HHS Public Access

Author manuscript

Biol Rev Camb Philos Soc. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

Biol Rev Camb Philos Soc. 2016 May ; 91(2): 288–310. doi:10.1111/brv.12170.

Looking into laminin receptor: critical discussion regarding the non-integrin 37/67-kDa laminin receptor/RPSA protein

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Abstract

The 37/67-kDa laminin receptor (LAMR/RPSA) was originally identified as a 67-kDa binding protein for laminin, an extracellular matrix glycoprotein that provides cellular adhesion to the basement membrane. LAMR has evolutionary origins, however, as a 37-kDa RPS2 family ribosomal component. Expressed in all domains of life, RPS2 proteins have been shown to have remarkably diverse physiological roles that vary across species. Contributing to laminin binding, ribosome biogenesis, cytoskeletal organization, and nuclear functions, this protein governs critical cellular processes including growth, survival, migration, protein synthesis, development, and differentiation. Unsurprisingly given its purview, LAMR has been associated with metastatic cancer, neurodegenerative disease and developmental abnormalities. Functioning in a receptor capacity, this protein also confers susceptibility to bacterial and viral infection. LAMR is clearly a molecule of consequence in human disease, directly mediating pathological events that make it a prime target for therapeutic interventions. Despite decades of research, there are still a large number of open questions regarding the cellular biology of LAMR, the nature of its ability to bind laminin, the function of its intrinsically disordered C-terminal region and its conversion from 37 to 67 kDa. This review attempts to convey an in-depth description of the complexity surrounding this multifaceted protein across functional, structural and pathological aspects.

Keywords

37 67 kDa laminin receptor; RPSA; 37LRP; 67LR; YIGSR; p40; 37LBP

I. INTRODUCTION

Laminins are a family of large (400–900 kDa) heterotrimeric glycoproteins typically found within the basal lamina region of the extracellular matrix. There are currently 15 known laminin proteins, each consisting of an α, β and γ-chain organized into a complex cruciform

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structure. Laminins have crucial and diverse rolls in physiology, influencing cellular adhesion, migration, homing, proliferation, polarity, differentiation, tissue development and cellular communication with the extracellular environment (Miner, 2008; Ryan *et al.*, 1996; Yurchenco, 2011).

Shortly after the discovery of laminins and observation of their importance in tumour metastasis, the search for cell-surface proteins mediating their effects identified receptors of two main classes: the integrins and the non-integrin laminin receptors. The first to be revealed was the non-integrin 67-kDa laminin receptor, identified *via* binding to immobilized laminin-1 (α1β1γ1) (Lesot, Kuhl & Mark, 1983; Malinoff & Wicha, 1983; Rao *et al.*, 1983). Further study demonstrated this protein might arise from a 32–33 kDa precursor that migrates at approximately 37 kDa in sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) (Rao *et al.*, 1989; Wewer *et al.*, 1986). Quite separately, a protein called p40 in a different line of investigation was found to be equivalent (Makrides *et al.*, 1988; McCaffery, Neve & Drager, 1990) and later confirmed to be a component of the 40S ribosome now called ribosomal protein SA (RPSA) (Tohgo *et al.*, 1994). Hence, this protein has been called 37/67-kDa laminin receptor (37LR, 67LR, LAMR1), 32 kDa laminin binding protein (LBP), 32 kDa laminin binding protein precursor (LBP-32, 37LRP), p40 and RPSA. This review notes that the most common descriptive term is 37/67-kDa laminin receptor and will refer to the protein as LAMR, designating the relevant species when possible in superscript (i.e. $LAMR^{37/67}$) even in instances referring to non-laminin binding homologs.

The functions of LAMR have proven to be surprisingly diverse, representing a repertoire that extends far beyond cell anchoring *via* laminins to include ribosomal biogenesis and translation, pre-rRNA processing, roles in cellular migration, invasion, viability and growth, cytoskeleton (re)organization as well as chromatin and histone binding. These functions reflect the protein's presence in the plasma membrane, ribosomes, cytosol and the nucleus. The importance of LAMR in development and differentiation has also been reported, and the cell signalling cascades LAMR participates in are beginning to be elucidated.

As proteins homologous to ancestral prokaryotic RPS2 superfamily members – not to be confused with eukaryotic RPS2 of the RPS5 family – RPSA/LAMR homologs are found in all taxonomic domains of life and have been studied specifically in mammals, birds, amphibians, a number of invertebrates, yeast, nematodes, plants, bacteria and archaea either for ribosomal or laminin binding function. Laminin binding appears to be a more recently acquired function particularly concentrated in metazoans, thus not all RPSA homologs have a laminin binding function.

LAMR has also been implicated in several pathological conditions, including neoplastic and metastatic cancers, neurodegenerative diseases, microbial infections and several developmental aberrations. The protein is perhaps most well studied for its overexpression in solid and haematological malignancies and its positive association with invasive and metastatic cell behaviour (Menard, Tagliabue & Colnaghi, 1998). Its role in other maladies appears to be a function of its ability to act as a receptor for several exogenous agents

including prion proteins (Vana *et al.*, 2009), viruses (Kielian, Chanel-Vos & Liao, 2010) and bacteria (Huang & Jong, 2009).

To date there are over 500 research publications specifically pertaining to LAMR/RPSA; they have been critically examined for expert commentary in this review. This topic has been reviewed previously by Nelson *et al.* (2008), Menard *et al.* (1997) and Rea *et al.* (2012). Because of the multifaceted nature of LAMR, its controversial role in laminin binding and the complexities of its study, this review emphasizes the strengths and weaknesses of the evidence for each of its putative roles. Additional attention is given to examination of LAMR's structural features with particular focus on implications for function. Lastly, an attempt is made to piece together various lines of evidence to arrive at probable signal transduction pathways to which LAMR may contribute.

II. 37/67-kDa LAMININ RECEPTOR IDENTITY

(1) Gene and genome

LAMR, officially RPSA, is encoded in humans by the ribosomal protein SA gene (*RPSA*, NCBI Gene ID: 3921, Accession No.: AC_000135). The gene is a 5833 bp stretch along chromosome location 3p22.2 (3p21.3 by *in situ* hybridization) consisting of seven exons and six introns (Jackers *et al.*, 1996*b*). Based on analysis of the avian gene promoter, no TATA or CAAT box was found, however, several specificity protein 1 (Sp1) and activator protein 1/2 (AP1/2) binding sites were noted in addition to response elements for glucocorticoids and consensus motifs for signal transducer and activator of transcription (STAT) proteins (Clausse *et al.*, 1996). Sequence comparison and prediction of transcription factor binding sites using the human promoter are in agreement with this report (Messeguer *et al.*, 2002). The promoter may also be responsive to p53 (Modugno *et al.*, 2002).

Within the introns of *RPSA*, there are two H/ACA box-type small nucleolar RNA (snoRNA) genes, *SNORA6* and *SNORA62*, understood to be important for rRNA processing as part of ribonucleoparticles (Kiss *et al.*, 2004; Lestrade & Weber, 2006; Ruff *et al.*, 1993).

It is unknown how many functional copies of the gene exist, but there are at least 64 pseudogenes spread throughout several chromosomes (Balasubramanian *et al.*, 2009), many of which appear to be processed retroposons (Jackers *et al.*, 1996*a*). Interestingly, the avian genome has only one gene copy and contains no pseudogenes, a convenience exploited for early efforts at gene description.

(2) The 37-kDa laminin receptor protein

The human *RPSA* gene produces a final mRNA of 1155 nucleotides (Accession No.: NM_002295) or a 1109 nt variant with an alternative 5' exon prior to the start codon (NM_001012321) – both encode the same protein. Northern blotting detects a single transcript of approximately 1.2–1.4 kb (Satoh *et al.*, 1992). The open reading frame of 885 bases encodes a 295 amino acid protein.

Of the seven exons in the human *RPSA* mRNA, the first is non-coding and 2–5 encode the N-terminal RPS2 domain [amino acids (a.a.) 1–209], which shares roughly 20–30%

sequence identity with prokaryotic rps2 proteins (>60% among eukaryotes). The latter two exons encode a C-terminal region (a.a. 210–295) absent in prokaryotes. Though highly homologous amongst vertebrates, this C-terminal portion is of variable length and sequence in eukaryotes (~80 a.a. in animals and plants *versus* ~45 in yeast and excavates, ranges of 18–98% identity); exon splicing structure also varies across kingdoms. The genetic origins of the C-terminal-encoding segments are unknown, but they have been implicated in laminin binding for vertebrates (see Section III.4).

LAMR^{37} is the species of protein produced upon transfection of mammalian cells with *RPSA* cDNA (Castronovo *et al.*, 1991*a*), recombinant expression in bacteria (Jamieson *et al.*, 2008) and with *in vitro* translation reactions (Grosso, Park & Mecham, 1991; Rao *et al.*, 1989). This species has been found in the cytosol, associated with the cytoskeleton, in the plasma membrane (Venticinque, Jamieson & Meruelo, 2011), in the nucleus (Scheiman *et al.*, 2010*a*) and associated with ribosomes (McCaffery *et al.*, 1990; Scheiman *et al.*, 2010*b*). Originally presumed to be simply a precursor to LAMR^{67}, LAMR^{37} has since been shown to be important for several intracellular roles and is most likely involved in laminin binding (see Section III).

The protein is potentially phosphorylated on Tyr-139 (Davis *et al.*, 1991; K. Kim *et al.*, 2005; Rush *et al.*, 2005), but all other potential post-translational modifications are typically discussed with respect to conversion to the 67-kDa species, LAMR^{67}.

(3) Higher molecular weight species

The first species of LAMR described was the 67-kDa LAMR^{67}, purified from cellular membranes by laminin-1 immobilized on sepharose and confirmed as a laminin binding protein *via* radiolabelled laminin overlay blots (Huard, Malinoff & Wicha, 1986; Lesot *et al.*, 1983; Malinoff & Wicha, 1983; Rao *et al.*, 1983). The precise identity of this protein remains uncertain, but it is presumed to be a higher molecular weight form of LAMR^{37}. There are several lines of evidence for this. First, following the development of an antibody derived from the purified 67-kDa protein (Liotta *et al.*, 1985), immunoscreening of a cDNA library identified *RPSA* coding sequences (Wewer *et al.*, 1986). Second, partial protein sequencing of the purified 67-kDa protein revealed a short peptide (MLAREVLR) corresponding to the LAMR^{37} sequence 177–184 (Wewer *et al.*, 1986) – human protein BLAST searches to date show only LAMR^{37}/RPSA as a direct match with 100% identity and coverage. Lastly, several antibodies raised against different synthetic peptides within the LAMR^{37} sequence recognize both 37-kDa and 67-kDa bands on immunoblots of cell lysates (Castronovo, Taraboletti & Sobel, 1991*b*). Indeed, numerous reports demonstrate that different antibodies cross-react between the two species (Buto *et al.*, 1997; Castronovo *et al.*, 1991*a*; Rao *et al.*, 1989; Wewer *et al.*, 1987). Clearly, it would appear that LAMR^{37} and LAMR^{67} are at least immunologically related. Of note, however, is the regularity with which LAMR antibodies recognize either the 37 or the 67-kDa proteins, but not both.

It has long been thought that there is a precursor relationship between the two species, that the 67-kDa protein is somehow derived from LAMR^{37}. This is a matter of some controversy and has been directly addressed by only two studies. The first tracks the conversion of LAMR^{37} to a higher molecular weight (HMW) 67-kDa form using pulse-chase radiolabelled

cells to monitor the transition over time. After immunoprecipitation of LAMR, the appearance of a weak 67-kDa signal begins to occur within 30–90 min of the pulse accompanied by decreased $LAMR^{37}$ detection (Castronovo *et al.*, 1991*a*). Complete conversion of $LAMR^{37}$ to 67-kDa is said to occur, an observation inconsistent with the known presence of $LAMR^{37}$ in cells. Crucially, in the same report, exogenous introduction of *RPSA* cDNA increases $LAMR^{37}$ but not the 67-kDa HMW form.

Though the precursor relationship is largely accepted, no data have emerged showing the production of a HMW species from a tagged $LAMR^{37}$ construct – only 37-kDa+Tag molecular weights have been observed (see for examples: Scheiman *et al.*, 2010*a*; Chen *et al.*, 2003; Castronovo *et al.*, 1991*a*; Gauczynski *et al.*, 2001; Amano *et al.*, 2005*b*). Anecdotal reports are discussed in Buto *et al.* (1998), Clausse *et al.* (1996) and Menard *et al.* (1997), who reference unpublished data and a conference abstract by Montuori *et al.* (1995) claiming to have demonstrated production of a 67-kDa protein from a histidine-tagged $LAMR^{37}$. Accounts claiming overexpression of $LAMR^{67}$ upon *RPSA* cDNA introduction are available, but problems with interpretation arise due to ambiguous demonstration of protein size (e.g. use of flow cytometry or failure to distinguish between 37 and 67 species; see Landowski, Uthayakumar & Starkey, 1995*b* and Tachibana *et al.*, 2004). In the future, the field would benefit from clear molecular weight distinguishers and precise terminology when referring to various LAMR species.

The second attempt to solidify a precursor relationship comes from a study hypothesizing that fatty acid acylation of $LAMR^{37}$ may be required for transition to the HMW form. In support of this, treatment of cells with cerulenin, an inhibitor of fatty acid synthase, reduces the detection of $LAMR^{67}$ in cells with a concomitant appearance of $LAMR^{37}$. Usage of hydroxylamine to strip thio-/oxy-ester bound fatty acids from proteins produces a similar effect (Buto *et al.*, 1998). The presence of palmitate, stearate and oleate fatty acid residues on purified $LAMR^{67}$ has been detected using gas chromatography–mass spectrometry (Landowski, Dratz & Starkey, 1995*a*).

Several groups have reported the presence of additional HMW LAMR species. Proteins of 32, 37, 45, 53, 55, 67, 80 and >110-kDa size have been isolated using laminin-1 columns in addition to the integrins (Clement *et al.*, 1990; Davis *et al.*, 1991; Douville, Harvey & Carbonetto, 1988; Kleinman *et al.*, 1988; Landowski *et al.*, 1995*a*; Languino *et al.*, 1989; Mercurio & Shaw, 1988; Tandon *et al.*, 1991; Weeks *et al.*, 1991). Cross-reactivity of $LAMR^{67}$ antiserum with some of these proteins has been reported, including a 110-kDa species and galactosidase beta-1 (GLB1, Protein Accession No.: P16278). GLB1 is a natively 67-kDa elastin/laminin binding protein often confused for $LAMR^{67}$, especially when lectin and elastin are involved (Mecham *et al.*, 1989; Weeks *et al.*, 1991). These reports serve as examples of possible shared epitopes and potential sources of contaminating sequences.

Taking into account the descriptions of known laminin binding proteins and the LAMR literature, it seems likely that reports of 32–45 kDa species correspond to $LAMR^{37}$. Curiously, 53–55 kDa entities (Graf *et al.*, 1987*b*; Karpatova *et al.*, 1996; Tandon *et al.*, 1991) may represent another HMW species, $LAMR^{53}$, distinct from the 67-kDa form – 37,

53 and 67 can be detected in cells with a single antibody. Unfortunately, very little published literature is available to address this possibility.

(4) Identity of LAMR^{67}

Given that LAMR^{67} is a stable protein species that conserves its molecular weight under denaturing and reducing conditions (Landowski *et al.*, 1995*a*), it is unclear what event is responsible for the increase in size if it is indeed formed from LAMR^{37}. Efforts to sequence the protein directly have met with little success, typically attributed to a blocked N-terminus and/or limited ability to isolate the protein in sufficient quantities and purity – bovine serum albumin (BSA) especially is reported to be difficult to eliminate upon co-purification (von der Mark & Risse, 1987; Wewer *et al.*, 1986). The amino acid composition of purified LAMR^{67} has been determined (Landowski *et al.*, 1995*a*), but efforts to sequence the protein using modern technologies appear to be absent from the literature.

It has been suggested that HMW LAMR species are not produced upon introduction of *RPSA* cDNA into cells because of the necessity for another protein, hence the hypothesis that LAMR^{67} is a heteromeric protein. A galectin family protein is the most frequently proposed candidate for a LAMR binding partner owing to reports demonstrating that lectin-targeted antibodies cross-react with LAMR^{67} (Buto *et al.*, 1998; Castronovo *et al.*, 1992; Mecham *et al.*, 1989). LAMR has been reported to be eluted from laminin with galactosides (Mecham *et al.*, 1989) and lectins do have laminin binding properties (Mercurio & Shaw, 1991). This issue is confused, however, by the presence of the 67-kDa elastin/laminin binding protein (GLB1) which also has lectin properties (Ochieng *et al.*, 1999), thus raising the possibility that identity errors have occurred. Indeed, there are directly contradictory reports that LAMR does not elute from laminin affinity columns with galactosides (Fulcher *et al.*, 1993) nor bind elastin (Grosso *et al.*, 1991). Complicating the matter further, there is evidence of a lectin protein that binds the carbohydrate support of sepharose columns; this protein is a common contaminant of integrin preparations and is reduced to 70-kDa subunits when denatured, introducing another source of uncertainty (Bao, Muschler & Horwitz, 1992; McCaffery *et al.*, 1990).

Amino acid composition analysis performed on purified LAMR^{67} is in agreement with the predicted composition of LAMR^{37}, which has been cited as evidence for homodimer formation of LAMR^{67} (Landowski *et al.*, 1995*a*). A potential galectin-3-LAMR^{37} heterodimer and GLB1 show significant deviations from this amino acid composition. Evidence for a homodimer is sparse, however. Two-hybrid testing failed to demonstrate LAMR^{37} could interact with itself or galectin-3 (Hundt *et al.*, 2001), however this trial was performed with a possibly abnormal N-terminally truncated LAMR$^{37(\Delta 1–43)}$ in yeast where modifications necessary for dimerization may not occur. Bacterially grown recombinant and *in vitro* translated LAMR^{37} remains monomeric (Grosso *et al.*, 1991; Jamieson *et al.*, 2008; Rao *et al.*, 1989) and exogenous expression of *RPSA* cDNA has not been clearly shown to produce LAMR^{67}.

It would appear the oligomeric state of LAMR^{67} remains unsolved. Alternative splicing or a separate transcript does not provide a satisfactory explanation, as the vast majority of reports detect a single *RPSA* mRNA of approximately 1.2 kb in several cell lines as well as tissue

samples (Satoh *et al.*, 1992). There are sparse examples of larger mRNAs (5.5 kb) being co-detected in low abundance in tumour cells using *RPSA* probes, but their identity is uncertain (Rabacchi, Neve & Drager, 1990; Yow *et al.*, 1988).

Why a protein–protein complex involving LAMR^{37} would be stable during denaturing/reducing SDS-PAGE is unclear, but a strong hydrophobic fatty-acid mediated interaction may contribute. Alternatively, covalently attached additions from post-translational modifications are possible. LAMR^{67} and LAMR^{37} appear to be acylated, but fatty-acid residues are low in molecular weight and not considered to be in abundance on LAMR (Buto *et al.*, 1998; Landowski *et al.*, 1995*a*). Glycosyl group addition is another potential low molecular weight modification, but LAMR shows no signs of glycosylation (Castronovo *et al.*, 1991*a*; Landowski *et al.*, 1995*a*). There is a singular report of LAMR detection by an antibody that recognizes moieties within glycosphingolipids that also demonstrates LAMR incorporation of labelled galactose and sialic acid during synthesis (Katagiri *et al.*, 2005).

There do exist post-translational modifications that can add significant mass to a protein by covalent attachment. Ubiquitin-like proteins (UBLs) such as ubiquitin, NEDD (neural precursor cell expressed developmentally down-regulated protein) and SUMO (small ubiquitin-like modifier) are within the mass range of 8–14-kDa and are capable of forming oligomeric chains (van der Veen & Ploegh, 2012). This possibility may have significant explanatory power with regard to LAMR^{67}.

Several large-scale proteomics screens for SUMOylated proteins have identified human LAMR as a target for SUMO-1, SUMO-2/3 and SUMO-4 modification (Blomster *et al.*, 2009; Golebiowski *et al.*, 2009; Guo *et al.*, 2005; Manza *et al.*, 2004; Schimmel *et al.*, 2008). SUMOylated RPS0 (the yeast RPSA/LAMR homolog) was also detected in a yeast screen (Wohlschlegel *et al.*, 2004). The primary LAMR^{37} structure has a consensus SUMOylation site near the N-terminus (Lys-11) and several non-consensus sites (Lys-212 and Lys-224) which happen to overlap with a putative laminin binding region within residues 205–229 (SUMOsp: Ren *et al.*, 2009). It is tempting to speculate that a single SUMOylation event might be responsible for the reported LAMR^{53} species while multiple modifications or SUMO oligomers might build LAMR^{67} and larger species; the predicted sizes of LAMR-SUMO species are consistent with this proposal.

SUMOylation is known to positively or negatively influence protein stability, protein trafficking, and protein–protein interactions. The latter influences occur due to creating or masking of a binding interface and/or inducing conformational changes within the SUMOylated protein while protein stability effects occur in conjunction with the ubiquitin/proteasome system (Wilkinson & Henley, 2010).

Definitive identification of the LAMR HMW species would seem to be lacking, leading to justifiable skepticism concerning their characteristics. Nonetheless, there appears to be sufficient evidence supporting that LAMR^{67} is a genuine entity and unique molecule related to LAMR^{37}, albeit abundance of the protein is likely low and dependent on various experimental and physiological conditions.

(5) LAMR membrane presence

LAMR[67] is considered to be primarily located at the plasma membrane, possibly concentrated in lipid rafts (Fujimura, Yamada & Tachibana, 2005). This has been sufficiently demonstrated using fluorescent microscopy, membrane fractionation and FACS on unpermeabilized cells (Abe *et al.*, 1996; Castronovo *et al.*, 1991*b*; Landowski *et al.*, 1995*b*; Liotta *et al.*, 1985).

The membrane abundance of both LAMR[67] and LAMR[37] is significantly less than the overall cytoplasmic content. LAMR[67] cytosolic levels in particular appear to be minimal. It is important to note that species abundance data are often difficult to judge because of the varying antibody affinities and the possibility that some epitopes are only exposed (or destroyed) upon protein denaturing.

Intriguingly, it appears that antibodies against epitopes C-terminal to the 104th residue tend to be capable of labelling cell surface LAMR without cell permeabilization, whereas more N-terminal-directed antibodies only detect total LAMR with permeabilization (Castronovo *et al.*, 1991*b*). This seemingly corroborates the prediction of a short, atypical transmembrane domain within LAMR[37] residues 86–101 (Rao *et al.*, 1989), which would result in approximately 100 intracellular N-terminal residues. No transmembrane region is apparent in the LAMR$^{37(9–205)}$ crystal structure, however, nor is the presence of an exposed amphipathic domain consistent with LAMR cytosolic solubility (see Section IV). The N-terminal regions may simply be masked in particular situations, and the targeted epitopes have not been determined for all LAMR antibodies. A transmembrane region need be considered only if clear evidence arises implicating LAMR in direct structural transduction of extracellular-to-cytosolic signals without the need for accessory proteins or translocation events.

LAMR[37] has no membrane-targeting signal peptide and a transmembrane domain is unlikely, leaving open the question of how association with the plasma membrane occurs. Electrostatic interactions with the membrane are unlikely as LAMR is predominantly negatively charged. Although fatty acid acylation appears to occur on LAMR, the pattern is inconsistent with that of a glycosylphosphatidylinositol (GPI) anchor (Karpatova *et al.*, 1996; Landowski *et al.*, 1995*a*). This situation brings up the possibility that membrane association could occur *via* a hydrophobic segment on LAMR[37] or a modification, an adhesion method not uncommon for exoplasmic peripheral membrane proteins. This mode of membrane attachment is supported by numerous reports of LAMR association with intact liposomes (Anilkumar & Sudhakaran, 1993; Lesot *et al.*, 1983; Sengupta *et al.*, 1991) and shedding of intact LAMR[67] into cell culture medium (Karpatova *et al.*, 1996), but definitive evidence is lacking.

Peripheral membrane proteins are often known to associate with other proteins for added stability in the membrane. Consistent with this hypothesis, LAMR has been demonstrated to interact with the α6 integrin subunit, presumably as part of a full integrin (Ardini *et al.*, 1997). This may explain how initial membrane targeting occurs; LAMR has been found to co-localize with integrins in cytoplasmic particles that may represent vesicular trafficking to the plasma membrane (Romanov *et al.*, 1994).

A heteromeric or otherwise modified HMW species may also associate with the membrane *via* the properties of its partner(s). The possibility of a LAMR^{67} homodimer having a considerably different conformation cannot be entirely ruled out either, but these options do not suffice to explain the conservation of protein properties or the membrane presence of LAMR^{37}. Several possibilities are depicted in Fig. 1.

The mechanism of membrane targeting also remains unresolved, but it is apparent that there are control systems in place to influence LAMR turnover in the plasma membrane. The anti-metastatic protein HEXIM1 (hexamethylene bis-acetamide inducible 1), for example, is found to serve a role in downregulation of LAMR content in the membrane without affecting total levels (Ketchart *et al.*, 2013). Membranous LAMR^{67} is also mediated by NEDD4, which can target the protein for ubiquitination and 26S proteasome degradation. Protection from ubiquitination events – and thus LAMR^{67} stabilization – can be conferred by the LAMR binding protein KRS (lysyl-tRNA synthetase), which is activated by laminin signalling (Kim *et al.*, 2012). It is yet unclear how a protein residing wholly in the outer plasma membrane layer could be regulated in this manner (Scenario 5 in Fig. 1).

SUMOylation is often brought about under conditions of cellular stress; it may also be a response to other signalling stimuli. Reports of specific proteins' plasma membrane association aided or disrupted by SUMOylation exist (Huang *et al.*, 2012; Martin *et al.*, 2007). SUMO modification could also play a role in regulating the stability of LAMR, whether by targeting it for degradation or as a competitive counter to ubiquitination, as it can for other proteins (Schimmel *et al.*, 2008). It is also possible that SUMO modification changes the laminin binding properties of membranous LAMR (i.e. in the 37- to 67-kDa transition, see Section II.4).

One particularly appealing speculative scenario is the alternating usage of ubiquitin and SUMO modifications on LAMR to regulate the degree of laminin binding when a cell may have need to migrate. This may be affected *via* changes in LAMR stability, targeting for endocytosis or degradation, or alteration of ligand binding affinity. Ribosomal incorporation (exclusively LAMR^{37}) and nuclear import of LAMR could similarly be regulated by these modifications.

III. 37/67-kDa LAMININ RECEPTOR FUNCTION

(1) Functional importance

Little is conclusively understood about the normal physiological province of LAMR and its various higher molecular weight species in cells. What is clear is that it functions in laminin binding and as a structural component of the ribosome. Further, we can conclude from the evidence that it is important for certain modes of cellular adhesion through laminin, and a factor in cellular migration. Homozygous *Rpsa* null mice fail to develop past embryonic day 3.5 while heterozygotes suffer only delayed embryonic growth, becoming otherwise phenotypically normal (Han, Logsdon & Ellis, 2008). A comprehensive assessment of the intricacies of LAMR remains elusive, but investigations using methods to reduce expression or modulate function are beginning to shed light on its numerous roles.

Depending on the cell line being investigated and the degree of knockdown, the effects of reduced LAMR are known to include: reduction in proliferation and induction of G^1-phase cell cycle arrest (Satoh *et al.*, 1999; Scheiman *et al.*, 2010*a*, *b*), attenuation of protein synthesis (Demianova, Formosa & Ellis, 1996; Ford, Randal-Whitis & Ellis, 1999; Scheiman *et al.*, 2010*b*; Venticinque *et al.*, 2011), disruption of pre-rRNA processing (Ford *et al.*, 1999; O'Donohue *et al.*, 2010), decreases in viability (Demianova *et al.*, 1996; Moodley & Weiss, 2013; Scheiman *et al.*, 2010*a*; Susantad & Smith, 2008), and reduced adhesive and migratory ability (Chen *et al.*, 2009; Poon *et al.*, 2011; Venticinque *et al.*, 2011). Unsurprisingly given RPS2 family homology, there may be distinctions between ribosomal and extraribosomal functions conferred by the N- and C-terminal regions, respectively (Scheiman *et al.*, 2010*a*). Antibody blockade studies are generally in agreement with LAMR involvement in adhesion, migration and invasion (Davis *et al.*, 1991; Omar *et al.*, 2012; Tandon *et al.*, 1991; Terranova & Lyall, 1986; Wewer *et al.*, 1987), and thus serve to partially alleviate concern over secondary effects arising from the small interfering RNA (siRNA) approach, which also compromises ribosomal function and protein synthesis. In addition, LAMR interacts with many individual proteins, presumably participating in several cell signalling cascades.

(2) Laminin binding

The most studied and rudimentary aspect of LAMR is its function in binding laminin. If this interaction goes beyond simple promotion of cell adhesion to the basement membrane, LAMR's involvement in transducing signals from laminin to affect cellular processes has not been clearly demonstrated. This has led to the proposal that cell surface LAMR functions only to stabilize or regulate the binding of laminin to other receptors (Ardini *et al.*, 1997; Pellegrini *et al.*, 1994), that LAMR is only necessary for particular stages of attachment (Basson *et al.*, 1990) or that accessory molecules are necessary for its function (Landowski *et al.*, 1995*a*).

Several laminin receptors are known to overlap in function (particularly adhesion and migration), although they do not seem to be entirely redundant or compensatory *in vitro*. With so many identified, there are inevitably cell-type-specific differences in laminin receptor profiles. This varied receptor complement can switch in response to certain stimuli – for example, haematopoietic stem cells have been shown to shift from α6 integrin display to LAMR during signal-induced mobilization for egress and migration (Selleri *et al.*, 2006). Development and differentiation (Hara, Satoh & Ide, 1997; McKenna *et al.*, 2001), malignant transformation (Menard *et al.*, 1998), tissue stimulus responses (Anilkumar & Sudhakaran, 1993; Baloui *et al.*, 2009; Stitt *et al.*, 1998) and other signalling molecules (e.g. cytokines, hormones) have also been noted to induce changes in LAMR expression (Castronovo *et al.*, 1989; Chen *et al.*, 2002; Clausse *et al.*, 1998; Raghunath *et al.*, 1993; Shi *et al.*, 1993). Some of these changes are linked to laminin expression in adjacent tissue and may be due to a need for a change in laminin binding propensity (positive or negative).

Cell membrane purified $LAMR^{67}$ binds native laminin isolated from Engelbreth Holm Swarm murine sarcoma (predominantly laminin-1) with an affinity (K_d) of 2 nM (Malinoff & Wicha, 1983; Rao *et al.*, 1983). In comparison, *Escherichia coli* purified recombinant

LAMR^{37} binds laminin-1 with a 700 nM K_d (Jamieson *et al.*, 2008; Zidane *et al.*, 2013). The difference in affinity is likely to reflect differences between the 67- and 37-kDa species, the contribution of any post-translational modifications (to cellular LAMR^{37}) as well as inter-assay and preparation variability. The only comparison of affinity in a consistent system found a similar K_d for both species, 300–400 nM, using surface plasmon resonance (Fatehullah *et al.*, 2010). It is challenging to speculate on the physiological significance – if any – of the differences in the dissociation constants, but a 37/67 expression ratio may factor into a laminin binding fine-tuning system.

(3) Laminin-1 binding sites for LAMR

Not many studies have directly examined LAMR binding to laminin in order to refine our knowledge of the binding site. Most of the information collected is for laminin-1. One low-resolution attempt used the native laminin-1 molecule to investigate the binding region of purified LAMR^{67}, employing rotary shadowing electron microscopy. The result showed the LAMR^{67} binding site to reside on the laminin long arm just below its intersection with the short arms (Cioce *et al.*, 1993), presumably on domain II, which adopts a triple coiled-coil of all three laminin subunits (Engvall & Wewer, 1996). Large laminin proteolytic fragments, C1 and P1 (Rao *et al.*, 1982; Rohde, Bachinger & Timpl, 1980), were used to substantiate this binding site. Information about the role of laminin domain II in cell binding is limited due to lack of applicable large fragments (Aumailley, 2013; Aumailley *et al.*, 2005), and detailed peptide analysis may be unfeasible because of quaternary structure.

Another approach to identify the LAMR binding region of laminin was taken with the use of antibodies derived against synthetic peptides from the β1 subunit of laminin-1. An antibody that blocked cell adhesion to laminin was identified, and screening of peptides nearby the targeted epitope identified CDPGYIGSR (Peptide 11) as being capable of similarly blocking cell attachment (Graf *et al.*, 1987*a*). The activity of this synthetic peptide was later refined to the minimal pentapeptide YIGSR on the laminin β1 short arm, a.a. 929–933 (Graf *et al.*, 1987*b*). CDPGYIGSR and YIGSR can influence cell attachment and migration in a manner generally consistent with that of a laminin analog or decoy (Kikkawa *et al.*, 2013). YIGSR peptides have also been demonstrated to elute LAMR^{67} from laminin columns (Graf *et al.*, 1987*a*, b) as well as associate with LAMR^{67} (Bushkin-Harav, Garty & Littauer, 1995; Hadley *et al.*, 1990; Starkey, Uthayakumar & Berglund, 1999). YIGSR's interaction with LAMR^{37} has not been examined in detail, but the peptide failed to co-crystallize with a LAMR$^{37(1–220)}$ recombinant protein (Jamieson, K.V. & Wu, J., unpublished data) – although it may only interact with LAMR^{67} or require full-length LAMR^{37}.

Skepticism about YIGSR and related peptides does exist in the literature. Some groups have failed to elute LAMR from laminin columns with the peptide, and others still express concern that its properties do not adequately mimic those of laminin binding or display LAMR specificity (Castronovo *et al.*, 1991*b*; Clement *et al.*, 1990; Maeda, Titani & Sekiguchi, 1994; Yamada *et al.*, 1990). YIGSR is certainly a bioactive peptide (Kikkawa *et al.*, 2013), but whether all its effects are mediated through LAMR or reflective of native laminin (folding state, receptor usage, etc.) is uncertain.

(4) LAMR binding sites for laminin

Several binding sites on LAMR have been suggested to interact with laminin. These sites are typically discussed as if they possess independent ability to bind laminin, although in native binding it is unclear if they function redundantly or in collaboration.

The most common approach of using synthetic peptides derived from the LAMR[37] primary sequence has identified two putative laminin binding regions. The first is referred to as Peptide G, residues 161–180 (Castronovo *et al.*, 1991*b*). The second site, typically referred to as the "direct binding region", is the stretch of amino acids between 205 and 229 (Landowski *et al.*, 1995*b*). Both peptides can bind laminin-1 and have bioactive properties *in vivo* (Landowski *et al.*, 1995*b*; Taraboletti *et al.*, 1993). These peptides also display heparan sulfate (HS) binding properties (Guo *et al.*, 1992; Kazmin *et al.*, 2000). The functional implications of HS binding are not clear, as laminin-1 preparations are often said to contain HS proteoglycan. Truncated constructs of LAMR are seemingly capable of binding HS and laminin simultaneously, while full-length LAMR[37] and LAMR[67] may bind HS more weakly or not at all (Fatehullah *et al.*, 2010; Zidane *et al.*, 2013). HS binding may act as a laminin binding stabilization or inhibitory event in these scenarios, but artifactual binding cannot be ruled out.

The palindromic sequence LMWWML (a.a. 173–178) contained within Peptide G has been suggested to be the minimal sequence responsible for laminin binding, the two consecutive tryptophan (W) residues considered suitable for protein–protein interaction (Jaseja *et al.*, 2005). Suspicions arise, however, due to the location of this sequence in the protein crystal structure: it is a helical stretch buried within the interior of the protein without obvious surface accessibility, calling into question its availability for protein–protein interaction while also accounting for the presence of the tryptophan residues. Nonetheless, high sequence conservation in this region was shown to correlate with laminin-expressing organisms while divergence of sequence occurs in non-laminin-expressing species (Ardini *et al.*, 1998). Though the RPS2 family domain (human residues 1–209) is highly conserved as a whole, this palindromic sequence has especially high sequence identity amongst metazoans.

Notably, the presence of both tryptophans does not appear to be required, as laminin binding has been observed in LAMR homologs even with sequences LMLWML (metazoan *Echinococcus granulosus*: Zhang *et al.*, 1997), LMFWLL (amoebozoa *Acanthamoeba healyi*: Hong *et al.*, 2004) and LMYWLL (alveolate *Toxoplasma gondii*: Furtado *et al.*, 1992). Thus, laminin binding exists even with sequence variation in the palindrome and is not limited to metazoans. Interestingly, the second tryptophan in particular (human residue W176) appears to be universally conserved, although it is also conserved in non-laminin-binding archaea (IVYWLL) and plants (CLFWLL).

Ultimately, the significance of Peptide G and the palindrome will have to be verified experimentally within the full protein. Peptide G and its possible availability for laminin binding is further discussed in Section IV.

A separate study using a phage peptide display identified 9-mer mimotopes similar in sequence to Peptide G and Peptide 205–229 as functional in binding laminin-1 (Kazmin *et al.*, 2000). This study also identified sequences similar to the five x(D/E)W(S/T) repeats in the C-terminus of LAMR (a.a. 247–9, 264–8, 273–7, 285–7, 291–5) as potential laminin binding contributors – offering a third laminin binding site. Although the homologous sequence mimotopes could be eluted from laminin-1 by YIGSR peptides, they may not represent actual LAMR functionality.

The only study to attempt a mutational approach to determine the laminin binding site identified three amino acids (Phe-32, Glu-35, Arg-155) in structural proximity to each other using a truncated $LAMR^{37(1–220)}$ recombinant protein; individual or mutations in combination resulted in significant reduction of laminin binding capacity (Jamieson, Hubbard & Meruelo, 2011). However, introduction of these mutations to the full-length $LAMR^{37(1–295)}$ protein did not significantly affect laminin-1 binding (DiGiacomo, V. & Jamieson, K.V., unpublished data).

There are reports that N-terminal portions of $LAMR^{37}$ (2–209 or 1–220) and C-terminal portions (210–295 or 225–295) can independently bind laminin-1 (Jamieson *et al.*, 2011, 2008; Zidane *et al.*, 2013), suggesting the four putative laminin binding sites work individually. Transference of the human C-terminal region (a.a. 210–295) to a non-laminin-binding archaeal LAMR homolog, *Archaeoglobus fulgidus* rps2P (Protein Accession No.: AAB90111), however, failed to confer laminin binding (DiGiacomo, V., unpublished data). The presence of multiple binding sites in the same construct does not appear to significantly alter target affinity – the full-length protein (four binding sites) engages laminin-1 with an approximately twofold higher K_d than N- and C-terminally truncated portions that each contain two proposed binding regions (Jamieson *et al.*, 2008; Zidane *et al.*, 2013).

The laminin binding regions will be discussed in detail with respect to the protein structure below, but it would seem as if the laminin binding site(s) is still a matter of debate (see Section IV). It may very well be that peptide analysis is insufficient for determining the true binding mode of LAMR to laminin, as it remains possible the binding site is a non-linear surface presented only by the full structure. It is also possible that $LAMR^{37}$ interacts with laminin differently than $LAMR^{67}$.

(5) Ribosomal functions

LAMR is likely to have originated as a ribosomal component. The most highly conserved portion of the protein, the N-terminal bulk (a.a. 1–209), is highly homologous to prokaryotic s2 family ribosomal proteins. Laminin binding functions may have evolved along with the appearance of laminin, although the nature of that development is incompletely understood (Ardini *et al.*, 1998).

The earliest signs of translational function came from an observation of cytosolic p40 being associated with ribosomal particles in mice (Auth & Brawerman, 1992). When that protein was purified from ribosomes and sequenced, it was equated with $LAMR^{37}$/RPSA (Tohgo *et al.*, 1994). It is now clear that $LAMR^{37}$ associates with the 40S small subunit of ribosomes (Anger *et al.*, 2013; Ben-Shem *et al.*, 2011; Malygin *et al.*, 2011; Scheiman *et al.*, 2010*a*, b)

and has direct contacts with RPS2 (RPS5 family), RPS17, RPS21 and sparse contact with rRNA in humans, insects, yeast, plants and *Tetrahymena* (Anger *et al.*, 2013; Armache *et al.*, 2010; Ben-Shem *et al.*, 2011; Rabl *et al.*, 2011). Treatment with RNase does not disassociate LAMR from 40S particles (Auth & Brawerman, 1992).

It appears the N-terminal domain of the protein is sufficient for ribosomal binding, as $LAMR^{37(1–220)}$ is incorporated into ribosomes and can rescue translational defects caused by LAMR siRNA knockdown (Scheiman *et al.*, 2010*a*). The C-terminus (210–295) may have been co-opted for binding additional proteins, stabilizing binding or interacting with rRNA (Malygin *et al.*, 2011). The wheat (*Triticum aestivum*) LAMR homolog, RPSA/S2p, for example, has been suggested to bind ribosomal RACK1 (receptor for activated protein C kinase 1) *via* the C-terminal region (Armache *et al.*, 2010). The C-terminus, encoded by separate exons (see Section II.2), alternatively may have evolved for laminin binding.

The function of LAMR ribosomal incorporation is not known outside the observation that it is important for protein synthesis and ribosome biogenesis (Demianova *et al.*, 1996; Scheiman *et al.*, 2010*a*, b; Venticinque *et al.*, 2011), although it is alleged LAMR may not be a constitutive component (Malygin *et al.*, 2011). While occurrence of ribosomal $LAMR^{37}$ may be enhanced in polysomes of actively growing cells (Garcia-Hernandez *et al.*, 1996) or by other stimuli (Fromm-Dornieden *et al.*, 2012), the protein is still found in free 40S subunits and present during initiation of translation (Ford *et al.*, 1999; Scheiman *et al.*, 2010*b*; Valasek *et al.*, 2003).

In addition to direct ribosomal function, LAMR is crucial for the processing of the 21S pre-rRNA into mature 18S rRNA. This function may involve binding and partial redundancy with RPS21, experimentally demonstrated in both humans and yeast (O'Donohue et al., 2010; Sato *et al.*, 2003, 1999; Tabb-Massey *et al.*, 2003). This appears to represent a ribosomal biogenesis function of LAMR as well as a nuclear/nucleolar role, as pre-40S subunits require LAMR for nucleolar exit (O'Donohue *et al.*, 2010).

(6) Nuclear functions

Although nuclear and nucleolar localization of $LAMR^{37}$ was noted early, the functional implications were not apparent until recently. There is no nuclear localization signal in LAMR (Sato *et al.*, 1996), and it is not clear if SUMO modifications play a role in nuclear import, a common function of SUMOylation. Part of the LAMR presence in the nucleus is likely explained by its association with nucleolar pre-40S ribosomes and small nucleolar ribonucleoproteins (snoRNPs: O'Donohue *et al.*, 2010). Beyond this, however, $LAMR^{37}$ potentially interacts with chromatin, directly to some extent and more tightly through histones (Kinoshita et al., 1998; Venticinque & Meruelo, 2012).

$LAMR^{37}$ may also serve to sequester the DNA damage repair proteins RNF8 (ring finger protein 8) and BRCA1 (breast cancer 1) to a waiting reserve in the nucleolus (Guerra-Rebollo *et al.*, 2012). Intriguingly, RNF8 is an E3 ubiquitin ligase, and in this context, evidence for a polyubiquitinated LAMR species was found. The importance of nuclear LAMR may be more widespread than was originally realized; potential for transcription factor or chromatin modifier activity is a possibility.

(7) Cytoskeletal functions

Soon after the identification of LAMR, its cytosolic presence was shown to co-localize with actin and cytoskeletal stress fibre features (Brown, Malinoff & Wicha, 1983; Keppel & Schaller, 1991; Yannariello-Brown *et al.*, 1988). It was suggested that LAMR may serve as a connection to extracellular laminin and the cytoskeleton in a manner analogous to integrins. In the likely absence of a transmembrane domain, however, it is unclear how LAMR would achieve such a function. Nevertheless, cell laminin binding is known to cause cytoskeletal reorganization events through a variety of mechanisms. LAMR staining patterns appear to react to adhesion and spreading on laminin, concentrating on leading edges of membrane ruffles and podia during migratory and attachment processes (Guirguis *et al.*, 1987; Venticinque *et al.*, 2011; Yannariello-Brown *et al.*, 1988). Because LAMR directly interacts and co-localizes with filamentous actin and focal adhesion complex members (K.J. Kim, Chung & Kim, 2005), it would appear this occurrence is an intracellular event. LAMR may also be separately concentrated to these reacting regions on the extracellular surface (Scenario 3 in Fig. 1).

LAMR interaction with the cytoskeleton also has a prominent intracellular role that likely explains its tight pattern of co-localization and physical binding with tubulin (Venticinque *et al.*, 2011). Critically, it would appear as if LAMR serves as a tether for ribosomes to microtubules, as its reduction results in loss of ribosomal localization to cytoskeletal structure, leading to dysfunction in protein synthesis (Auth & Brawerman, 1992; Venticinque *et al.*, 2011).

(8) Development, differentiation and tissue response

Because laminin has been shown to influence a great many developmental programs and tissue responses to various stimuli such as injury or differentiation signals, it is likely that LAMR's involvement in such functions is due to its laminin binding. Patterning, homing and establishing polarity may also fall within this purview. Given LAMR's importance in protein translation and potential nuclear roles, however, it is necessary also to consider the contributions from such functions.

Examination of the literature reveals that LAMR tends to be more highly expressed on the cell surface of undifferentiated and developing tissue with subsequent decline in adulthood (Amano *et al.*, 2005*a*; Biragyn *et al.*, 2007; Khalfaoui *et al.*, 2013; Laurie *et al.*, 1989; Laurie, Stone & Yamada, 1991; Masuda *et al.*, 2009; McKenna *et al.*, 2001; Rao *et al.*, 1994; Rescan *et al.*, 1990; Weeks *et al.*, 1991). LAMR has been shown to be important for imaginal disc development in *Drosophila melanogaster* (Melnick, Noll & Perrimon, 1993), for limb bud development in chicks (Hara *et al.*, 1997), cardiomyopathy in mice (Asano *et al.*, 2004) and quite strikingly in the development of the spleen in humans (Bolze *et al.*, 2013). In the latter case, mutations found in the *LAMR/RPSA* gene are strongly associated with congenital asplenia, representing the only known polymorphisms in LAMR associated with human pathology.

In more well-differentiated cells, LAMR expression is typically confined to its intracellular localization except when a stimulus triggers cell surface upregulation. Upregulation of

LAMR has been shown to occur in microglia following traumatic injury to the spinal cord in association with re-expression of laminin (Baloui *et al.*, 2009) and in vasculopathic neovascularization events associated with ischaemic injury in the retina (Stitt *et al.*, 1998). In normal cell behaviour, LAMR upregulation seems to occur in response to hormone or cytokine signalling that triggers chemotaxis (Castronovo *et al.*, 1989; Chen *et al.*, 2002; Poon *et al.*, 2011; Selleri *et al.*, 2006; Shi *et al.*, 1993) while downregulation occurs with anti-tumorigenic-associated cytokines (Clausse *et al.*, 1998). Increases in LAMR were also reported for other cytokine classes (Raghunath *et al.*, 1993; Wenzel *et al.*, 2010). Transforming growth factor (TGF), interferons, tumour necrosis factor (TNF), granulocyte-macrophage colony stimulating factor (GM-CSF) and gonadotropin releasing hormone 2 (GNRH-II) are amongst the effective signalling molecules described. Depending on cell type, differentiation or growth-promoting molecules like retinoids and phorbol esters have also been shown to alter LAMR expression levels (Annabi *et al.*, 2007; Bryant *et al.*, 1986; Hendrix *et al.*, 1990; Montuori *et al.*, 1999; Ross, Ahrens & De Luca, 1994; Tachibana *et al.*, 2004).

(9) Modification of extracellular matrix

A particularly unexpected function of LAMR came to light when it was discovered that the HMW LAMR^{67} is shed (or secreted) from the cell surface in cell cultures (Karpatova *et al.*, 1996). The function of this shed form (LAMR$^{67\text{-Shed}}$) is unknown, but it may feed into a theorized system of modifying laminin to promote cellular migration.

Synthetic Peptide G, a putative laminin binding segment on LAMR, has been shown to cause cytoskeletal changes in cells and to increase the presence of LAMR on the plasma membrane, especially within filopodia, consequently promoting a more invasive phenotype (Berno *et al.*, 2005). While it is unclear what physiological role this might play, Peptide G has also been shown to increase the rate of laminin degradation by proteolytic enzymes when the extracellular matrix molecule is exposed to the peptide, releasing a laminin fragment that can promote cellular migration (Ardini *et al.*, 2002). This has led to speculation that LAMR contact with laminin modifies the laminin and subsequently alters cell adhesion and mobility.

Stromelysin-3 (MMP-11), a secreted extracellular matrix proteinase, has been shown to interact with and cleave LAMR, presumably liberating LAMR-derived fragments that may function similarly to Peptide G (Amano *et al.*, 2005*a*, b). This system may act on both membrane anchored LAMR and LAMR$^{67\text{-Shed}}$ (Fig. 1). Similarly, LAMR$^{67\text{-Shed}}$ has been suggested to alter the profile of angiostatin fragments produced from plasmin, thereby reducing their anti-angiogenic activity; LAMR would thus promote angiogenesis in this manner (Moss *et al.*, 2006). Plasmin normally functions to degrade extracellular matrix components and activate collagenases. LAMR activation has also been proposed to lead to plasmin activation by urokinase-type plasminogen activator (uPA, Soeda *et al.*, 1994) and to upregulate the production of collagenases (Turpeenniemi-Hujanen *et al.*, 1986).

The existence of these intricate systems may serve to promote laminin remodelling when necessary, shifting the environment toward one conducive to migration or, perhaps, invasion in a tumour context where many of these proteins are overexpressed.

(10) Signal transduction

Mounting evidence is beginning to point toward a role for LAMR as a mediator of cell signalling, interconnected with many pathways involved in diverse responses (Fig. 1). A proteomics screen for LAMR binding proteins recently confirmed this, identifying interacting proteins involved not only in cell adhesion and ribosomal biogenesis, but in metabolism, transcription, chromatin functions and signalling (Venticinque & Meruelo, 2012).

The earliest reports suggesting that LAMR might participate in cell responses came with the observation that laminin treatment of cells resulted in the dephosphorylation of a 67-kDa laminin binding protein and that phosphatase inhibitors prevented laminin-induced process formation. Protein kinase C stimulators caused similar process formation blockage (Weeks, DiSalvo & Kleinman, 1990). LAMR has subsequently been confirmed to be a phosphorylated protein (Davis *et al.*, 1991; Rush *et al.*, 2005). Protein phosphatase 1 (PP1) has been shown to affect LAMR phosphorylation after being targeted to the protein *via* LAMR interactions with the TGF-inhibited membrane-associated protein TIMAP (K. Kim *et al.*, 2005), representing one possible mechanism leading to downstream effects. Laminin treatment of cells has also been reported to decrease the phosphorylation of extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs) and p38 proteins, an event that can be partially relieved by decreasing LAMR expression — lower LAMR levels result in increases of phosphorylated ERK, JNK and p38 (Givant-Horwitz, Davidson & Reich, 2004). It appears, then, that LAMR is involved in kinase/phosphatase axes and in laminin-induced signalling. It is important to consider, however, that the direct relationship to mitogen-activated protein kinase (MAPK) pathways is unclear because diminishing LAMR potentially triggers cell stress, to which the discussed pathways are known to respond (see Section III.1).

Laminin-induced signals also seem to lead to the phosphorylation of phosphoprotein enriched in astrocytes 15 (PEA-15/PED), an adaptor protein that binds LAMR (Formisano *et al.*, 2012). Phosphorylation events on this protein lead to growth signals through the ERK cascade as well as blockage of caspase activation, linking LAMR to laminin pro-survival signalling.

Since laminin signalling is best known to result in cytoskeletal reorganization associated with migratory and adhesion changes, it is not surprising that LAMR has been implicated in membrane proximal focal adhesions as well. LAMR has been demonstrated to interact with actin, focal adhesion kinase (FAK) and paxillin, all crucial cytoskeletal rearrangement participants (K.J. Kim *et al.*, 2005; Venticinque *et al.*, 2011). Because these components, in addition to LAMR, are known to associate with integrins, involvement in signalling by large macromolecular focal adhesion complexes seems likely. In this case, it is difficult to interpret whether LAMR is required to be extracellular, transmembrane or intracellular, although the latter is at least necessary for binding FAK and actin.

In more specialized conditions, LAMR has also been shown to interact with the GM-CSF receptor (Ando *et al.*, 2011; Chen *et al.*, 2003), insulin-like growth factor receptors I and II (Ku *et al.*, 2012), insulin receptor and insulin receptor substrates (IRS-1/2/4) (Ku *et al.*,

2009), the t-cell specific adaptor protein TSAd (Park *et al.*, 2009). LAMR also potentially serves as a receptor for both the anti-angiogenic agent pigment epithelium-derived factor (PEDF) (Bernard *et al.*, 2009) and the pro-survival pro-angiogenic midkine protein, which may induce nuclear localization of LAMR (Salama *et al.*, 2001).

Functionally, it seems LAMR may play a role in MAPK signalling and participate in events occurring within focal adhesions. This may translate to downstream processes promoting growth and survival as well as the more specific responses that have been described. Difficulty arises in piecing together an accurate understanding of how LAMR mediates or otherwise participates in these events, as there is considerable confusion about the relevant species and locations of LAMR involved, the transduction mechanism, and the potential need for membrane spanning in the explanation of some effects.

IV. STRUCTURE AND IMPLICATIONS

The crystal structure of human $LAMR^{37(1–220)}$ has been solved at resolution of 2.15 Å; amino acids 9–205 were resolved (Jamieson *et al.*, 2008). The structure represents the RPS2 family domain, homologous in sequence and structure to prokaryotic ribosomal s2 proteins. This N-terminal domain (NTD, 1–209) is globular, consisting of a central β-sheet flanked by α-helices, while the C-terminal region (CTR, 210–295) is considered to be intrinsically disordered as demonstrated by circular dichroism spectrometry and several analytical folding assessment methods (Ould-Abeih *et al.*, 2012; Schlessinger *et al.*, 2009). The CTR is also highly negatively charged, incorporating a large content of glutamic and aspartic acid residues (>20%, net $^{-}$16 charges) particularly concentrated in the 205–229 area suspected to be a laminin binding region (net $^{-}$5 charges).

For discussion, we have built a hypothetical model of the full-length protein (Fig. 2A) based on known structure, homology modelling, *ab initio* folding and experimental data (Roy, Kucukural & Zhang, 2010; Xu & Zhang, 2012; Zhang, Liang & Zhang, 2011).

(1) Membrane association, structural divergence and localization

By examination of the LAMR structure, we can recognize that the proposed transmembrane domain residing approximately within residues 86–105 (Rao *et al.*, 1989) is comprised of an α-helical stretch packed against the central structure and a β-strand participating in the core β-sheet (Fig. 2A). Any conformational change that would occur to enable membrane spanning would likely have drastic consequences for the folding of the protein. A transmembrane LAMR is thus properly considered implausible.

Notably, residues 112–116 (IQAAF) form an outward projected loop with significant hydrophobic burden, unusual for solvent-accessible regions (Fig. 2A,B). This loop is structurally divergent from the corresponding region of the archaeal homolog rps2P, in which it is pinned against the globular core (PDB: 1VI6) and from bacteria (PDB: 2AVY) which possess a larger extended structure for rRNA binding (Badger *et al.*, 2005; Brodersen *et al.*, 2002; Schuwirth *et al.*, 2005; Wimberly *et al.*, 2000).

It is conceivable that hydrophobic loops could serve as membrane-inserted segments capable of attaching LAMR as a peripheral membrane protein. Whether loops such as that containing IQAAF could serve in such a capacity is unclear and highly speculative, as shallow membrane insertion depth would be expected (Lomize *et al.*, 2012). Prokaryotic RPSA/LAMR homologs are purely intracellular and thus have no need for membrane insertion capability, suggesting that divergence in this region could have been an adaptive trait. The hydrophobic nature of the IQAAF loop, however, is not entirely conserved in all species with laminin expression (such as nematodes, IQKTF). As with many peripheral membrane proteins, additional modifications or contacts with other proteins may be required (see Section II.5).

Curiously, the 112–116 loop appears to be in an archaeal-like “pinned back” conformation when human LAMR is within the ribosomal context (PDB: 3J3A). This loop has the same feature in the ribosome structures of several eukaryotes as shown in Fig. 2B (Anger *et al.*, 2013; Armache *et al.*, 2013, 2010; Badger *et al.*, 2005; Ben-Shem *et al.*, 2011; Rabl *et al.*, 2011; Weisser *et al.*, 2013). Since RPSA homolog structures outside of the ribosomal context are not available for invertebrate laminin-expressing species, it is difficult to say if this loop adopts different conformations dependent on its environment. Such a capacity may explain the ability to sustain differentially localized LAMR populations. Admittedly, this loop deviation in the monomeric human structure may be an artifact of crystallization, as it is occupied by the equivalent site in a symmetric partner in the crystal packing. Structural artifacts introduced by resolution inadequacies must also be considered, as cryo-electron microscopy (EM) structures of metazoan ribosomes often use non-metazoan X-ray structures as homology models to fit structural features into EM density maps. Alternatively, this loop may represent a physiological dimerization interface or protein–protein interaction site. Such hypotheses can be tested empirically with simple mutagenesis/deletion experiments in cells or by using synthetic liposomes to determine if they represent a plausible mode of membrane attachment and/or protein interaction (e.g. with exoplasmic integrin segments). Mutation of this region did not dramatically affect the laminin binding of purified $LAMR^{37(1–220)}$ (Jamieson *et al.*, 2011).

(2) Peptide G and its proximal “guarding” loop

Unfortunately, only two of the four proposed laminin binding sites are represented in the available crystal structures. The leading putative laminin binding region, Peptide G (a.a. 161–180), and the palindrome it contains (LMWWML) is buried beneath the protein surface (Fig. 2C). Only Lys-166 and His-169 are reasonably exposed to solvent (>50% surface area). Small portions of residues 164–168 are partially exposed. The consecutive tryptophan residues are buried as well, projecting in opposite directions – Trp-175 towards the protein interior and Trp-176 towards the exterior. Considering its placement within the structure, then, Peptide G becomes an improbable interaction site.

Mutations to this region commonly result in improperly folded recombinant proteins, making confirmation studies difficult. Mutations of surface-exposed Lys-166 only minimally affect laminin binding in $LAMR^{37(1–220)}$ (Jamieson *et al.*, 2011). Trp-175 mutation did not

produce protein while a W176A mutant has been purified, although its laminin binding activity is unknown (Zidane *et al.*, 2013).

There is emerging evidence that conformational changes may expose a segment of Peptide G and possibly free it for ligand binding. These conformational changes involve the shift of a segment packed against the Peptide G helix (a.a. 197–209) and a proximal loop (a.a. 188–196, Fig. 2A,D). In molecular dynamics simulations, this “guarding” loop exhibits flexibility, possibly allowing it to flip out from the structure, an event that may further expose Peptide G residues – specifically Arg-180 (Di Giovanni, Grottesi & Lavecchia, 2012).

Further support for conformational shifting was gathered using a combination of techniques to assess folding states of $LAMR^{37}$. In this analysis, $LAMR^{37}$ was interpreted to have alternate conformations at biological temperatures (i.e. 37°C) that may not have been reflected in the crystal structure (crystals grown at 17°C). More than half of the $LAMR^{37}$ population could be in an intermediate state between fully ordered (i.e. crystal structures) and denatured (Ould-Abeih *et al.*, 2012). It is conceivable that true physiological events expose the palindrome for laminin binding by releasing the guarding loop from its interactions with Peptide G.

With the available data, it is not clear how substantial structural changes may be or what region(s) they affect, but the presence and ratio of multiple conformers could explain the diversity of LAMR functions. The equilibrium between different conformers may be skewed toward one species depending on sub-cellular localization or by stabilization of one state by protein–protein binding.

Examination of the aforementioned structures for the LAMR/RPSA homologs of yeast, *Tetrahymena*, *D. melanogaster* and *T. aestivum* as well as several archaea and bacteria hints at variable conformations of the region that guards the Peptide G helix as well. These structures are solved in the ribosomal context, where the flexible 188–196 loop appears to be either stretched out linearly across the posterior helix (“flat”) or gathered as in the free human monomer (“up”). Peptide G is still buried in both scenarios (Fig. 2D).

While archaea and bacteria lack the human-like “up” conformation, it appears as if several eukaryotes may have the pinched loop “up” structure, though there is a limited data set on which to base this comparison. Since non-laminin-expressing tetrahymenidae and yeast also display the “up” loop conformation, its contribution to laminin binding is unclear, though both these groups do have reports of laminin binding capabilities (Furtado *et al.*, 1992; Lopez-Ribot *et al.*, 1994; Narasimhan *et al.*, 1994; Sepulveda *et al.*, 1996). Ribosomal context does not seem to influence the conformation of this region, and in humans, mutation of the guarding loop does not directly affect laminin binding *in vitro* (Jamieson *et al.*, 2011).

Ultimately, the significance of Peptide G and possible conformational changes to its guarding loop for both laminin binding and other physiological events remains to be experimentally demonstrated.

(3) The Phe-32, Glu-35 and Arg-155 binding face

The second proposed laminin binding site with available structural information is the protein face presented by the structurally proximal Phe-32, Glu-35, Arg-155 residues (FER). Here, there are no obvious physiochemical features or structural grooves indicative of protein binding, but protein–protein interactions can be confined to small surface area contacts. These residues are not conserved by non-laminin binding LAMR/RPSA homologs (Jamieson *et al.*, 2011). Mutations in this region drastically affect laminin binding of the truncated LAMR$^{37(1–220)}$, which also contains Peptide G and possibly the 205–229 receptor site (or a portion). It is not clear, however, how these mutations affect the binding of the full-length protein, which supposedly contains additional binding sites. Interestingly, the FER motif is near surface-exposed Peptide G residues and the model-predicted position of the 205–229 receptor site (Fig. 2E).

(4) The C-terminal tail, DWS repeats and peptide 205–229

The CTR of LAMR and the 5 (D/E)W(S/T) repeats themselves do not seem to adopt significant secondary structure (Ould-Abeih *et al.*, 2012; Schlessinger *et al.*, 2009). Indeed, it is not clear if any ordered regions exist after residue 205 in the free protein's native conformation – residues 206–220 are not resolved in the crystal structure. Secondary structure in the CTR could conceivably be contextually induced under certain conditions, however (e.g. upon laminin or ribosome binding).

There is some evidence suggesting the NTD and CTR may weakly interact, imparting some order to the random coils of the CTR. Additional α-helicity is reported in the full-length protein over the summated secondary structures of the separated constructs (Ould-Abeih *et al.*, 2012). Indeed, NTD and CTR unification appears to translate to small differences in strength of laminin binding and interaction capacity with other substrates (Fatehullah *et al.*, 2010; Zidane *et al.*, 2013). Intrinsically disordered protein termini ("tails") frequently contribute to protein interactions by adopting structure in ligand-bound contexts (Uversky, 2013), although fold-upon-binding behaviour is not always necessary for the activity of such proteins (Sigalov, 2011).

The availability of a *de novo* model of the wheat RPSA C-terminal region fit to a cryo-EM map of the *T. aestivum* ribosome (*ta*RPSA, PDB: 3IZ6) allowed us to virtually construct the human LAMR CTR$^{210–295}$ and estimate its position relative to the NTD for representation in our model (Fig. 2A). This model and secondary structure prediction suggests α-helical structure could arise within Peptide 205–229, a putative laminin binding region. This theoretical helix is draped perpendicularly to the anterior face of the linker segment guarding Peptide G and has long been thought to adopt a helical structure (Landowski *et al.*, 1995*b*). Whether this model accurately represents human LAMR, however, is unclear given that its basis, the wheat RPSA structure, is a non-laminin binding protein in the ribosomal context.

The origins of the LAMR CTR are unknown, but the presence of this region and any function associated with it, was clearly subsequent to the genesis of the ribosomal RPS2 domain represented by the NTD. It is tempting to attribute the acquisition of laminin binding capability with evolutionary gain-of-function arising from the CTR. Indeed, given that

LAMR regions 210–295 and 225–295 have independent laminin binding activity, this may be the case. Thus, the C-terminal tail of LAMR is likely a pivotal laminin binding component that may also have implications for localization and nucleic acid binding (e.g. ribosome, membrane, chromatin, RNA). And yet, the isolated NTD (2–209) also binds laminin with similar affinity (Zidane *et al.*, 2013, see Section III.4).

Given the revelations from the crystal structure and the apparent complexities inherent to interpretation of the data available for the laminin binding sites, it seems prudent to conclude the precise nature of the interaction with laminin is poorly understood. The most outstanding questions awaiting clarification are surely: (1) which of the four proposed laminin binding sites can be physiologically verified, and (2) given the presence of multiple binding sites, why can isolated NTD and CTR constructs engage laminin independently and at affinities not dissimilar to the full-length protein?

Based on evidence that truncated proteins and synthetic peptides may behave abnormally, it is necessary to consider the true laminin binding site may not be a purely linear peptide in nature. Binding to a multi-partite face of the N-terminal domain that is subsequently stabilized by involvement of the CTR (or *vice versa*) represents a promising new explanatory paradigm for laminin interaction. Further research is necessary to clarify this issue with attention paid to using physiologically relevant constructs and conditions. Co-crystal structures or chemical crosslinking studies with laminin peptides – laminin in whole may be too challenging a molecule – and/or structural nuclear magnetic resonance (NMR) data addressing conformational changes would be enormously helpful in resolving the mechanism of laminin engagement by LAMR.

Fig. 3 attempts to summarize the suggested modes of LAMR:laminin interaction.

V. DISEASE AND THERAPY

(1) Cancer

LAMR is well known to be involved in cancer, where its functions in promoting adhesion and migration likely promote invasive and metastatic phenotypes. It is also possible that LAMR's ribosomal functions support tumour progression. Indeed, there are many studies examining the expression of LAMR in samples of human cancers. Longstanding investigations examining the use of LAMR as a prognostic indicator in a large variety of both solid and haematological malignancies have compiled over 100 individual reports, although many are small data sets (<20–50 patients). Many of these studies have been reviewed previously (Menard *et al.*, 1997, 1998; Montuori & Sobel, 1996). The larger studies (400+ patients) are focused on breast carcinomas, colorectal carcinomas and lymphomas (Carbone *et al.*, 1995; Colnaghi, 1994; Martignone *et al.*, 1993; Sanjuan *et al.*, 1996; Tagliabue & Pastorino, 1996; Viacava *et al.*, 1997), but gastric, ovarian, lung, thyroid, prostate, laryngeal and renal/adrenal tumours have also been investigated in addition to mesotheliomas, melanomas, leukaemias, astrocytomas, hepatocarcinomas, and the various metastatic sites of these cancers.

It is beyond the scope of this review to attempt a meta-analysis of the available clinical data, but the general trend appears to support a correlation between higher LAMR expression and several disease features. Decreased overall survival, poorer disease-free progression, advanced tumour stage, lesser extent of tumour differentiation, increased metastatic risk and lymph node involvement, higher intratumoral microvessel density, increased presence of invasive tumour fronts and changes in tumour responsiveness to therapy have all been linked to higher LAMR expression (either by mRNA or protein levels in histological sections). It is important to consider that a significant number of studies have found no correlation of LAMR with the previously listed indicators, and that there is likely to be variation of involvement depending on the particular malignancy.

The field awaits a large, prospective study adequately controlled for multiple comparisons, which have been weaknesses in the retrospective studies available to date. Description of membrane *versus* overall levels may also prove important in using LAMR as a predictive marker of disease course and outcome.

(2) Bacterial, viral and parasite infection

Several meningitis-causing bacteria have been implicated in using LAMR as a target of bacterial surface adhesins. Among them, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* and *E. coli* have been investigated to determine the nature of the tropism (Abouseada *et al.*, 2012; Chung *et al.*, 2003; K.J. Kim *et al.*, 2005; Orihuela *et al.*, 2009). The best-studied system is *E. coli* interaction *via* cytotoxic necrotizing factor 1 (CNF1) binding to LAMR (Chung *et al.*, 2003; K.J. Kim *et al.*, 2005). This interaction appears to trigger cytoskeletal rearrangements conducive to bacteria internalization.

Infection has also been shown to be partly mediated by LAMR for viruses capable of using the protein in a receptor capacity. Sindbis, Venezuelan equine encephalitis, Dengue, Adeno-associated, West Nile, Tick-borne encephalitis and Japanese encephalitis viruses have been reported to have LAMR tropism (Akache *et al.*, 2006; Bogachek *et al.*, 2008; Ludwig, Kondig & Smith, 1996; Strauss *et al.*, 1994; Thepparit & Smith, 2004; Thongtan *et al.*, 2012; Wang *et al.*, 1992).

A single report demonstrates the parasitic protozoan *Toxoplasma gondii* may use LAMR to enhance laminin-mediated cell surface interactions (Furtado *et al.*, 1992).

Importantly, it is acknowledged that LAMR likely does not represent a singular receptor for these infectious species, as many others have been described. LAMR may not be strictly necessary for pathogenesis either, but its presence in lipid rafts may be involved in tropism or enhancing primary receptor interactions (Simons & Ehehalt, 2002). Indeed, for pathogen infectivity as well as for the pathogenic agents described below, it is important to consider that blockade of cell-surface LAMR may be altering cellular uptake mechanisms in a broader context and not necessarily in a ligand-specific manner.

(3) Prion and neurodegenerative diseases

Prions are recently described infectious agents responsible for transmissible spongiform encephalopathies that appear to co-opt LAMR as part of a mechanism of cellular

internalization and propagation. This came to light when LAMR was proposed to interact with the PrP^{C} protein, a normally functioning endogenous molecule that can be converted to a protease-resistant, misfolded prion form (PrP^{Sc}) (Gauczynski *et al.*, 2001; Rieger *et al.*, 1997; Simoneau *et al.*, 2003). A similar circumstance exists for the yeast Sup35 prion-forming protein (Pampeno, Derkatch & Meruelo, 2014).

The PrP^{Sc} prion form is a pathological molecule in bovine spongiform encephalopathy in cattle (BSE, mad cow disease) and Creutzfeldt-Jakob disease in humans (Rieger, Lasmezas & Weiss, 1999). The physiological relevance of LAMR-PrP binding is still being investigated. N-terminally truncated $LAMR^{37(44–295)}$ and smaller LAMR fragments with uncertain folding states have been used to probe the nature of the interaction, revealing similarities to laminin binding. Nonetheless, methods to modulate LAMR function or expression seem to interfere with prion infection and propagation (Gauczynski *et al.*, 2006; Leucht *et al.*, 2003; Zuber *et al.*, 2008*a*, b).

Because of the commonalities of amyloid beta (Aβ), an etiological agent in Alzheimer's Disease, with prion proteins and the association of PrP^{C} in Aβ related pathology, it has been suggested LAMR may play a role in Alzheimer's Disease (Da Costa Dias *et al.*, 2011; Vana *et al.*, 2009). The evidence for this is preliminary but mounting. LAMR has been found to contain irregular oxidative modifications in a small-scale proteomics investigation of the brains of Alzheimer's model mice (Shin *et al.*, 2004). Modulation of LAMR has also recently been reported to affect Aβ cytotoxicity (Da Costa Dias *et al.*, 2013) and its release from cells (Jovanovic *et al.*, 2013, 2014).

(4) Therapeutic approaches

Given the diverse roles LAMR plays in many key cellular processes, it is not surprising that this protein has been linked to pathology. LAMR's overexpression in cancer and its receptor behaviour for pathological agents make it a tempting target for therapeutics.

Attempts to exploit LAMR for therapeutic purposes have been frequent endeavours that have met with various degrees of success. Several approaches have been taken. The first efforts attempted to use antibodies intended to block cell-surface LAMR binding to laminin. Indeed, antibodies used in this manner successfully reduce experimental metastasis formation of injected tumour cells in mice (Narumi *et al.*, 1999). Similarly, synthetic peptides designed to mimic laminin (YIGSR peptides) have shown equivalent effects in the same experimental systems (Iwamoto *et al.*, 1987; Nakai *et al.*, 1992; Yamamura *et al.*, 1993). This success led to efforts to derivatize YIGSR and related peptides into more effective forms (e.g. cyclic peptides, extended peptides, tripartite repeats, terminal modifications) and use for tumour targeting of liposomes (Kikkawa *et al.*, 2013). Because YIGSR's effects have not been conclusively demonstrated to work through LAMR, however, results should be examined with open mindedness for other targets (Maeda *et al.*, 1994).

Other approaches attempting to treat malignancies have focused on a LAMR tumour-associated antigen referred to as oncofetal antigen immature laminin receptor protein (OFA-iLRP). This avenue of research led to tumour vaccine studies encouraging antibodies to develop against OFA-iLRP. The undertaking has produced promising results and recruitment

for an early-phase clinical trial is in progress (Barsoum *et al.*, 2009; Biragyn *et al.*, 2007; Friedrichs *et al.*, 2008). Oncolytic viruses carrying LAMR-silencing short hairpin RNA (shRNA) payloads have been used to similar effect (Scheiman *et al.*, 2010*b*).

Knowledge of LAMR has also been applied in developing treatments for prion diseases (Omar et al., 2011; Sakaguchi, Ishibashi & Matsuda, 2009) and to advance tissue engineering (Gu & Masters, 2010).

Ultimately, small molecule inhibitors are often the most desirable therapeutic interventions. The green-tea-derived polyphenol, (−)-epigallocatechin-3-gallate (EGCG), is one such small molecule that has been reported to affect cells through LAMR^{67} (Tachibana *et al.*, 2004). EGCG has also been reported to interact with LAMR^{37} (Zidane *et al.*, 2013). EGCG is often described as having broad health-promoting benefits in a wide range of human pathologies (Chen *et al.*, 2008; Mak, 2012). Unfortunately, EGCG suffers from low bioavailability with poor oral absorption as well as significant stability issues in plasma (Chow *et al.*, 2003). This would suggest EGCG may better serve as a lead compound for aid in designing improved LAMR-targeted small molecules.

Numerous investigations into the mechanisms of LAMR-dependent EGCG actions have been conducted and point toward cytoskeletal involvement (Umeda, Tachibana & Yamada, 2005; Umeda *et al.*, 2008*a*, b). Curiously, EGCG efficacy appears to be blocked by LAMR antibodies, which do not trigger the same effects, indicating that the polyphenol may be acting agonistically or allosterically. This observation also leads to the conclusion that EGCG may be acting on extracellular LAMR, leaving the upstream mechanism and the signal transduction process unclear. It is also noted that in many of these studies, the adverse effects of LAMR knockdown described herein do not seem to be observed. Because EGCG has been reported to influence a large number of cellular targets, using this compound as a tool for investigating LAMR functions and signal transduction pathways becomes complex and difficult, but the therapeutic implications are clear.

Strikingly, a screen to disrupt the KRS:LAMR interaction, a laminin-induced event that stabilizes the presence of LAMR^{67} at the plasma membrane (see Section II.5), has led to the discovery of a KRS-targeted small molecule with anti-metastatic activity (Kim *et al.*, 2014).

VI. CONCLUSIONS

1. The 37/67-kDa laminin receptor/RPSA protein is a demonstrably important biological molecule with roles in some of the most fundamental cellular processes. Alongside its normal physiological functions, LAMR has been strongly linked to neoplastic diseases, bacterial and viral infection, developmental abnormalities and neurodegenerative conditions.

2. The nature of conversion of the 37-kDa LAMR protein to higher molecular weight species (53- and 67-kDa) remains poorly understood. SUMOylation is a candidate

modification, but it is undetermined if other proteins contribute to multimerization. The functional purview of each protein species is similarly incompletely described.

3. The process by which LAMR is directed to cytosol, ribosomes, nucleus and the outer plasma membrane is unknown. Although ribosomal proteins are often multifunctional, it is unclear how the cell differentially distributes this protein and maintains the particular ratios necessary for homeostatic function.

4. Native laminin interaction most likely occurs on a protein face apparent only in the full structure of LAMR rather than at discrete linear segments. Binding could be a collaborative event between several binding sites and clearly involves engagement of the intrinsically disordered C-terminal tail. A similar situation may exist for laminin where, again, linear peptides (e.g. YIGSR) may not adequately capture native binding states.

5. Intracellular functions of LAMR include anchoring ribosomes to microtubules, processing of pre-rRNA, signalling at focal adhesions to laminin and yet undescribed roles in histone interactions and chromatin regulation.

6. Knowledge of LAMR extracellular functions is considerably more difficult to place into physiological context, especially as it concerns extra- to intracellular signal transduction. Although cell-surface LAMR appears to bind laminin, it is uncertain if this is solely in an adhesion capacity or if LAMR modulates migratory processes directly (i.e. exclusive of intracellular functions). In the probable absence of a transmembrane region, mechanistic progression of signal to response will be a required area of future research.

7. LAMR cellular biology reflects involvement of translational and transcriptional machinery as well as extracellular signals acting non-exclusively across several sub-cellular locations. This significantly complicates the dissection of the pathways relevant to discrete events. These broad and crucial functions are most likely operating in conjunction and, therefore, highly relevant for understanding the true contribution of LAMR to physiology and disease.

Acknowledgments

We thank Drs. Christine Pampeno, Lisa Venticinque, Tomer Granot and Jonathan Scheiman for critical reading of this manuscript and valuable input concerning its content. This work was supported by US Public Health grant CA100687 from the National Cancer Institute, National Institutes of Health and Department of Health and Human Services as well as Institutional National Research Service Award T32-CA009161 (Levy). Protein structure graphics were generated using the PyMOL Molecular Graphics System, Schrödinger, LLC.

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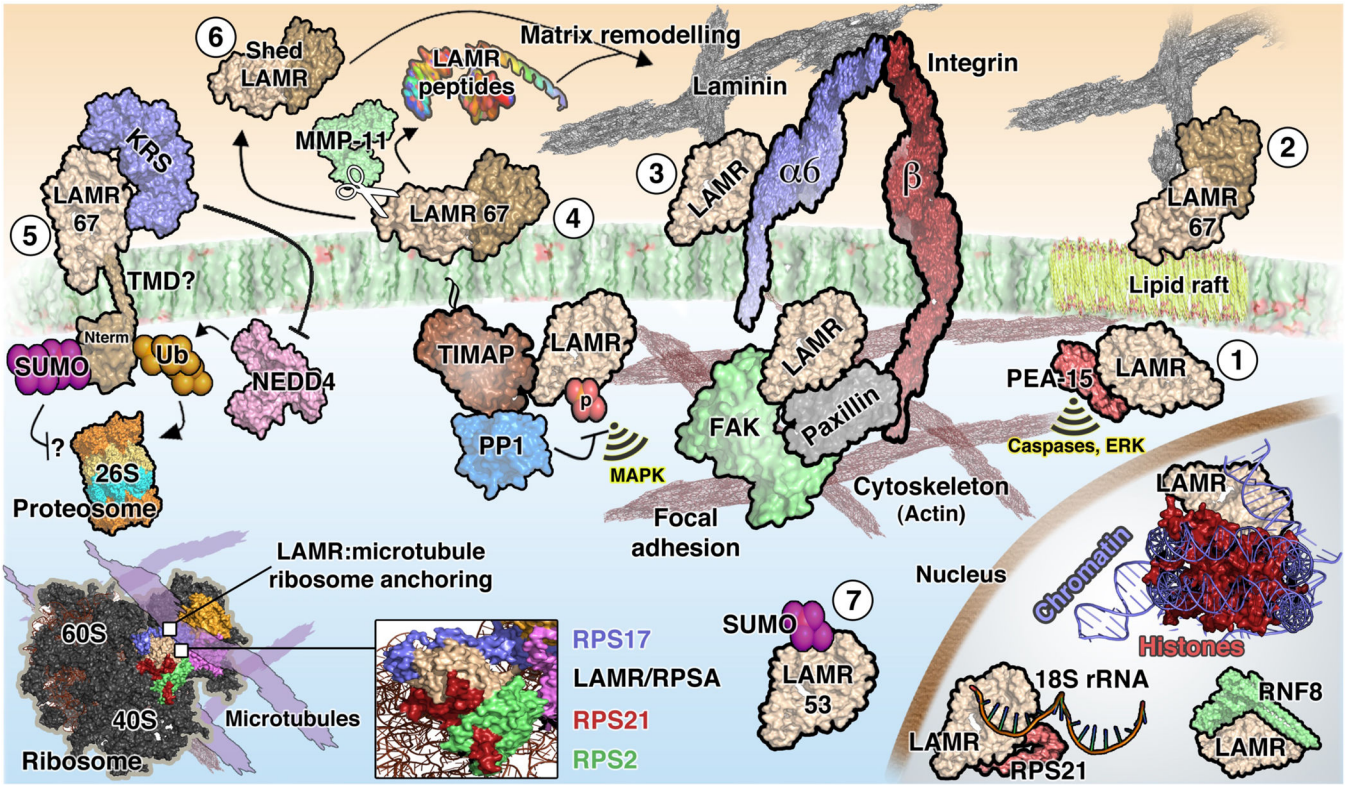

Figure 1.

Theoretical cellular biology of laminin receptor (LAMR/RPSA). Several possible LAMR species are depicted including (1) intracellular LAMR[37]; (2) extracellular peripheral membrane LAMR[67] capable of independently binding laminin; (3) extracellular peripheral membrane LAMR[37] supporting integrin laminin binding; (4) LAMR[67] membrane association *via* the properties of a homo- or heteromer; (5) LAMR[67] with hypothetical transmembrane domain (TMD). It is unclear how LAMR membrane presence is dynamically regulated by intracellular proteins in the absence of a TMD; (6) shed LAMR[67] and (7) intracellular SUMOylated LAMR[53]. Ribosomal, cytoskeletal and nuclear localizations of LAMR in addition to its presence at focal adhesions are also depicted. All protein–protein contacts represent experimentally demonstrated interactions. Signalling indications (yellow) represent preliminary evidence for signalling cascades involving LAMR. Because of ambiguity in the data, the subcellular locations of each protein are not necessarily accurate and represent only predictions based on available evidence. Similarly, the species of LAMR (i.e. 37/67 kDa) depicted for each function is not meant to suggest exclusivity or a definitive understanding of the relevant molecule(s). p, phosphorylation. Nterm, intracellular N-terminus of LAMR. Ub, ubiquitin. SUMO, small ubiquitin-like modifier. NEDD4, neural precursor cell expressed developmentally down-regulated protein 4. RPS, ribosomal protein small subunit. MMP-11, matrix metalloproteinase-11/stromelysin-3. KRS, lysyl-tRNA synthetase. TIMAP, TGF-inhibited membrane-associated protein. PP1, protein phosphatase-1. FAK, focal adhesion kinase. PEA-15, phosphoprotein enriched in astrocytes-15. RNF8, ring finger protein 8. MAPK, mitogen-activated protein kinase pathways. ERK, extracellular signal-regulated kinase pathways.

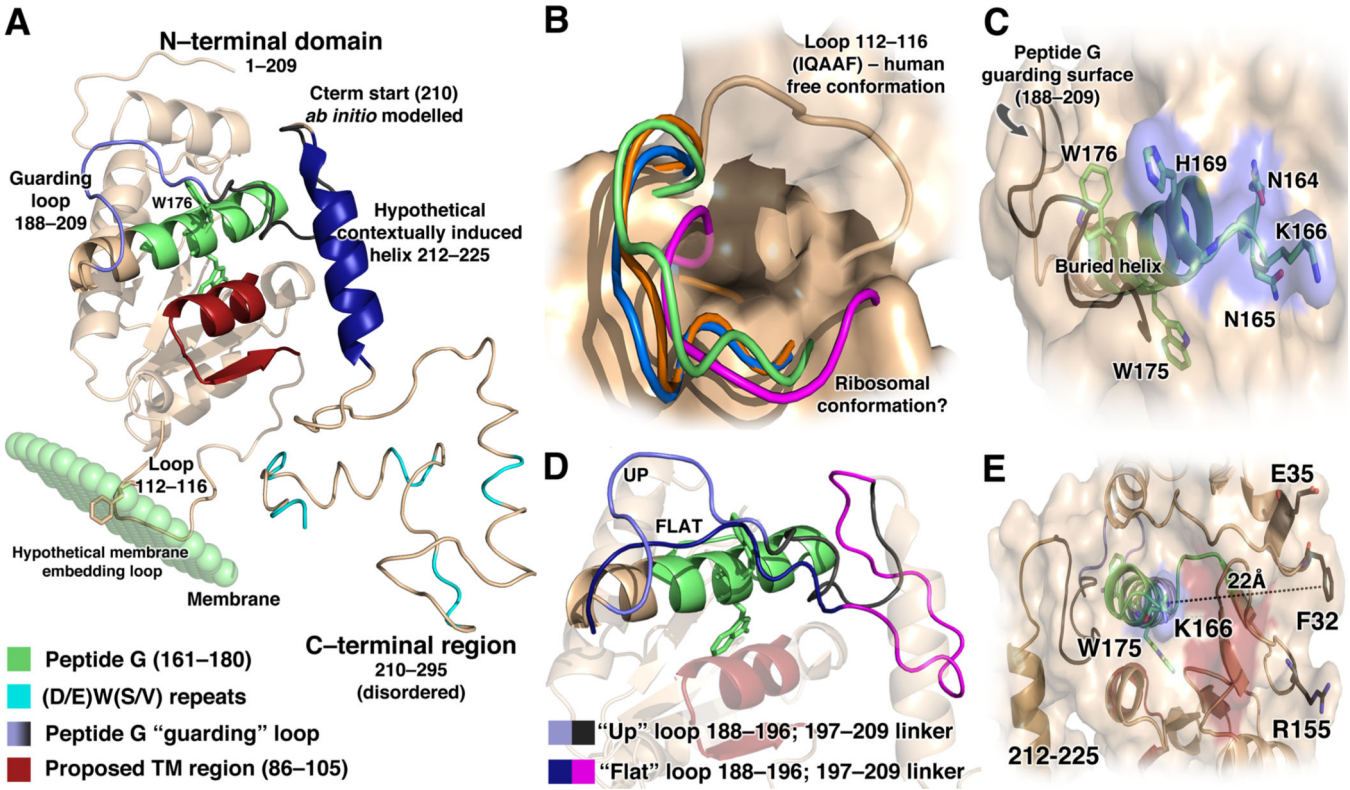

Figure 2.

Model of full-length 37-kDa laminin receptor. (A) Model of LAMR 1–295 built from the structures of human LAMR$^{9–205}$ (PDB: 3BCH) and *T. aestivum* RPSA (PDB: 3IZ6) using a combination of homology threading and *ab initio* folding. The model depicts three proposed laminin binding regions: Peptide G (green), intrinsically disordered Peptide 205–229 in a hypothetical laminin-induced helical structure (blue), and five disordered DWS repeats (cyan). A proposed transmembrane (TM) region is shown packed up against the core of the structure in a conformation not indicative of a transmembrane helix (red). A speculative membrane-embedding mechanism *via* a hydrophobic loop is also suggested. (B) Structural divergence of the 112–116 loop in human LAMR/RPSA (beige, 3BCH) *versus* archaea rps2P (green, 1VI6). The ribosomal context conformations of the same loop in human (orange, 3J3A), wheat (magenta, 3IZ6) and *Tetrahymena thermophila* (blue, 4BPE) RPSA are also shown. Yeast (3U5B) and fly (3J38) ribosomal structures demonstrate loops structurally homologous to ribosomal human RPSA. (C) The buried Peptide G helix shown in green with surface-exposed residues N164–H169 indicated by blue surface overlay. Peptide G guarding loop in black. (D) Highlight of the 188–196 loop in the "up" (light blue) or "flat" (dark blue) conformations. The 197–209 linker could also adopt different conformations: a small turn (black) or an extended protruded loop (magenta). (E) A fourth proposed laminin binding site composed of Phe-32, Glu-35 and Arg-155 shown relative to Peptide G (22 Å from Lys-166 side chain) and a theoretical laminin binding helix (212–225). A hypothetical laminin binding surface is shaded in red.

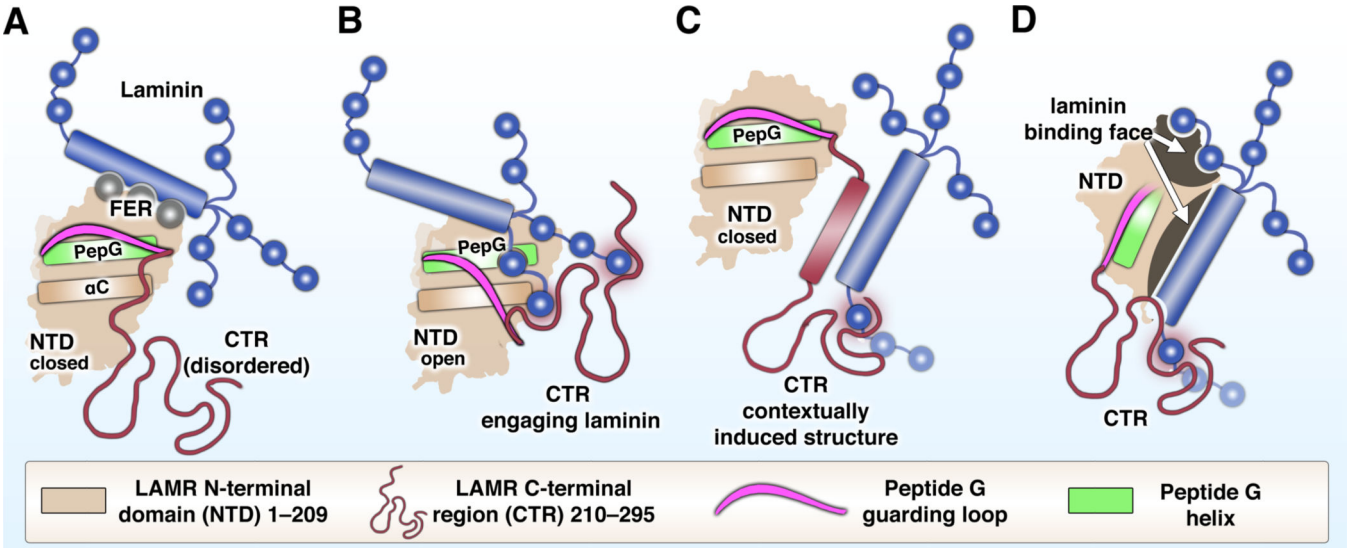

Figure 3.

LAMR interaction with laminin. Several theoretical modes of LAMR:laminin binding are proposed for discussion. (A) LAMR interaction with laminin through the N-terminal domain (NTD) only. Binding is *via* the Phe-32, Glu-35, Arg-155 (FER) motif while Peptide G (PepG, green) remains buried by a guarding loop in the "closed" position (magenta) above the C-helix (αC). (B) Guarding loop in the theorized "open" position, allowing laminin interaction with previously buried Peptide G. The C-terminal region (CTR, red) could also cooperatively engage laminin while remaining unfolded. (C) Laminin interaction through the CTR exclusively. The CTR could hypothetically adopt secondary structure in the laminin-bound context. (D) Laminin interaction *via* a non-linear multipartite protein face on the NTD with involvement of the CTR. The representations of laminin (blue) are not meant to imply particular interaction sites and are not to scale.