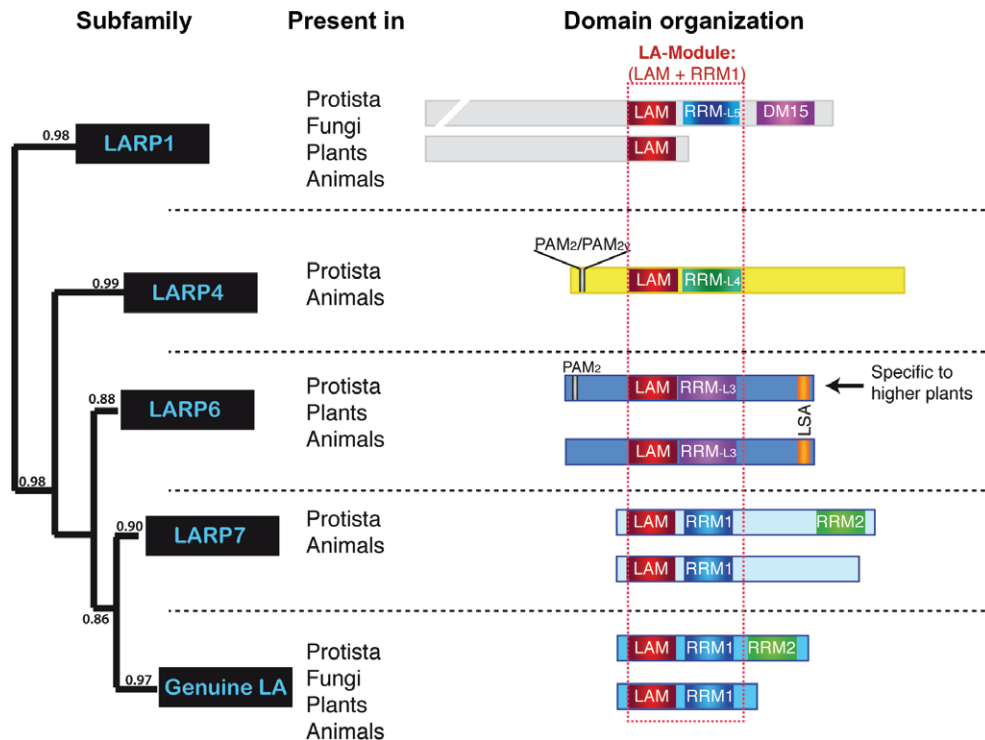


FIGURE 1 | Phylogenetic relationship and domain organizations among La-Motif containing proteins (Reprinted with permission from Ref 15. Copyright 2009 Cold Spring Harbor Laboratory Press). La-Motif proteins fall into five evolutionarily conserved families. Members of a given family share conserved domain organization. As for the genuine La proteins, the LAM-RRM1 or La-Module is found in every LARP subgroup. With the exception of the LARP7 family, which has a canonical RRM1, other LARP families display specific variant RRM1, labeled RRM-L (RRM-Like). Additional conserved motifs, specific to each La and Related subfamilies, can also be found. The LARP1 proteins display a highly conserved C-terminus called DM15. The LARP4 and higher plant LARP6 have a PAM2 domain, a small structured region that directly fits into the MLE domain found at the C-terminus of the Poly(A) Binding Proteins (PABP). LARP proteins displaying a PAM2 domain display a divergent LAM (labeled with vertical black bars). The LARP6 proteins also display a short conserved domain named LSA (for LAM and S1 Associated). The genuine La and LARP7 proteins have a second non-canonical C-terminal RRM, labeled RRM2.

demonstration that LARP1 has RNA-binding abilities and suggest that both the DM15 and La-module containing regions could carry such function. The relative contributions of these domains for binding efficiency and specificity remain nonetheless to be understood.

Using UV-CrossLinking and ImmunoPrecipitation based approaches (CLIP and PAR-CLIP) Castello et al.⁴ and Baltz et al.³ identified HsLARP1 as a member of the mRNA-binding proteome of HeLa and HEK293 cells, providing the first strong indication that HsLARP1 is indeed an mRNA-RBP *in vivo*. LARP1 from all tested organisms (fly,^{35,39} worm,³² human,⁴⁰ and plant⁴¹) were consistently localized in the cytoplasm. In the worm germline, it accumulates in p-bodies,³² while in Arabidopsis roots and onion epidermal cells, it localizes to p-bodies and more largely to stress granules.⁴¹ LARP1 is also found associated to actively translating ribosomes both in human^{33,40,42} and Arabidopsis.⁴¹ Another evolutionarily conserved feature of LARP1 is its ability to interact with the poly(A)-RBP and components of the

translation initiation machinery such as eIF4F and eIF4A (Refs 33, 35, 40, results of our unpublished yeast-two hybrid and co-immunoprecipitation assays conducted with AtLARP1). Finally, AtLARP1 interacts with XRN4, the plant homolog of the cytoplasmic 5'-3' exoribonuclease XRN1.⁴¹ This body of evidence demonstrates that LARP1 proteins are mRNA-RBPs likely involved in the post-transcriptional control of gene expression through regulation of mRNA translation and/or stability.

A ROLE FOR LARP1 IN ANIMAL REPRODUCTION

So far the roles of LARP1 proteins in whole organism development and survival have been investigated in three species: *C. elegans*,^{32,43,44} *D. melanogaster*,^{35,39} and *A. thaliana*.⁴¹ While worm and fly LARP1 retain a crucial function in reproduction, no fertility deficiencies were observed in Arabidopsis *null Atlarp1* mutant

BOX 2

LESSONS FROM THE EVOLUTIONARY HISTORY OF LARP1 PROTEINS IN FUNGI

LARP1 proteins are found in all fungi with the exception of the Microsporida phylum. All Basidiomycota species possess a 'simplified' (type 2) LARP1 version, with a C-terminal LAM as single conserved element (Figure 5). In Ascomycota, the Saccharomycotina and Taphrinomycotina subphyla contain only the 'simplified' LARP1 version while a 'complete' (type 1) LARP1 is found in Pezizomycotina as well as in all basal fungi lineages (Figure 5). Eukaryote DM15 motifs are composed of three related, well-conserved repeats (Lahr et al., manuscript in preparation), but the situation of Ascomycota LARP1 is here again exceptional. Ascomycota DM15 repeats were allowed to drift from ancestral sequences (Lahr et al., manuscript in preparation) suggesting that they possess a neofunctionalized DM15, distinct from other eukaryote LARP1 proteins. A phylogenetic analysis using sequences from fungi LARP1 LAMs further revealed that, surprisingly, the two *Saccharomyces cerevisiae* proteins, Slf1p and Sro9p are not included in the Ascomycota clade (Figure 6). A second phylogenetic analysis, this time focusing on 18 Saccharomycotina species, confirmed that LARP1 from *S. cerevisiae* as well as from two highly related species are clearly exceptional (data not shown), suggesting that their LAM was recently reorganized and likely neofunctionalized. This information implies that conclusions drawn from the molecular analysis of these two proteins may not all be readily extrapolated outside of this precise fungi family. In summary, although LARP1 sequences and structures are well conserved throughout eukaryotes, three important reorganizations happened in the fungi lineage: (1) the loss of the C-terminal region in Basidiomycota, and in two Ascomycota subphyla, (2) the reorganization and putative neofunctionalization of the DM15 region for Ascomycota 'complete' LARP1 and (3) the reorganization and putative neofunctionalization of the LARP1 LAM in *S. cerevisiae* and closely related species.

(Ref 41, our unpublished results). The requirement for LARP1 in animal fertility seems to be linked to its molecular functions as an mRNP protein.

In *C. elegans* hermaphrodites, the *larp-1* mRNA is expressed both in germline and soma.^{32,45} Nevertheless, RNAi-mediated and loss-of-function (*larp-1(0)*)

mutant has little impact on adults, causing them to grow more slowly.^{32,46,47} *larp-1* deletion causes some low penetrance embryonic defects (*larp-1(0)* mutants produce fewer and smaller eggs, 6% of which are dead),^{32,48} which are proposed to be at least in part the consequence of CeLARP1 function in oogenesis.³² Around 50% of *larp-1(0)* hermaphrodites display a higher than wild-type number of smaller oocytes arranged in multiple rows.³² This phenotype is severely increased when both the CeLARP1 and NOS-3 proteins are deleted.⁴⁴ NOS-3 is one of the three homologs in *C. elegans* of the Drosophila Nanos protein, that forms a complex with Pumilio in flies to repress translation of specific germline mRNAs.^{49–51} *C. elegans* hermaphrodites, possess a germline containing proliferative (mitotic germcells), transition, and meiotic zones. While somatically female, larvae produce sperm up to the L4 developmental stage, where the germline switches to a female program and only produces oocytes.¹³ While 100% of the single *larp-1(0)* and *nos-3(q650)* null hermaphrodites have both sperm and oocytes, more than 50% of double (*larp-1(0);nos-3(q650)*) mutants display a Mog (Masculinization of germline) phenotype consisting of adults with no oocytes. This reveals a function for CeLARP1, redundant to that of NOS-3 in the sperm-to-oocyte switch. Another important function for CeLARP1 in germline development and fate is revealed in the *nos-2* null background. NOS-2 is another of the three *C. elegans* homologs of the Drosophila Nanos protein and is required redundantly with NOS-3 to switch from sperm to oocyte.⁵⁰ Surprisingly CeLARP1 and NOS-2 do not act redundantly to control the sperm-oocyte switch but act together in the germline formation as demonstrated by the observation that 79% of the (*nos-2(RNAi);larp-1(0)*) individuals have no germlines or only developmentally arrested germline.⁴⁴ At the cellular level, the CeLARP1 protein was also found to positively regulate the number of proliferating cells in the mitotic region of the germline: *larp-1(0)* hermaphrodites contain on average 20% fewer mitotic germcells. It is not known, however, if CeLARP1 promotes mitosis or inhibits entry into meiosis.⁴⁴

The cellular and molecular basis for CeLARP1 functions in *C. elegans* germline control and oocyte development are far from being understood. The *larp-1(0)* oocyte development defect is proposed to be the consequence of the misregulation of the Ras-MAPK signaling pathway, which is involved in multiple steps of oocyte development. More precisely, *larp-1* loss of function increases mRNA and protein levels of *let-60* (coding for the Ras homolog), *mpk-1* (coding for the main MPK kinase in worm) and

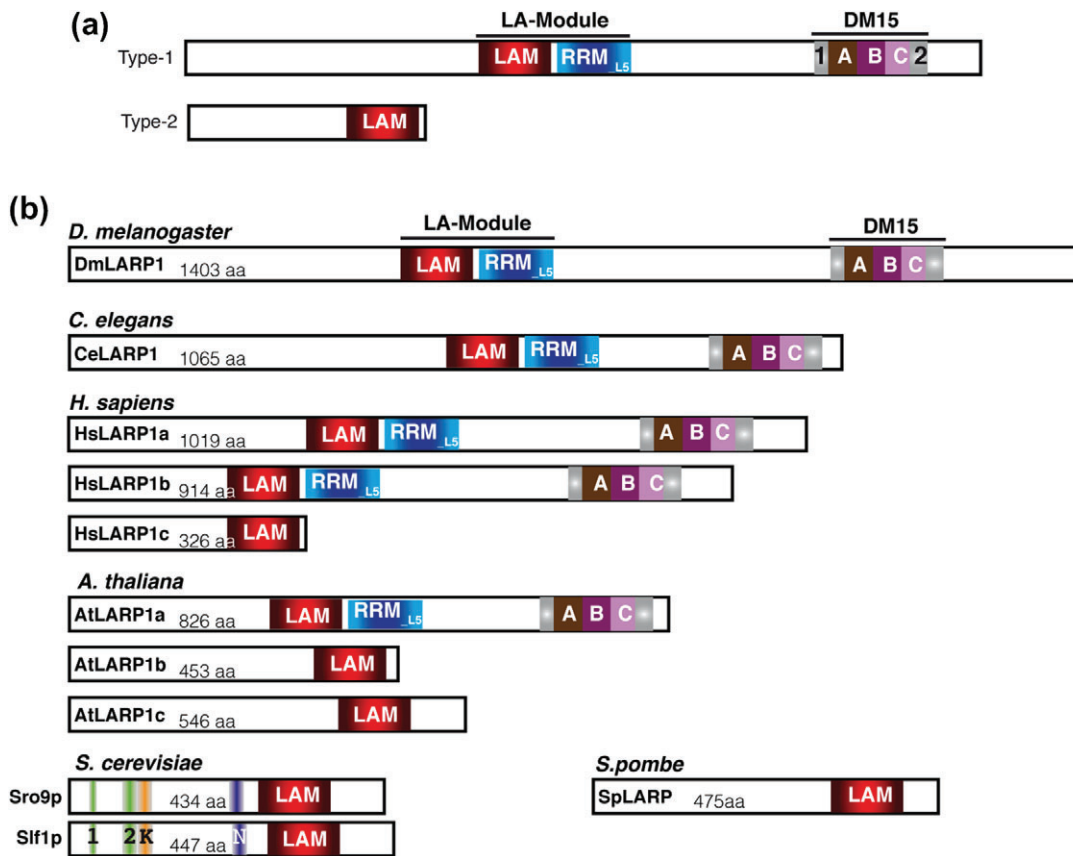


FIGURE 2 | Structural features of the LARP1 proteins. (a) Schematic representation of the two types of LARP1 proteins. (b) Representation of the structural arrangement of LARP1 proteins from *Drosophila melanogaster* (NP_733244), *C. elegans* (NP_001040868), *H. sapiens* (LAR1a: NP_056130, LARP1b (formerly LARP2): NP_060548, LARP1c: XP_001715526), *A. thaliana* (LAR1a: AT5G21160; LARP1b: AT5g66100; LARP1c: AT4G35890), *S. cerevisiae* (Sif1p: YDR515W and Sro9p: YCL037C) and *S. pombe* (SpLARP: SPAC1527.03). The La-Motif (LAM) is in red, RRM_{L5} in blue and the DM15 domain represented by three colored boxes corresponding to the A, B and C motifs bordered by conserved boxes 1 and 2 in gray. The *S. cerevisiae* proteins were proposed to have two conserved patches (1 and 2, represented in green boxes), a lysine (K)-rich and an asparagine (N)-rich region located upstream to their LAM.³¹

lip-1 (coding for an inhibitor of MPK-1 activity) in the germline. Moreover, the *larp-1(0)* oocyte developmental phenotype is alleviated in an hypoactive *Ras* (*let-60(n2021rf)*) mutant and exacerbated in an hyperactive *Ras* (*let-60(n1046gf)*) background. Together, these data suggest that CeLARP1 acts to downregulate the Ras-MAPK signaling pathway, perhaps through an mRNA destabilizing activity in the p-bodies.³² The cellular and molecular bases of CeLARP1 and NOS-3 redundancy in oocyte development still remain unexplored.

In addition to NOS-2 and NOS-3, TRA-1 is also involved in controlling the switch from sperm to oocyte production in worm hermaphrodites. TRA-1 belongs to the family of the Gli-transcription factors and is a final sex determination regulator that favors oogenesis by repressing male-specific gene expression. TRA-1 is repressed by CUL-2 and three FEM proteins that target it to the proteasome for degradation.

After a transient period of sperm production at larval stage L3, repression of FEM-3 protein production is required to switch to the female program (for review see Ref 13). *fem-3(e2006)* temperature-sensitive loss of function hermaphrodites are almost 100% female at high temperature (25°C),⁴⁴ while gain of function mutants show Mog phenotypes (more or less penetrant according to the allele).⁴³ CeLARP1 has been proposed to promote oogenesis through negatively regulating *fem-3* mRNA levels. Hermaphrodites (*larp-1(0);nos-3(q650)*) lose their Mog phenotype in the *fem-3(e2006)* null context and displays 95% feminization. More significantly, loss of *larp-1* function increases the Mog phenotype of two *fem-3* gain of function mutants (*fem-3(q22)* and *fem-3(q23)*).^{43,44} A direct assessment of *fem-3* mRNA levels in *larp-1(0)* L4 hermaphrodites show a two- to three-fold increase as compared to wild-type. As for the mRNAs coding for Ras signaling components, the proposed model

so far, given its potential mRNA-binding ability and its presence in processing bodies, is that CeLARP1 is a direct negative regulator of *fem-3* stability.^{32,44} Since NOS-3 was suggested to act as a repressor of *fem-3* translation,⁵⁰ one appealing model is that CeLARP1 and NOS-3 cooperate to downregulate FEM-3 production.

The *Drosophila* LARP1 protein was found so far to be mostly required for reproduction and have only subtle somatic impacts. *dmlarp1* mutant flies are 100% male and female sterile (allele *dmlarp1^{mtr-null}*). Mutant embryos present some cellular deficiencies but their exact level of viability has yet to be determined.^{35,39} Using low penetrance *dmlarp1* mutants, Blagden and colleagues found that embryos show multiple mitotic phenotypes with cells displaying multipolar spindles and defects in chromosome segregation, as supported by the presence of cells devoid of nuclei or conversely with polyploid nuclei.³⁵ Male sterility of *dmlarp1* null mutants is at least in part the consequence of gametogenesis deficiencies, as supported by the observation that 30–40% of their ‘onion-stage’ (i.e., after completion of meiosis II) spermatids have multiple meiotic phenotypes: chromosome segregation and cytokinesis defects as well as unequal mitochondria partitioning. The *dmlarp1-null* meiotic spermatocytes and mitotic embryo phenotypes are the consequence of altered progression through M phase, seemingly linked to deficiencies in spindle pole formation, organization and function.^{35,39} Inactivation of the *dmlarp1* gene function is likely to have yet uncovered developmental consequences. Indeed, 100% of homozygous null *lar¹^{mtr-null}* females do not lay eggs, suggesting that the female fertility problem is not solely linked to embryonic development deficiencies. Also, whatever the *dmlarp1* deficient allele tested, males are always 100% sterile, while retaining 58–70% normal spermatids.^{35,39} The molecular mechanisms governing DmLARP1 function in cell cycle progression remains largely unknown at present. Nevertheless it has been proposed that it could regulate the stability and/or translation of key regulators of the cell cycle. This is supported by the observations that DmLARP1 directly or indirectly interacts with the poly(A) binding protein (Pabp) in D-Mel cells (a cell line derived from *Drosophila* embryos) and shows an increased penetrance of male meiotic defects of an hypomorphic *pabp* background.³⁵

A ROLE FOR HSLARP1 IN CELL PROLIFERATION AND DIVISION

The loss of human LARP1 function in several malignant and non-malignant cell lines, through

shRNA-mediated depletion, results in a cell cycle arrest at G0/G1 as demonstrated by FACS DNA content analyses and decrease in cell proliferation. These deficiencies appear to be the consequence of a general downregulation of protein synthesis through inhibition of translation initiation.³³ Work conducted by Burrows et al., also documented a role for HsLARP1 in promoting general translation and cell cycle progression.⁴⁰ But, rather than affecting G1, siRNA-mediated inactivation of HsLARP1 in HeLa cells hinders progression through the M phase. In agreement with such deficiency, HeLa and U-2OS (bone osteosarcoma derived cell line) *lar¹*-depleted cells show chromosomal defects (abnormal chromatin condensation and chromosome migration) as well as defects in spindle pole formation and centrosome migration.⁴⁰ Despite the discrepancies between these studies, a role for HsLARP1 in animal M phase progression seems likely given that similar observations were reported in the more ‘natural’ context of the *Drosophila* *dmlarp1* mutant (Refs 35, 39 and see above). This does not exclude an additional role for HsLARP1 in G1 as discrepancies between Burrows and Tcherkezian studies might be related to differences in levels of HsLARP1 inactivation and/or cell types analyzed (Table 1).

AN ONCOGENIC ROLE FOR THE HUMAN LARP1 PROTEIN

Several independent studies reported that human LARP1 expression is misregulated in cancer cell lines and malignant tissues.^{36,64–66} A survey of 15 hepatocellular cancer cell (HCC) lines showed that both HsLARP1 mRNA and protein are significantly upregulated in malignant cells as compared to an immortalized normal liver epithelial cell line (THLE3).⁶⁶ Moreover, when comparing protein levels by western blotting and immunohistochemistry between HCC and adjacent non-cancerous tissues, Xie et al. found a marked increase in HsLARP1 levels in HCC lesions.⁶⁶ A similar study conducted on human cervical squamous carcinoma cells (SCC) showed increased HsLARP1 mRNA and protein levels as compared to non-cancerous cervical tissue.³⁶ When reviewing the Oncomine cancer microarray database,³⁶ Mura and colleagues observed that HsLARP1 mRNA expression is generally increased in epithelial malignancies. HsLARP1 splicing was also found to be misregulated in breast cancer cell lines. An alternatively spliced HsLARP1 mRNA was detected and found to allow the production of a 1096 amino acids long N-terminally extended protein in three types of breast cancer cell lines.⁶⁴ The functional implication of this

TABLE 1 | LARP1 Family Members and Function

| Protein | Organism | Function | Ref |
|-----------------|---------------------------------|---|------------------------|
| Sro9p | <i>Saccharomyces cerevisiae</i> | <p>Associates with Ydj1p and Hsp70p to the high molecular weight complex formed around Hap1p and is involved in Hap1p repression in the absence of heme.</p> <p>Indirectly required for formation/stabilization of actin cytoskeleton.</p> <p>Acts as a multicopy suppressor of the <i>rbp4</i>-Δ thermosensitive phenotype, likely through promoting pol II transcription and mRNA stability.</p> <p>Positively regulates levels of mRNAs coding for protein synthesis components, among which ribosomal proteins.</p> <p>Associates co-transcriptionally to mRNAs and shuttles in an mRNA-dependent manner between nucleus and cytoplasm. Associates to translating ribosomes, translation initiation factors, PABP, stress granules and to a lesser extend p-bodies.</p> | 1, 52, 31, 53–59 |
| Slf1p | <i>Saccharomyces cerevisiae</i> | <p>Acts as a suppressor of the copper sensitive <i>cup14</i> mutation. Is required for copper resistance and detoxification and for oxidative stress (H₂O₂) survival. Promotes stability of copper resistance transcripts. Promotes translation of oxidative stress response genes in stress situation when translation is massively downregulated.</p> <p>Positively regulates the levels of protein synthesis components, in particular ribosomal protein coding transcripts (together with Sro9p).</p> <p>Associates to translating ribosomes, translation initiation factors, PABP and stress granules.</p> | 1, 52, 31, 54, 60 |
| AtLARP1a | <i>Arabidopsis thaliana</i> | <p>Localizes in the cytosol under normal conditions, associates to polyribosomes, stress granules and to a much lesser extend p-bodies in response to heat stress. Regulates the level of stress coding transcripts at 20°C.</p> <p>Downregulates through rapid degradation, the levels of housekeeping/growth coding transcripts during heat stress. Acts as a heat specific cofactor of XRN4 (homologue of animal XRN1), and is required for its recruitment to polysomes. Assists XRN4 in the co-translational decay process of specific transcripts in response to heat stress.</p> | (41, 67). |
| AtLARP1c | <i>Arabidopsis thaliana</i> | <p>Putative role in senescence. Overexpression causes premature leaf senescence. Positively regulates levels of tested Senescence Associated Genes (SAG) mRNAs. <i>lar1c</i>-deficient plants show reduced senescence of leaves when exposed to senescence and defence-related hormones.</p> | 61 |
| CeLARP1 | <i>Caenorhabditis elegans</i> | <p><i>lar1</i> mRNA is present in soma and germline. Homozygous hermaphrodite mutants are viable and only slow growing. CeLARP1 acts redundantly with NOS-3 to control the sperm-oocyte switch in hermaphrodites and partially redundantly to control oocyte arrangement and cell number in the mitotic zone. CeLARP1 is redundantly required with NOS-2 for germline formation (79% double mutant hermaphrodites have no germline). CeLARP1 is found in p-bodies in germline cells. CeLARP1 is a negative regulator of mRNA levels of Ras-MAPK signaling components and <i>fem-3</i> mRNA.</p> | 13, 32, 44, 46 |
| DmLARP1 | <i>Drosophila melanogaster</i> | <p>Required for male and female fertility and for embryonic development. DmLARP1 defective embryos show defect in M-phase progression, linked to spindle pole formation, centrosome migration, chromosome segregation. <i>lar1</i> mutant male shows defects in gametogenesis at meiosis.</p> <p>Forms a complex with the poly(A) binding protein and shows increased male meiotic defects when deleted in a <i>pabp</i> hypomorphic background.</p> | 35, 39 |
| HsLARP1a | <i>Homo sapiens</i> | <p><i>lar1a</i>-deficient cell lines show proliferation and cell cycle defects (arrest at G0/G1 and deficient progression through M phase). <i>lar1</i>-deficient cell lines show a global decrease of protein production linked to translation inhibition. Associates to translating ribosomes and translation initiation factors (PABP, eIF4A). Is phosphorylated in an mTOR-dependent manner and might be a direct target of the mTORC1 complex. Positively regulates the polysomal engagement of TOP mRNAs and positively regulates their stability. Also acts to stabilize mTOR mRNA and promotes mTOR protein production at least in HeLa and PC-9 cell lines.</p> | 33, 36, 38, 40, 62, 63 |

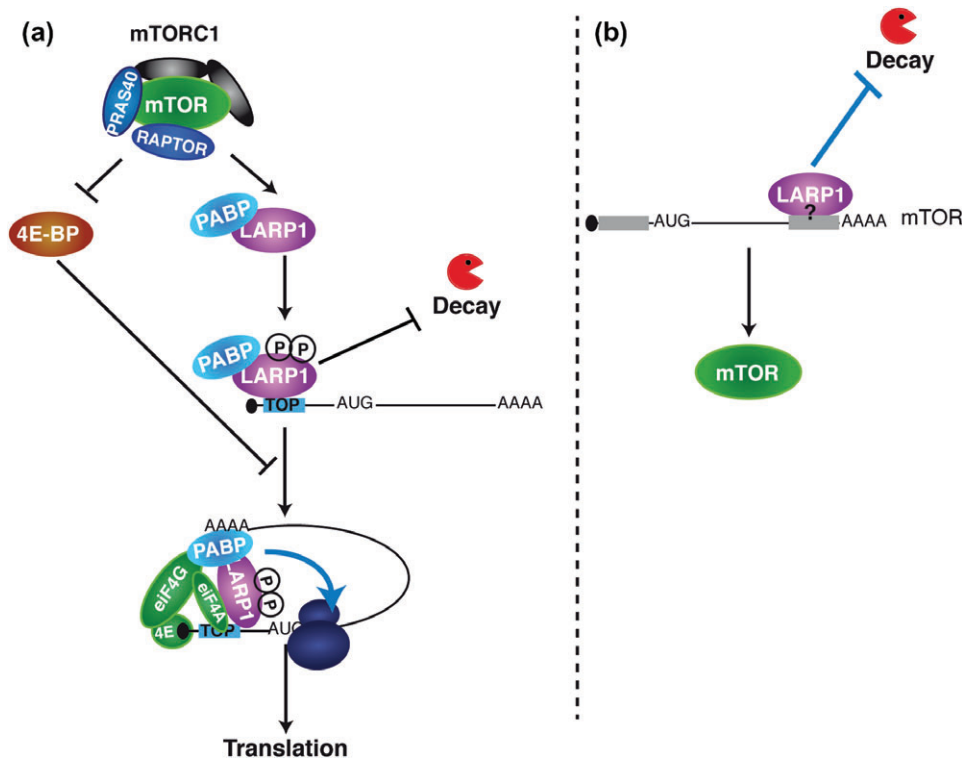


FIGURE 3 | Model for Human LARP1 role in the mTOR pathway. (a) mTOR-dependent phosphorylation of LARP1 would stimulate TOP-mRNAs translation and protect them from decay. LARP1 association with the cap-binding complex is dependent upon mTOR activity and blocked by eIF4E-BP association with eIF4E (Refs 33, 38, 62, 63; Lahr et al., manuscript in preparation), (b) LARP1 is proposed to bind to the mTOR transcript, possibly at its 3'-UTR, and would act to stabilize it in the cytoplasm.³⁶

is unknown; except for this amino extension, the longer protein is identical to the constitutive form (in particular retaining both normal La-Module and DM15 regions) and cancerous lines accumulate both long and short proteins. The overaccumulation of LARP1 mRNA and protein in malignant cells and tissues is convincing. Further, data in Refs 36, 66 suggest that elevated HsLARP1 levels is correlated with an adverse prognosis making HsLARP1 a putative useful biomarker.

Work by S. Blagen's team suggests that HsLARP1 contributes to cancer progression.^{36,40} They show that siRNA-mediated depletion of HsLARP1 significantly decreases cell migration and invasion abilities [tested in HeLa and PC-9 (human adenocarcinoma from lung) cell lines], while stable overexpression of HsLARP1 has opposite effects. Consistent with a positive role in cell migration, HsLARP1 promotes lamellipodia formation and is more concentrated in lamellipodia at the leading edge of migrating cells.⁴⁰ Finally *in vivo* analyses suggest that HsLARP1 increases tumorigenicity: mice injected with HeLa cells overexpressing HsLARP1 show an increased tumor progression as compared to those injected with non-transgenic HeLa cells.³⁶ Altogether

these data support that the human LARP1 protein has an oncogenic potential.

A LINK BETWEEN HSLARP1 AND MTOR REGULATION AND FUNCTION

The mTOR (mammalian Target Of Rapamycin) protein is an evolutionarily conserved serine/threonine kinase that acts as a master signaling hub regulating cell proliferation, growth, motility, apoptosis, and autophagy. In mammals, the mTOR kinase exists in two multiprotein complexes (mTORC1 and mTORC2) composed of common and specific factors. In particular, the mTORC1 complex specifically contains the RAPTOR and PRAS40 proteins. mTORC1, which is activated by nutrient, energy, oxygen, and growth factors and inactivated by stress, positively regulates cell growth and proliferation through promotion of specific mRNAs translation and global changes in protein synthesis, among other processes. The role of mTORC1 in translation is mediated by the S6-Kinases (S6K1/2) and the 4E-BPs (4E-BP1/2), which are both direct targets of mTOR. Activated phospho-S6K promotes translation

while mTOR-catalyzed phosphorylation of 4E-BPs releases them from eIF4E, allowing association of the cap-binding complex and cofactors to the mRNA cap and subsequent initiation of translation. mTORC1 hyperactivation or dysregulation has been associated with several cancer types and roles in cancer biology. The role of mTORC1 in cancer progression is linked to the dysregulated translation of several factors with pro-invasive/metastatic, proliferative, and anti-apoptotic properties (for a recent review see Ref 68). Some of the most recent data on human LARP1 suggest that it plays a role in mTOR signaling pathway related to translation control.³³

In human cells, the LARP1 protein was found to be required to promote global translation, at least at the level of initiation, and consistently was identified as a cap-binding complex-interacting factor.^{33,40} HsLARP1 function in translation relies on its ability to bind the poly(A) binding protein, as it is no longer found associated to the cap complex nor to polyribosomes when unable to contact PABP.³³ HsLARP1 was also found to form a complex with eIF4A, suggesting that its function in translation also requires an association with this helicase. HsLARP1 ability to bind to the cap complex is clearly proportionate to the mTORC1-mediated inhibition of 4E-BPs, but this is to be expected as the majority of the cap complex associated factors were found to be likewise regulated by mTOR activity.³³ Nonetheless, several studies suggest that HsLARP1 role in translation might be to directly stimulate TOP-mRNA translation in a distinct mTORC1-regulated process^{33,38,62,63} (Figure 3). The 5'-Terminal Oligo Pyrimidine (TOP) track is a conserved RNA domain shared by multiple mRNAs coding for components of the translation apparatus that serves to coordinate and coregulate their expression in response to hostile growth conditions.⁶⁹ The translation of TOP mRNAs is highly sensitive to mTORC1 inhibitors, and 4E-BPs inactivation by TOR is prerequisite necessary but not sufficient, to promote their translation.^{70,71} The HsLARP1 protein was found to preferentially promote the polysomal engagement of TOP-mRNAs sensitive to mTOR as compared to non-TOP mTOR-insensitive transcripts. In addition, these mRNAs were specifically enriched in a HsLARP1-directed immunoprecipitation assay³³ and *in vitro* analyses demonstrated the ability of the DM15 domain to directly bind to various TOP sequences (Lahr et al., manuscript in preparation), further supporting a direct role for HsLARP1 in TOP-mRNA translation. HsLARP1 was also proposed to stabilize TOP mRNAs, as its inactivation leads to the downregulation of mature TOP mRNAs without an equivalent decrease in TOP pre-mRNA levels.³⁸

HsLARP1 depletion phenocopies a drug-mediated inhibition of mTOR on cell cycle progression and cell proliferation, but without affecting S6K and 4E-BP phosphorylation, suggesting that HsLARP1 is not a key member of the mTORC1 core complex but more likely one of its direct target. Indeed, HsLARP1 was found to associate with the mTORC1 scaffolding protein RAPTOR³³ and two independent phosphoproteomic surveys identified several HsLARP1 phosphopeptides that are negatively regulated by three different mTOR inhibitors: rapamycin, torin-1 and K0063794.^{62,63} Although evidence for a direct HsLARP1-RAPTOR interaction remain elusive, the sum of published results posit the exciting possibility that HsLARP1 is a mediator of mTORC1 regulatory function on TOP-mRNA translation (see Figure 3 for a proposed model).

In RIP-Chip (RNA ImmunoPrecipitation and micro-array) analyses, Mura and co-workers identified the mTOR mRNA among the several thousand putative targets of HsLARP1. They observed that siRNA-mediated downregulation of HsLARP1 reduces mTOR mRNA half-life and protein levels. Consistent with mTOR downregulation, they report that the phosphorylated levels of 4E-BPs and RPS6 (a target of phospho-S6K) decrease in these HsLARP1 depleted cells. They propose that HsLARP1 acts as a positive regulator of mTOR transcript stability at least in HeLa and PC-9 cell lines.³⁶ In contrast, Tcherkezian and co-workers,³³ using similar western blot analyses although from different cell types, did not observe a significant impact of HsLARP1 depletion on 4E-BPs and RPS6 phosphorylation levels. Therefore, the capacity of HsLARP1 to regulate TOR activity remains an open question.

FUNCTION OF ATLARP1 IN THE STRESS-ACCLIMATION PROGRAM IN PLANTS

The requirement for AtLARP1 in fertility, embryogenesis and cell cycle progression appears so far to be restricted to animals. A full knock out of the Arabidopsis LARP1 protein has no impact on global plant fertility⁴¹ and specific analyses of meiotic figures of *atlarp1-null* gametes show no deficiency (Grelon, M., Bousquet-Antonelli, C. and Deragon, JM, unpublished results). Nevertheless, the expression profiles of AtLARP1 mRNAs suggest that the AtLARP1c rather than AtLARP1a protein could be required for male gametogenesis, a possibility that remains to be explored. Another non-mutually exclusive possibility is that the AtLARP1 proteins show some level of

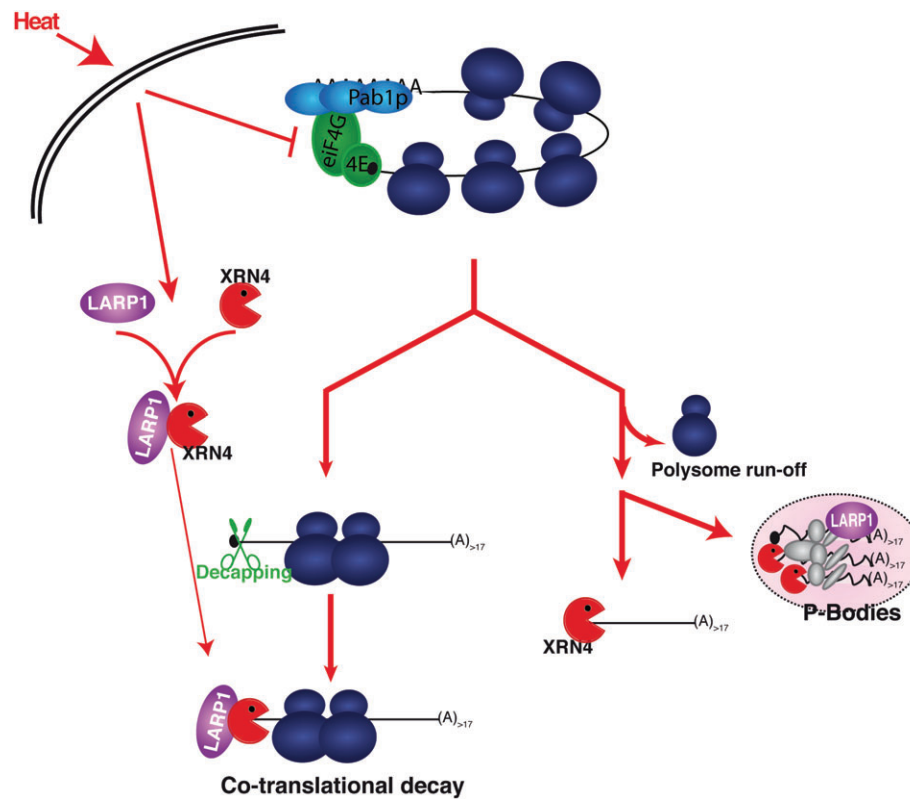


FIGURE 4 | Model for *Arabidopsis thaliana* LARP1 function in response to heat stress. Heat stress triggers the accelerated decay of several thousand mRNAs coding for housekeeping/growth related functions. These transcripts are degraded by a 5'-directed mechanism, catalyzed by XRN4 following a decapping step. Arabidopsis LARP1 is a cofactor of this heat-induced mRNA decay process. In response to heat, it forms a complex with XRN4 and acts to target this enzyme to polysomes, one of the heat triggered mRNA decay sites.⁴¹

redundancy and that multiple mutants need to be analyzed to uncover their physiological roles.

Knockout of the *Arabidopsis AtLARP1* gene does not have any measurable impact on global translation but affects steady-state levels of several hundred to thousands of mRNAs.⁴¹ To test the *AtLARP1* requirement for regulating mRNA levels, whole seedlings were grown at 20°C under continuous light or exposed to a 15 min heat stress at 38°C in the dark.⁴¹ Deletion of *AtLARP1* at 20°C alters levels of less than 450 mRNAs (220 up and 115 downregulated) that mostly code for stress response factors (oxidative, heat, light). Strikingly, *AtLARP1* function is massively reprogrammed under heat stress; the set of genes dependent upon *AtLARP1* at 38°C is completely distinct to that requiring *AtLARP1* at 20°C. When plantlets are shifted at 38°C, more than 4500 mRNAs coding for growth and development housekeeping functions are downregulated in a *AtLARP1*-dependent manner. This downregulation process is, at least in part, the consequence of a heat-induced degradation process through which mRNAs are decapped and rapidly 5'-digested by

XRN4,²⁴ the *Arabidopsis* homolog of the cytoplasmic XRN1 5'-3' exoribonuclease.^{72,73} *AtLARP1* was found to act as a cofactor of the heat induced mRNA degradation process. It putatively forms a direct interaction with XRN4 in response to heat and acts at least, to target XRN4 to the polyribosomes where a subset of transcripts were found to be decapped and co-translationally 5'-digested (Refs 24, 67) (Figure 4). Hence under heat stress, *AtLARP1* appears to have a destabilizing effect on its mRNA targets. In addition to being targeted to polyribosomes in response to heat, *AtLARP1* was also found to be localized to stress granules, suggesting that it might have an additional role in the stress-acclimation response.⁴¹

MOLECULAR AND PHYSIOLOGICAL ROLES OF THE SACCHAROMYCES CEREVISIAE LARP1 PROTEINS: SLF1P AND SRO9P

Saccharomyces cerevisiae only bears three LAM-containing proteins: the genuine La (Lhp1p)²³ and two LARPs: Slf1p and Sro9p^{15,52} (Figure 2(b)).

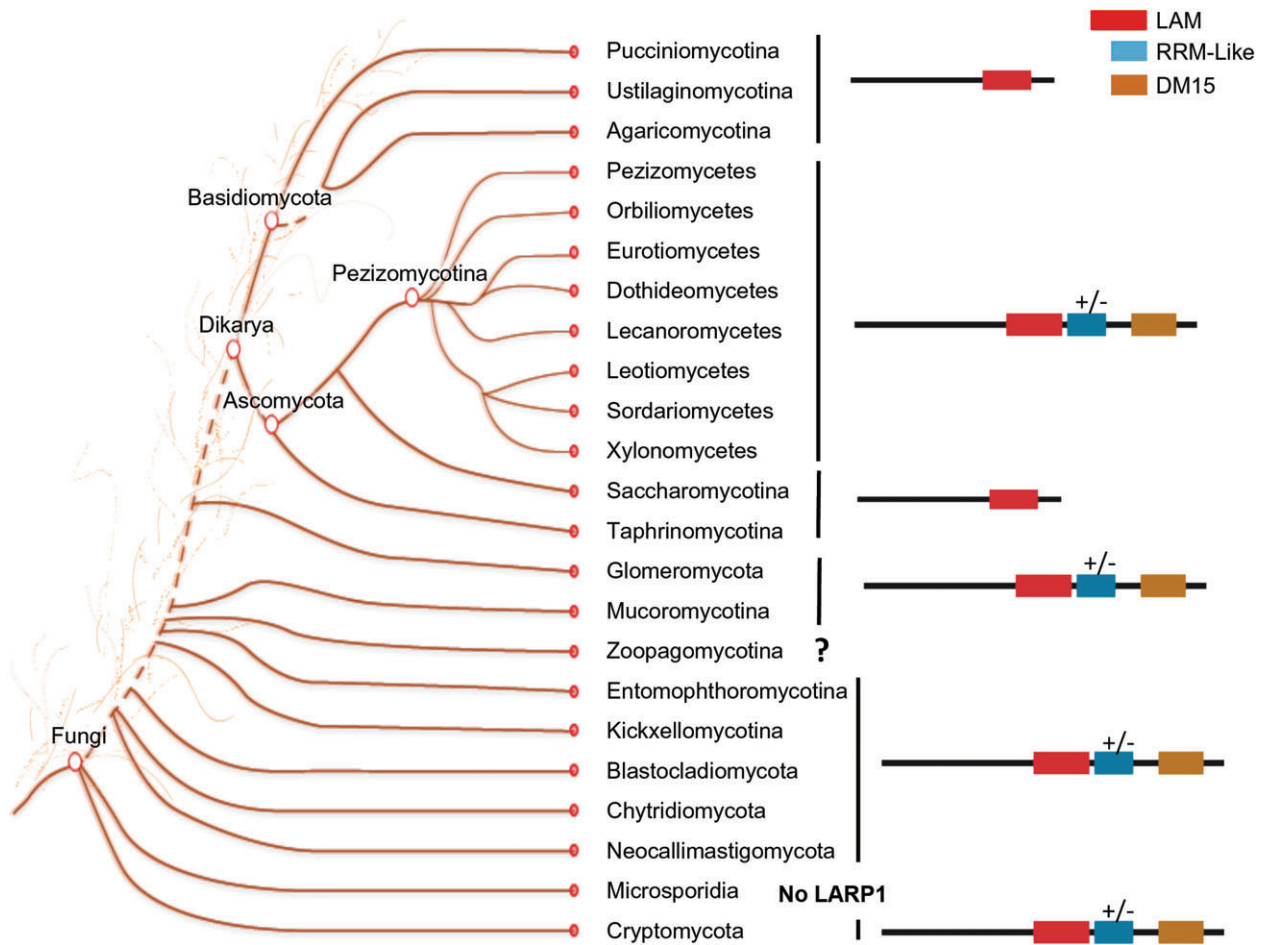


FIGURE 5 | Relationships between major groups of fungi and corresponding structural organization of LARP1 proteins. There is no LARP1 protein in species from the Microsporidia phylum. Since a genome of a basal Zoopagomycotina species has yet to be sequenced, the presence of LARP1 in this subphylum is uncertain. Since the RRM-Like in the LARP1 family is not conserved at the primary sequence level, it is not known if the complete fungi LARP1 proteins also present a La-module. The figure of relationships between major groups of fungi is from the MycoCosm web site.⁷⁴

Even though both Slf1p and Sro9p have a C-terminally located LAM and lack both the RRM1 and DM15 motifs, a comprehensive evolutionary analysis of fungi proteins clearly establishes that they actually belong to the group of LARP1 proteins (Box 2). Very recently, they were also found to share two small boxes (labeled 1 and 2), a lysine (K)-rich patch and an asparagine (N)-rich patch, located upstream of their LAM (Figure 2(b)). These motifs were proposed to be present in LARP homologs from other yeasts, although neither the list of tested yeasts nor the alignment were displayed.³¹

Sro9p and Slf1p are RNA-binding factors⁵² that act as mRNP proteins.¹ They are mainly localized in the cytosol,^{52–54} as well as in stress granules and to a lesser extent in p-bodies.¹ Sro9p but not Slf1p shuttles between the nucleus and the cytoplasm in an mRNA-dependent manner^{53,54} and associates with mRNPs co-transcriptionally⁵³ (Figure 7). They

were both found to bind to actively translating ribosomes^{31,52} and to control the steady-state levels of several hundred mRNAs affecting common but also distinct sets of transcripts.^{31,54} These data suggest that, as LARP1 proteins from other eukaryotes, Sro9p and Slf1p are mRNA-binding factors involved in the post-transcriptional control of RNA-regulon expression through regulation of their translation and/or stability.

Several genetic screens identified Sro9p as a multicopy suppressor of various mutations.^{55–57} Sro9p was found to suppress the thermosensitive phenotype of the null mutant of *rbp4*, a subunit of the RNA polymerase II.⁵⁷ Transcription assays conducted with *rbp4-null* crude extracts showed that addition of Sro9p recombinant protein enhances the accumulation of select mRNAs *in vitro*. *In vivo*, Sro9p overexpression corrected the defect of induction of multiple heat shock genes as well as some inducible

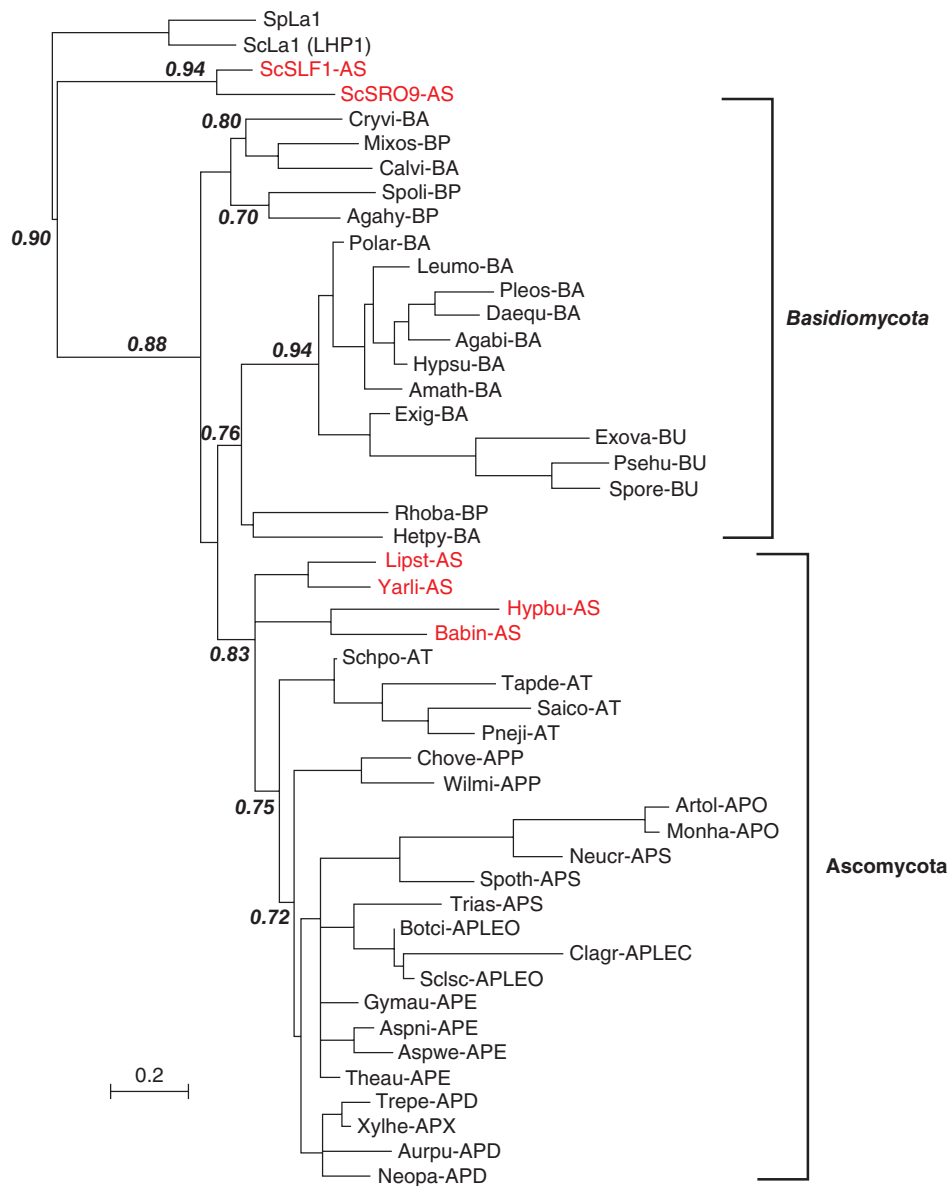


FIGURE 6 | Phylogenetic analysis of fungi LARP1 proteins based on the alignment of their LAM. Two fungi genuine La proteins (LHP1 from *S. cerevisiae* and SpLa1 *S. pombe*) are used as outgroup. Selected informative statistical supports (approximate likelihood-ratio test (aLRT) data) are indicated. The common names (ScSLF1, ScSRO9) for the two *S. cerevisiae* LARP1 are used. For all other LARP1, a species code name is indicated followed by a code for its classification (see below and Figure 1). LARP1 from species in the same subphylum as *S. cerevisiae* are in red. The species codes are the following: Agabi: *Agaricus bisporus*, Agahy: *Agaricostilbum hyphaenes*, Amath: *Amanita thiersii*, Artol: *Arthrobotrys oligospora*, Aspni: *Aspergillus niger*, Aspwe: *Aspergillus wentii*, Aurpu: *Aureobasidium pullulans*, Babin: *Babjeviella inositovora*, Botci: *Botrytis cinerea*, Calvi: *Calocera viscosa*, Chove: *Choireomyces venosus*, Clagr: *Cladonia grayi*, Cryvi: *Cryptococcus vishniacii*, Daequ: *Daedalea quercina*, Exigl: *Exidia glandulosa*, Exova: *Exobasidium vaccinii*, Gymau: *Gymnascella aurantiaca*, Hetpy: *Heterogastrium pycnidioideum*, Hypbu: *Hyphopichia burtonii*, Hypsu: *Hypholoma sublateralium*, Leumo: *Leucogyrophana Mollusca*, Lipst: *Lipomyces starkeyi*, Mixos: *Mixia osmundae*, Monha: *Monacrosporium haptotylum*, Neopa: *Neofusicoccum parvum*, Neucr: *Neurospora crassa*, Pnej: *Pneumocystis jirovecii*, Pleos: *Pleurotus ostreatus*, Polar: *Polyporus arcularius*, Psehu: *Pseudozyma hubeiensis*, Rhoba: *Rhodotorula sp.*, Saico: *Saitoella complicate*, Schpo: *Schizosaccharomyces pombe*, Scpsc: *Sclerotinia sclerotiorum*, Spoli: *Sporobolomyces linderiae*, Spore: *Sporisorium reilianum*, Spoth: *Sporotrichum thermophile*, Theau: *Thermoascus aurantiacus*, Trep: *Trematosphaeria pertusa*, Trias: *Trichoderma asperellum*, Spoth: *Sporotrichum thermophile*, Wilmi: *Wilcoxina mikolae*, Xylhe: *Xylona heveae*, Yarli: *Yarrowia lipolytica*. The classification codes are the following: APD: Ascomycota Pezizomycotina Dothideomycetes, APE: Ascomycota Pezizomycotina Eurotiomycetes, APLEC: Ascomycota Pezizomycotina Lecanoromycetes, APLEO: Ascomycota Pezizomycotina Leotiomycetes, APO: Ascomycota Pezizomycotina Orbiliomycetes, APP: Ascomycota Pezizomycotina Pezizomycetes, APS: Ascomycota Pezizomycotina Sordariomycetes, APX: Ascomycota Pezizomycotina Xylonomycetes, AS: Ascomycota Saccharomycotina, AT: Ascomycota Taphrinomycotina, BA: Basidiomycota Agaricomycotina, BP: Basidiomycota Pucciniomycotina, BU: Basidiomycota Ustilaginomycotina.

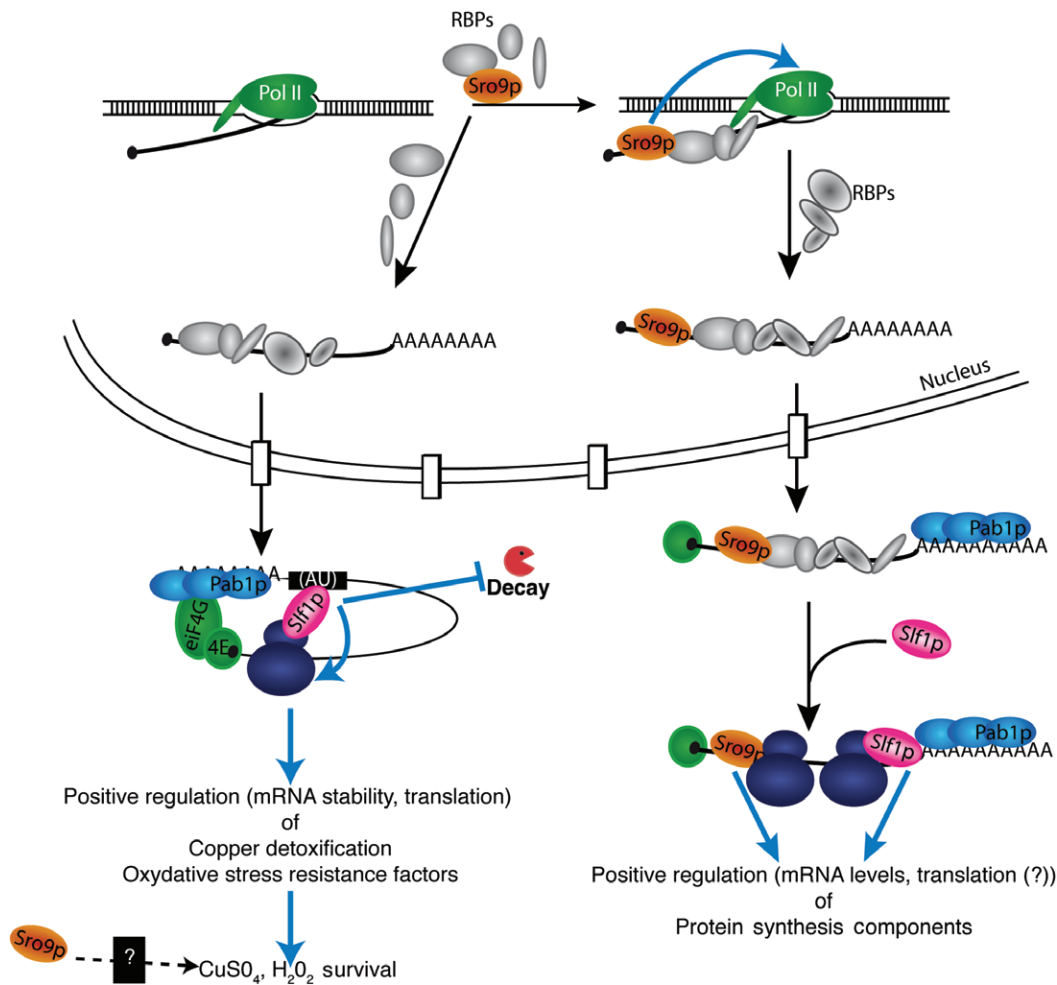


FIGURE 7 | Model for *S. cerevisiae* Slf1p and Sro9p function.^{31,53,54} Slf1p and Sro9p are mRNA-binding proteins¹ with distinct and overlapping functions. Sro9p, but not Slf1p was found to shuttle between nucleus and cytoplasm and to associate to mRNPs co-translationally.⁵³ Sro9p is proposed to promote pol II transcription and/or cytoplasmic stability of its mRNA targets.⁵⁷ Sro9p and Slf1p are proposed to cooperate to promote expression (through mRNA stabilization and/or translation stimulation) of protein synthesis components.^{31,54} Slf1p specifically stabilizes mRNAs coding for copper detoxification factors⁵⁴ and stimulates translation of oxidative stress response genes in the context of oxidative stress.³¹ Slf1p could directly bind to a 3'-UTR located, 21-nt long AU rich element shared by oxidative stress response mRNAs enriched in the Slf1p bound fraction.³¹ Sro9p is required for yeast survival to copper and H₂O₂ exposure, suggesting that it might also be required for stress acclimation but through a distinct molecular mechanism.^{31,54}

transcripts such as GAL1. A stimulatory role for Sro9p in pol II transcription is supported by its role as nucleocytoplasmic protein, but work by Ref 57 also established that Sro9p has a global role in promoting mRNA stability. Hence the *rbp4-null* phenotype suppression mediated by Sro9p overexpression is probably the result of a combination of both its transcriptional and post-transcriptional activities. Sro9p was also identified as a multicopy suppressor of deficiencies in the secretory pathway⁵⁵ and bud formation,⁵⁶ most likely because it promotes actin cytoskeleton formation and/or stability.⁵⁶ The molecular roles of Sro9p underlying such functions remain unknown at present, but given its mRNA-binding

ability one can propose that it does not directly act to assist actin filament formation and consistently Sro9p was not found to co-sediment with actin filaments.⁵²

Complex purification assays identified Sro9p as part of the high molecular weight complex (HMC) formed around Hap1p, a transcription factor which activity is repressed by the Ydj1-Hsp70 chaperone and putatively Sro9p in the absence of heme.^{58,59} The biochemical characterization of Hap1p HMC supports that Sro9p is an actual component of the complex,⁵⁹ suggesting a role distinct to that of an mRNP protein. La and LARPs (except for LARP1 which could not be tested for technical reasons) are known RNA chaperones.⁷⁵ These Sro9p results raise

the intriguing possibility that a LARP could also act as a protein chaperone or co-chaperone.

Despite the observation that combined deletions of the *SRO9* and *SLF1* genes has no phenotypic impact on yeast growth under normal conditions,⁵² molecular studies suggest that they have distinct but also partially redundant functions.^{31,54} Genome-wide analyses establish an overlapping positive regulatory role of Slf1p and Sro9p on levels of mRNAs coding for protein synthesis components.^{31,54} Likewise, the common pool of their putative mRNA targets identified by RIP-seq/Chip assays, code for factors belonging to the 'protein synthesis' functional category and code for ribosomal proteins. Sro9p and Slf1p could hence cooperate to promote (through transcript stabilization and/or translation), the production of components of the protein synthesis machinery of the cell (Figure 7).

SLF1 was identified as a suppressor of the copper hypersensitive *cup14* mutant.⁶⁰ Slf1p promotes copper detoxification through stabilization of mRNAs coding for copper resistance genes.⁵⁴ How Slf1p acts to protect these mRNAs from degradation is not clear, but mutations found to be required for the genuine La RNA-binding activity made in the Slf1p-LAM abrogate its ability to confer copper resistance.⁵⁴ Consistent with a function in copper resistance, Slf1p was also found to be necessary for oxidative stress survival (exposure to H₂O₂). Here again, *slf1* deletion downregulates levels of oxidative stress response transcripts and its putative mRNA targets (identified by RIP-seq assays) encode factors enriched in 'oxidative stress response'.³¹ Although a direct role of Slf1p in stabilizing at least some of these mRNAs is a possibility that was not tested, work by Ref 31 supports that Slf1p promotes translation of specific oxidative resistance genes in the context of stress-induced general translation inhibition. It is not known what molecular mechanism governs Slf1p function in translation, but its recruitment to polysomes was found to require both its LAM and the conserved N-terminal patches 1 and 2 (Figure 2(b)). Also, analysis of Slf1p putative oxidative stress targets identified a shared AU-rich repeat in their 3'-UTR, suggesting that Slf1p might coregulate their translation by binding to this putative regulatory sequence³¹ (Figure 7).

Slf1p and Sro9p are RBPs^{1,52} and their LAM is required for their function,^{31,54,57} and appear to contribute to selective mRNA-binding.⁵⁴ However, the LAM is not able to bind RNA by itself,^{26–28} and additional *cis*-domains that would cooperate with the LAM in *S. cerevisiae*LARPs have not been detected so far.^{15,31} Hence, how Slf1p and Sro9p bind RNA remains a challenging enigma.

CONCLUSION

In summary, LARP1 proteins constitute an emerging group of mRNP factors that are physiologically important during developmental or environmental transitions, when cells modify their pattern of gene expression to divide, adopt new identities or new metabolic activities. De facto, *larp1* inactivation has only limited physiological impacts in somatic tissues, quiescent cells or under normal growth conditions. LARP1 proteins work by either regulating specific key transcripts, such as *fem-3* in worms, or 'RNA-operons' as suggested by data from human, yeast, and Arabidopsis. At the molecular level, LARP1 seems to both promote translation and hence protect its target from decay, but also to actively participate in mRNA degradation. Whether this functional duality results of lineage specific evolutionary specialization or is a conserved characteristic of most eukaryote LARP1 proteins is not clear at present. Nonetheless, from an evolutionary point of view, it is likely that both properties were at least initially present in ancestral LARP1, since distantly related lineages (such as *C. elegans* and Arabidopsis or yeast and human) possess proteins with similar properties (promoting respectively decay or translation). Common functional themes for LARP1 in eukaryotes are also emerging such as its requirement for the post-transcriptional regulation of genes coding for ribosomal proteins and component of the protein production machinery, its ability to bind the PABP and to associate with translating ribosomes, its association with p-bodies and stress granules and its role in regulating cell proliferation and division in animals. Altogether these observations suggest that LARP1, according to the developmental, cellular, and environmental context, could shift from one molecular function to the other.

To better understand the precise mechanistic functions of LARP1 proteins, the next challenge will be to identify their direct mRNA and protein targets in the various developmental and environmental contexts where they play key roles. How LARP1 proteins recognize and accommodate their RNA targets are other intriguing questions. The DM15 motif is so highly conserved that more than 90% identity can be observed when respectively aligning the A, B, and C modules from protist, fungal, plant, and animal proteins,¹⁵ but its only known function so far is to bind TOP sequences, which are not found in every eukaryotes. Obtaining an atomic resolution of how the DM15 motif accommodates TOP sequences is a necessary step toward the understanding of LARP1 function, as it will shed light on what makes a good DM15 RNA ligand. How LARP1 protein functions

are controlled and reprogrammed is also a promising path to explore. Given HsLARP1 role as putative direct target of the mTORC1 complex and its potential

use as a biomarker in several cancer types, it might not be long before we read again exciting articles about LARP1 proteins.

ACKNOWLEDGMENTS

We would like to thank Andrea J. Berman (Department of Biological Sciences, University of Pittsburgh) for generously accepting to share data about the Human LARP1 DM15 structure and function prior to publication. We also want to thank her for the critical reading of the manuscript. The authors of this article are funded by the University of Perpignan (UPVD) and the CNRS.

REFERENCES

- Mitchell SF, Jain S, She M, Parker R. Global analysis of yeast mRNPs. *Nat Struct Mol Biol* 2013, 20:127–133.
- Ambrosone A, Costa A, Leone A, Grillo S. Beyond transcription: RNA-binding proteins as emerging regulators of plant response to environmental constraints. *Plant Sci* 2012, 182:12–18.
- Baltz AG, Munschauer M, Schwanhausser B, Vasile A, Murakawa Y, Schueler M, Youngs N, Penfold-Brown D, Drew K, Milek M, et al. The mRNA-bound proteome and its global occupancy profile on protein-coding transcripts. *Mol Cell* 2012, 46:674–690.
- Castello A, Fischer B, Eichelbaum K, Horos R, Beckmann BM, Strein C, Davey NE, Humphreys DT, Preiss T, Steinmetz LM, et al. Insights into RNA biology from an atlas of mammalian mRNA-binding proteins. *Cell* 2012, 149:1393–1406.
- Keene JD. RNA regulons: coordination of post-transcriptional events. *Nat Rev Genet* 2007, 8: 533–543.
- Decker CJ, Parker R. P-bodies and stress granules: possible roles in the control of translation and mRNA degradation. *Cold Spring Harb Perspect Biol* 2012, 4:a012286.
- Garneau NL, Wilusz J, Wilusz CJ. The highways and byways of mRNA decay. *Nat Rev Mol Cell Biol* 2007, 8:113–126.
- Parker R. RNA degradation in *Saccharomyces cerevisiae*. *Genetics* 2012, 191:671–702.
- Liu B, Qian SB. Translational reprogramming in cellular stress response. *WIREs RNA* 2014, 5:301–315.
- Kedersha N, Ivanov P, Anderson P. Stress granules and cell signaling: more than just a passing phase? *Trends Biochem Sci* 2013, 38:494–506.
- Balagopal V, Fluch L, Nissan T. Ways and means of eukaryotic mRNA decay. *Biochim Biophys Acta* 2012, 1819:593–603.
- Barckmann B, Simonelig M. Control of maternal mRNA stability in germ cells and early embryos. *Biochim Biophys Acta* 2013, 1829:714–724.
- Zanetti S, Puoti A. Sex determination in the *Caenorhabditis elegans* germline. *Adv Exp Med Biol* 2013, 757: 41–69.
- Bayfield MA, Yang R, Maraia RJ. Conserved and divergent features of the structure and function of La and La-related proteins (LARPs). *Biochim Biophys Acta* 2010, 1799:365–378.
- Bousquet-Antonelli C, Deragon JM. A comprehensive analysis of the La-motif protein superfamily. *RNA* 2009, 15:750–764.
- Wolin SL, Cedervall T. The La protein. *Annu Rev Biochem* 2002, 71:375–403.
- Francoeur AM, Mathews MB. Interaction between VA RNA and the lupus antigen La: formation of a ribonucleoprotein particle in vitro. *Proc Natl Acad Sci USA* 1982, 79:6772–6776.
- Lerner MR, Boyle JA, Hardin JA, Steitz JA. Two novel classes of small ribonucleoproteins detected by antibodies associated with lupus erythematosus. *Science* 1981, 211:400–402.
- Rinke J, Steitz JA. Precursor molecules of both human 5S ribosomal RNA and transfer RNAs are bound by a cellular protein reactive with anti-La lupus antibodies. *Cell* 1982, 29:149–159.
- Stefano JE. Purified lupus antigen La recognizes an oligouridylylate stretch common to the 3' termini of RNA polymerase III transcripts. *Cell* 1984, 36:145–154.
- Chambers JC, Kenan D, Martin BJ, Keene JD. Genomic structure and amino acid sequence domains of the human La autoantigen. *J Biol Chem* 1988, 263: 18043–18051.
- Van Horn DJ, Yoo CJ, Xue D, Shi H, Wolin SL. The La protein in *Schizosaccharomyces pombe*: a conserved yet dispensable phosphoprotein that functions in tRNA maturation. *RNA* 1997, 3:1434–1443.
- Yoo CJ, Wolin SL. La proteins from *Drosophila melanogaster* and *Saccharomyces cerevisiae*: a yeast homolog of the La autoantigen is dispensable for growth. *Mol Cell Biol* 1994, 14:5412–5424.

24. Merret R, Martino L, Bousquet-Antonelli C, Fneich S, Descombin J, Billey E, Conte MR, Deragon JM. The association of a La module with the PABP-interacting motif PAM2 is a recurrent evolutionary process that led to the neofunctionalization of La-related proteins. *RNA* 2013, 19:36–50.
25. Dong G, Chakshumathi G, Wolin SL, Reinisch KM. Structure of the La motif: a winged helix domain mediates RNA binding via a conserved aromatic patch. *EMBO J* 2004, 23:1000–1007.
26. Martino L, Pennell S, Kelly G, Busi B, Brown P, Atkinson RA, Salisbury NJ, Ooi ZH, See KW, Smerdon SJ, et al. Synergic interplay of the La motif, RRM1 and the interdomain linker of LARP6 in the recognition of collagen mRNA expands the RNA binding repertoire of the La module. *Nucleic Acids Res* 2015, 43:645–660.
27. Alfano C, Sanfelice D, Babon J, Kelly G, Jacks A, Curry S, Conte MR. Structural analysis of cooperative RNA binding by the La motif and central RRM domain of human La protein. *Nat Struct Mol Biol* 2004, 11:323–329.
28. Teplova M, Yuan YR, Phan AT, Malinina L, Ilin S, Teplov A, Patel DJ. Structural basis for recognition and sequestration of UUU(OH) 3' termini of nascent RNA polymerase III transcripts by La, a rheumatic disease autoantigen. *Mol Cell* 2006, 21:75–85.
29. Kotik-Kogan O, Valentine ER, Sanfelice D, Conte MR, Curry S. Structural analysis reveals conformational plasticity in the recognition of RNA 3' ends by the human La protein. *Structure* 2008, 16:852–862.
30. Clery A, Blatter M, Allain FH. RNA recognition motifs: boring? Not quite. *Curr Opin Struct Biol* 2008, 18:290–298.
31. Kershaw CJ, Costello JL, Castelli LM, Talavera D, Rowe W, Sims PFG, Ashe MP, Hubbard SJ, Pavitt GD, Grant CM. The yeast related protein Slf1p is a key activator of translation during oxidative stress response. *PLoS Genet* 2015, 11:e1004903.
32. Nykamp K, Lee MH, Kimble J. *C. elegans* La-related protein, LARP-1, localizes to germline P bodies and attenuates Ras-MAPK signaling during oogenesis. *RNA* 2008, 14:1378–1389.
33. Tcherkezian J, Cargnello M, Romeo Y, Huttlin EL, Lavoie G, Gygi SP, Roux PP. Proteomic analysis of cap-dependent translation identifies LARP1 as a key regulator of 5'TOP mRNA translation. *Genes Dev* 2014, 28:357–371.
34. Chauvet S, Maurel-Zaffran C, Miassod R, Jullien N, Pradel J, Aragnol D. *dlarp*, a new candidate Hox target in *Drosophila* whose orthologue in mouse is expressed at sites of epithelium/mesenchymal interactions. *Dev Dyn* 2000, 218:401–413.
35. Blagden SP, Gatt MK, Archambault V, Lada K, Ichihara K, Lilley KS, Inoue YH, Glover DM. *Drosophila* Larp associates with poly(A)-binding protein and is required for male fertility and syncytial embryo development. *Dev Biol* 2009, 334:186–197.
36. Mura M, Hopkins TG, Michael T, Abd-Latip N, Weir J, Aboagye E, Mauri F, Jameson C, Sturge J, Gabra H, et al. LARP1 post-transcriptionally regulates mTOR and contributes to cancer progression. *Oncogene* 2015. doi:10.1038/nc.2014.428. Available at: <http://www.nature.com/nc/journal/vaop/ncurrent/full/nc2014428a.html>.
37. Schmid M, Davison TS, Henz SR, Pape UJ, Demar M, Vingron M, Scholkopf B, Weigel D, Lohmann JU. A gene expression map of *Arabidopsis thaliana* development. *Nat Genet* 2005, 37:501–506.
38. Aoki K, Adachi S, Homoto M, Kusano H, Koike K, Natsume T. LARP1 specifically recognizes the 3' terminus of poly(A) mRNA. *FEBS Lett* 2013, 587:2173–2178.
39. Ichihara K, Shimizu H, Taguchi O, Yamaguchi M, Inoue YH. A *Drosophila* orthologue of larp protein family is required for multiple processes in male meiosis. *Cell Struct Funct* 2007, 32:89–100.
40. Burrows C, Abd Latip N, Lam SJ, Carpenter L, Sawicka K, Tzolovsky G, Gabra H, Bushell M, Glover DM, Willis AE, et al. The RNA binding protein Larp1 regulates cell division, apoptosis and cell migration. *Nucleic Acids Res* 2010, 38:5542–5553.
41. Merret R, Descombin J, Juan YT, Favory JJ, Carpentier MC, Chaparro C, Charng YY, Deragon JM, Bousquet-Antonelli C. XRN4 and LARP1 are required for a heat-triggered mRNA decay pathway involved in plant acclimation and survival during thermal stress. *Cell Rep* 2013, 5:1279–1293.
42. Reschke M, Clohessy JG, Seitzer N, Goldstein DP, Breitkopf SB, Schmolze DB, Ala U, Asara JM, Beck AH, Pandolfi PP. Characterization and analysis of the mammalian riboproteome. *Cell Rep* 2013, 4:1276–1287.
43. Zanetti S, Grinschgl S, Meola M, Belfiore M, Rey S, Bianchi P, Puoti A. The sperm-oocyte switch in the *C. elegans* hermaphrodite is controlled through steady-state levels of the *fem-3* mRNA. *RNA* 2012, 18:1385–1394.
44. Zanin E, Pacquelet A, Scheckel C, Ciosk R, Gotta M. LARP-1 promotes oogenesis by repressing *fem-3* in the *C. elegans* germline. *J Cell Sci* 2010, 123:2717–2724.
45. Reinke V, Smith HE, Nance J, Wang J, Van Doren C, Begley R, Jones SJ, Davis EB, Scherer S, Ward S, et al. A global profile of germline gene expression in *C. elegans*. *Mol Cell* 2000, 6:605–616.
46. Gonczy P, Echeverri C, Oegema K, Coulson A, Jones SJ, Copley RR, Duperon J, Oegema J, Brehm M, Cassin E, et al. Functional genomic analysis of cell division in *C. elegans* using RNAi of genes on chromosome III. *Nature* 2000, 408:331–336.
47. Kamath RS, Fraser AG, Dong Y, Poulin G, Durbin R, Gotta M, Kanapin A, Le Bot N, Moreno S, Sohrmann M, et al. Systematic functional analysis of the *Caenorhabditis elegans* genome using RNAi. *Nature* 2003, 421:231–237.

48. Sonnichsen B, Koski LB, Walsh A, Marschall P, Neumann B, Brehm M, Alleaume AM, Artelt J, Bettencourt P, Cassin E, et al. Full-genome RNAi profiling of early embryogenesis in *Caenorhabditis elegans*. *Nature* 2005, 434:462–469.
49. Kadyrova LY, Habara Y, Lee TH, Wharton RP. Translational control of maternal cyclin B mRNAs by Nanos in *Drosophila* germline. *Development* 2007, 134:1519–1527.
50. Kraemer B, Crittenden S, Gallegos M, Moulder G, Barstead R, Kimble J, Wickens M. NANOS-3 and FBF proteins physically interact to control the sperm-oocyte switch in *Caenorhabditis elegans*. *Curr Biol* 1999, 9:1009–1018.
51. Sonoda J, Wharton RP. Recruitment of Nanos to hunchback mRNA by Pumilio. *Genes Dev* 1999, 13:2704–2712.
52. Sobel SG, Wolin SL. Two yeast La motif-containing proteins are RNA-binding proteins that associate with polyribosomes. *Mol Biol Cell* 1999, 10:3849–3862.
53. Rother S, Burkert C, Brunger KM, Mayer A, Kieser A, Strasser K. Nucleocytoplasmic shuttling of the La motif-containing protein Sro9 might link its nuclear and cytoplasmic functions. *RNA* 2010, 16:1393–1401.
54. Schenk L, Meinel DM, Strasser K, Gerber AP. La-motif-dependent mRNA association with Slf1 promotes copper detoxification in yeast. *RNA* 2012, 18:449–461.
55. Tsukada M, Gallwitz D. Isolation and characterization of SYS genes from yeast, multicopy suppressors of the functional loss of the transport GTPase Ypt6p. *J Cell Sci* 1996, 109(Pt 10):2471–2481.
56. Kagami M, Toh-e A, Matsui Y. SRO9, a multicopy suppressor of the bud growth defect in the *Saccharomyces cerevisiae* rho3-deficient cells, shows strong genetic interactions with tropomyosin genes, suggesting its role in organization of the actin cytoskeleton. *Genetics* 1997, 147:1003–1016.
57. Tan Q, Li X, Sadhale PP, Miyao T, Woychik NA. Multiple mechanisms of suppression circumvent transcription defects in an RNA polymerase mutant. *Mol Cell Biol* 2000, 20:8124–8133.
58. Hon T, Lee HC, Hach A, Johnson JL, Craig EA, Erdjument-Bromage H, Tempst P, Zhang L. The Hsp70-Ydj1 molecular chaperone represses the activity of the heme activator protein Hap1 in the absence of heme. *Mol Cell Biol* 2001, 21:7923–7932.
59. Lan C, Lee HC, Tang S, Zhang L. A novel mode of chaperone action: heme activation of Hap1 by enhanced association of Hsp90 with the repressed Hsp70-Hap1 complex. *J Biol Chem* 2004, 279:27607–27612.
60. Yu W, Farrell R, Stillman D, Swinge D. Identification of SLF1 as a new copper homeostasis gene involved in copper sulfide mineralization in *Saccharomyces cerevisiae*. *Mol Biol Cell* 1996, 16:2464–2472.
61. Zhang B, Jia J, Yang M, Yan C, Han Y. Overexpression of a LAM domain containing RNA-binding protein LARP1c induces precocious leaf senescence in *Arabidopsis*. *Mol Cells* 2012, 34:367–374.
62. Hsu PP, Kang SA, Rameseder J, Zhang Y, Ottina KA, Lim D, Peterson TR, Choi Y, Gray NS, Yaffe MB, et al. The mTOR-regulated phosphoproteome reveals a mechanism of mTORC1-mediated inhibition of growth factor signaling. *Science* 2011, 332:1317–1322.
63. Yu Y, Yoon SO, Poulgiannis G, Yang Q, Ma XM, Villen J, Kubica N, Hoffman GR, Cantley LC, Gygi SP, et al. Phosphoproteomic analysis identifies Grb10 as an mTORC1 substrate that negatively regulates insulin signaling. *Science* 2011, 332:1322–1326.
64. Eswaran J, Horvath A, Godbole S, Reddy SD, Mudvari P, Ohshiro K, Cyanam D, Nair S, Fuqua SA, Polyak K, et al. RNA sequencing of cancer reveals novel splicing alterations. *Sci Rep* 2013, 3:1689.
65. Selcuklu SD, Donoghue MT, Rehmet K, de Souza GM, Fort A, Kovvuru P, Muniyappa MK, Kerin MJ, Enright AJ, Spillane C. MicroRNA-9 inhibition of cell proliferation and identification of novel miR-9 targets by transcriptome profiling in breast cancer cells. *J Biol Chem* 2012, 287:29516–29528.
66. Xie C, Huang L, Xie S, Xie D, Zhang G, Wang P, Peng L, Gao Z. LARP1 predict the prognosis for early-stage and AFP-normal hepatocellular carcinoma. *J Transl Med* 2013, 11:272.
67. Merret R, Nagarajan VK, Carpentier M-C, Park S, Favory J-J, Descombin J, Picart C, Charng Y-y, Green PJ, Deragon J-M, et al. Heat-induced ribosome pausing triggers mRNA co-translational decay in *Arabidopsis thaliana*. *Nucleic Acids Res* 2015. In press.
68. Tsukumo Y, Laplante M, Parsyan A, Ruggero D, Fonseca B. mTOR and regulation of translation. In: Parsyan A, ed. *Translation and Its Regulation in Cancer Biology and Medicine*. Dordrecht: Springer; 2014, 307–343.
69. Meyuhos O, Kahan T. The race to decipher the top secrets of TOP mRNAs. *Biochim Biophys Acta* 2014. doi:10.1016/j.bbagr.2014.08.015. Available at: <http://www.sciencedirect.com/science/article/pii/S1874939914002466>.
70. Hsieh AC, Liu Y, Edlind MP, Ingolia NT, Janes MR, Sher A, Shi EY, Stumpf CR, Christensen C, Bonham MJ, et al. The translational landscape of mTOR signalling steers cancer initiation and metastasis. *Nature* 2012, 485:55–61.
71. Thoreen CC, Chantranupong L, Keys HR, Wang T, Gray NS, Sabatini DM. A unifying model for mTORC1-mediated regulation of mRNA translation. *Nature* 2012, 485:109–113.
72. Kastenmayer JP, Johnson MA, Green PJ. Analysis of XRN orthologs by complementation of yeast mutants and localization of XRN-GFP fusion proteins. *Methods Enzymol* 2001, 342:269–282.

73. Kastenmayer JP, Green PJ. Novel features of the XRN-family in Arabidopsis: evidence that AtXRN4, one of several orthologs of nuclear Xrn2p/Rat1p, functions in the cytoplasm. *Proc Natl Acad Sci USA* 2000, 97:13985–13990.
74. Grigoriev IV, Nikitin R, Haridas S, Kuo A, Ohm R, Otilar R, Riley R, Salamov A, Zhao X, Korzeniewski F, et al. MycoCosm portal: gearing up for 1000 fungal genomes. *Nucleic Acids Res* 2014, 42: D699–D704.
75. Hussain RH, Zawawi M, Bayfield MA. Conservation of RNA chaperone activity of the human La-related proteins 4, 6 and 7. *Nucleic Acids Res* 2013, 41:8715–8725.

FURTHER READING

In 2010 a group of scientists from many disciplines with a shared interest in the study of La-Motif containing proteins decided to gather and created The LARP Society logo (<http://www.larp-society.com/>). Our Society is a non profit scientific organization aimed at promoting the highest standards of research into La-domain containing proteins, favouring the exchange of information in all aspect of research into the La and LARP proteins and providing support and education to junior researchers in the field. The LARP Society has been organizing biennale international conferences since 2010. Information about meetings, La and LARP protein sequences, news, etc. are freely available through the LARPSoc website and its facebook page at <https://www.facebook.com/Larpsociety?ref=hl>.



Logo of the LARP society.