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Association of progerin-interactive partner proteins with lamina proteins: Mel18 is associated with emerin in HGPS

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ABSTRACT **Objective**: The Hutchinson-Gilford progeria syndrome (HGPS or progeria) is a childhood disorder with features of premature aging and is caused by mutations in the lamin A gene resulting in the production of an abnormal protein, termed progerin. To investigate the underlying pathogenic mechanism, we studied the nuclear co-localization and association of progerin interactive partner proteins (PIPPs) with lamina proteins. **Methods**: Both wild-type (WT) and progeria fibroblasts were studied by various methods including confocal microscopy, immunoprecipitation and Western blot. **Results**: All PIPPs discovered so-far co-localized with lamin A/C. In addition, the PIPPs were selectively associated with lamina proteins. An increased immunofluorescent staining signal was found for Mel18 in HGPS as compared to WT cells. An association of Mel18 with emerin was observed in HGPS, but not in WT cells. **Conclusion**: Based on these findings, we propose that PIPPs, along with associated lamina proteins may form a pathogenic progerin-containing protein complex.

KEY WORDS Progeria; Lamin type A; Nuclear envelope; Nuclear lamina

The Hutchinson-Gilford progeria syndrome (HGPS or progeria) with a reported incidence of approximately 1 in 8 million is characterized by features of premature aging in childhood [1]. HGPS has been determined to be a laminopathy resulting from genetic defects of the *LMNA* gene that encodes lamin A/C[2-3]. Lamin A/C is a component of the nuclear la-mina[4] and nuclear envelope (NE)[5]. The NE is composed of inner and outer nuclear membranes (INM and ONM, respectively). The INM has been modeled as a subcompartment of the endoplasmic reticulum (ER) where proteins integrated in the INM can migrate between the INM and the ER[6]. The INM may also function as a bed anchoring lamina filaments that interact with nucleoplasmic ring structures of adjacent nuclear pore complexes (NPC)[6].

In most HGPS cases, a silent mutation, G608G, results in a splicing error that produces a truncated protein, progerin, that lacks 50 amino acid residues involving exons 11 – 12 near to the C-terminus of prelamin A[3]. Progerin disrupts the nuclear structure and results in intranuclear aggregations through a dominant negative effect[7]. To investigate the underlying mechanism, we previously sought to determine if progerin generates novel interaction(s) that normally does not involve lamin A/C. We identified four novel progerin-interactive partner proteins (PIPPs), including hnRNP E1, Mel18, UBC9, and EGF, which also were found to interact with lamin A/C in normal cells[7]. We have conducted further studies of these PIPPs to determine if there are any altered associations with lamina proteins.

1 Materials and Methods

1.1 Fibroblasts

Both wild-type (WT) and progeria (HGPS) fibroblasts were obtained from our institutional cell culture core facility. The HGPS cell lines were previously demonstrated to carry a G608G mutation[3] and had a mutant progerin band on western blots [7].

1.2 Immunofluorescent studies

Confocal microscopy was employed to monitor and detect the staining fluorescence. Fibroblasts were seeded one day before staining on cover slips. Cultivated fibroblasts were fixed with 3.2% paraformaldehyde/PBS at room temperature for 20 minutes, then permeabilized with 1% NP-40/PBS (or 0.2% Triton X-100/PBS) for five minutes and blocked with 0.1% Brij58/5% horse serum and labeled with a primary monoclonal antibody at 37 ℃ for one hour. A secondary Ab was developed and the cells were immediately examined. In addition to the antibodies described below, an mAb of anti-mitochondria (#RDI-MitochonabmX, RDI Research Diagnostics, Flanders, NJ) was used as a non-nuclear protein marker.

1.3 Co-immunoprecipitation (co-IP)

The procedures for co-IP using a Seize® Protein A/G Immunoprecipitation Kit (Pierce, IL) were carried out following our published protocols[7]. Briefly, fibroblast cells were lysed in 50 mmol/L Tris-HCl/pH 7.4 containing 1% Triton X-114 and a proteinase inhibitor cocktail to enrich for the membranous proteins; and freeze-thawed three times. Aliquots of cellular extracts were quantified with a BCA kit (Pierce, IL) and equal amounts of protein were applied for co-IP. For Ab binding to the protein A/G pre-coated wells, each well was washed three times with 200 μL IP buffer (provided in the kit) before the Ab was bound to the well. Each Ab was diluted in IP buffer to 10 – 100 mg/L, depending on the titer of the Ab, and the antibody solution was added to the wells. Then the

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strip wells (for multiple samples) were covered with Plate Sealing Tape (provided in the kit), incubated at room temperature for 1 hour and washed five times with 200 μL IP Buffer. To capture the antigens and their interactive partner protein, the cell lysate was diluted 1∶1 to 1∶100 in IP buffer and added to the appropriate wells. If the lysate solution was dilute (i.e., < 0.1 mg/L) and was in a large volume, the antigen sample was added in three separate aliquots and incubated for 20 minutes each. The wells were incubated at room temperature for 1 hour, washed five times with 200 μL IP Buffer and the last wash incubated for 5 minutes. Finally, the protein complex was eluted with 20 μL of elution buffer.

Antibodies used for immunoprecipitation were obtained from three sources. The polyclonal anti-hnRNP E1 was provided by Xiao et al[8]. An anti-progerin polyclonal Ab was generated in-house[7]. Commercially available monoclonal antibodies (mAb) for lamin A/C (#MAB3211) and mAb for lamin B1 (#MAB3213) were purchased from Chemicon International (Temecula, CA), a mAb for EGF (#ab10409) and a polyclonal Ab (pAb) for Mel18 (#ab5267) from Abcam (Cambridge, MA), a mAb for UBC9 from ProteinTech Group (#10070-1-AP, Chicago, IL), a mAb for emerin from NeoMarkers (# MS-175, Fremont, CA), mAbs for SREBP (#557036) and LAP2 (#L74520) from BD Biosciences (Frankin Lakes, NJ), and mAb for BI-1, the Bax-inhibitor 1, an ER protein used as a negative control, from Santa Cruz BioTechnology (#sc-12393, Santa Cruz, CA).

Western blotting was performed using standard procedures. The eluate of the co-IP described above or the total proteins extracted from cells were mixed with 20 μL of protein sample buffer (10 mmol/L DTT, 62.5 mmol/L Tris pH 6.8, 10% glycerol, 2% SDS), boiled for five minutes, and applied to 10% PAGE-SDS gel. This was subjected to electrophoresis at 100 volts in a Tricine buffer until the tracking dye had fully run out. The proteins were transferred onto a PVDF membrane and probed by antibodies for lamin A/C, progerin, EGF, hnRNP E1, UBC9, and Mel18, respectively.

2 Results

2.1 Co-localization of PIPPs with lamina proteins

Double-staining of PIPPs and lamina proteins was carried out to investigate potential differences of PIPP localization between wild type (WT) and progeria (HGPS) cells. The hnRNP E1 staining overlapped signals with lamin A/C, lamin B1, and emerin (Figure 1); as did UBC9, Mel18, and EGF with lamin A/C (Figure 2). No significant difference was detected in comparing the WT and HGPS fibroblasts for hnRNP E1, UBC9, and EGF. However, the Mel18 staining signal was much stronger in HGPS than in WT (Figure 2B), irregardless of whether the HGPS cells were stained by anti-lamin A/C (HGPS) or anti-progerin (HGPS-P) antibody.

2.2 Differential association of Mel18 with emerin

To determine if Mel18 has differential association with lamina proteins and PIPPs, other than lamin A/C where there was no differential interaction found before[7], three lamina proteins, lamin B1, LAP2β, and emerin, that have been determined to associate with lamin A/C and participate in assembling the nuclear envelope[6], along with PIPPs, were used for co-IP with Mel18 in wild-type (WT) and progeria (HGPS) fibroblasts (Figure 3). The 40 000 of Mel18 band probed by anti-Mel18 mAb in the lanes with HGPS (M) cells was stronger than lanes with wild-type (W) cells. No Mel18 band was detected in the lane 5 where anti-emerin antibody was applied for co-IP of Mel18 with emerin from cultured HGPS fibroblasts. Interestingly, the anti-Mel18 (lane 9) did not precipitate Mel18 in HGPS cells either, although the Mel18 band from wild-type cells detected at lane 10 was weaker than the others.

2.3 Co-immunoprecipitation of PIPPs with lamina proteins

To determine if there were differential associations between the PIPPs and lamina proteins, hnRNP E1, EGF, and UBC9 were also applied to co-IP with lamina proteins (Figure 4), followed by immuno-probing with antibodies anti-lamin A/C (Figure 4A), anti-progerin (Figure 4B), anti-EGF (Figure 4C), anti-hnRNP E1 (Figure 4D) and anti-UBC9 (not shown).

No significant difference was detected. Both lamin A/C (Figure 4A) and progerin (Figure 4B) were shown to associate with hnRNP E1 (lane 1). The majority of hnRNP E1 associated with lamin C (Figure 4A, c) rather than lamin A (Figure 4A, a). It seemed that most of the lamin A protein was degraded, as we have reported earlier[7], to a smaller size fragment that is shown at a lower position than lamin C (Figure 4A, s). The association of hnRNP E1 with progerin is much stronger than with lamin A/C. The lamin A/C showed associations with lamina proteins LAP2β, SREBP, and lamin B1 (Figure 4A, lanes 3 – 5 respectively); but not with emerin (lane 2). There was no lamin A/C (Figure 4A, lane 7), nor progerin (Figure 4A, lane 6), protein bands detected on Western blots, which likely resulted from the protein degradation. Other than hnRNP E1 and progerin itself, the anti-progerin Ab did not pick up any signals of lamina proteins in wild-type (WT) cells (Figure 4B). However, a band was detected at lane 2 of HGPS, where the mAb of anti-emerin co-immunoprecipitated progerin, indicating that there was an increased association between progerin and emerin.

PIPPs showed selective association with lamina protein(s). The EGF (Figure 4C) was associated with lamina proteins of lamin B1 (lane 1), emerin (lane 2), and SREBP (lane 3), but not with LAP2 β (lane 4). Although binding to UBC9 (lane 6), EGF did not associate with Mel18 (lane 9) suggesting that anti-Mel18 Ab blocks the binding domain of Mel18 with which the EGF associates. The hnRNP E1 (Figure 4D) associates with progerin and Mel18. The pattern of hnRNP E1 is different between lane 5 or lane 9 and

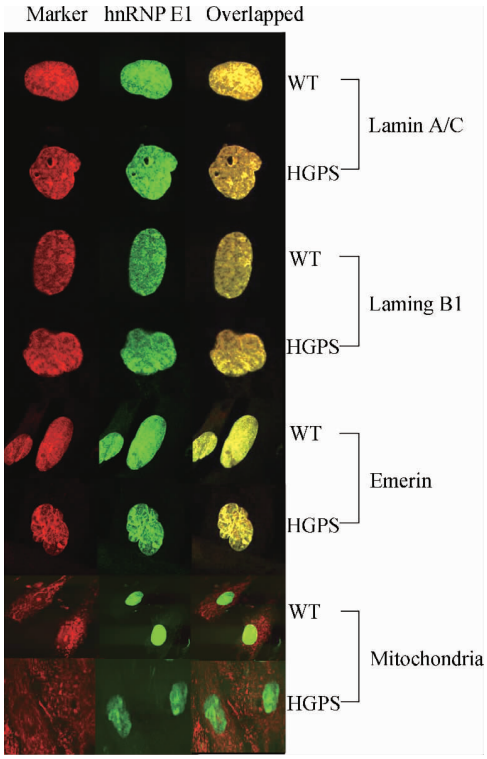
other lanes. Apparently, the patterns of these two lanes are not the predominant protein bands, compared to that shown in the lane Ce, the cellular extract. The band of hnRNP E1 with Mel18 is similar to that shown on Figure 3 (lanes 1 – 2), suggesting the protein complex of hnRNP E1 associating with Mel18 is quite strong and was not disassociated with the experimental conditions. An usual hnRNP E1 band with a smaller size in lane 5 suggested that progerin has enriched the unusual hnRNP E1 variant form. This is in agreement with the strong signals of progerin detected in lane 1 of Figure 4A. UBC9 also showed selective association with lamina proteins (not shown). It associated with lamin B1, SREBP, LAP2β, but not emerin.

3 Discussion

A-type and B-type nuclear lamins are the two main proteins components of the nuclear lamina [9-10]. The association between lamin A/C and lamin B, along with other lamina proteins such as lamina-associated peptides (LAP) and emerin, is the structural basis for assembly of the nuclear envelope[4-6]. Disruption of the envelope, which results from *LMNA* gene mutation (s), may cause laminopathy disorders in which phenotypes are correlated with the position of the mutation (s) at *LMNA*-encoded proteins[2-3, 11-22]. A silent mutation, G608G, is the underlying genetic defect in the majority of HGPS cases[2-3]. This mutation generates a cryptic splicing site in the *LMNA* gene and produces a truncated protein progerin. The mutant progerin lacks 50 amino acids in the exon 11 – 12 encoded region at the carboxyl terminus of pre-lamin A and abolished an internal cleavage site involved with the post translational processing of pre-lamin A and removal of the farnesylated carboxy-terminal cysteine[23-24]. This interferes with lamin A/C forming a parallel coiled-coil homodimers, then forming head-to-tail strings, and ultimately a higher-order filamentous meshwork of lamina structure[25-26]. To investigate the details of how progerin interferes with the lamina structure formation, we previously employed progerin to screen for newly generated interactions with novel partner protein (s). In fact, four protein-interactive partner proteins (PIPPs) were obtained[7]. However, these PIPPs did not show differential interactions with normal lamin A/C. To further investigate if these PIPPs are involved in any pathogenic alteration (s) with lamina structure in HGPS, we undertook these studies of co-localization and co-immunoprecipitation. Our results provided evidence that PIPPs are localized at nuclei, although there was no significant difference found between the wild-type and HGPS cells, and the association with lamina proteins.

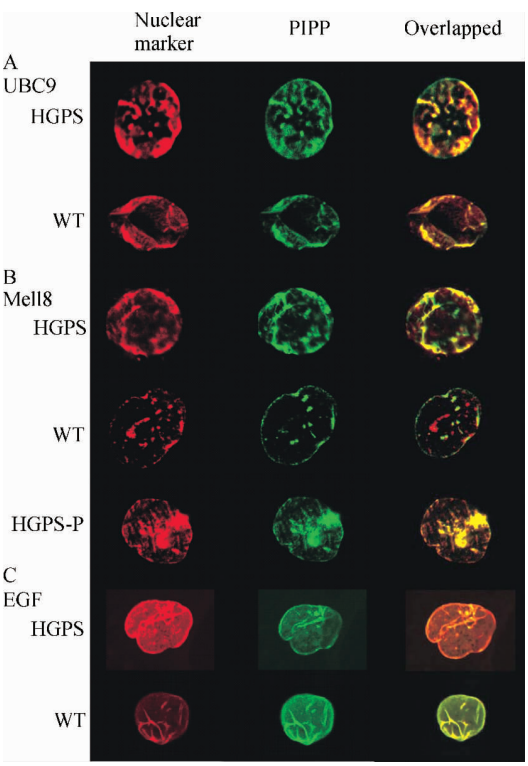
Emerin binds to lamin A/C and to chromatin through BAF, the barrier to autointegration factor[27-28]. Emerin is anchored at the inner nuclear membrane through a hydrophobic stretch and protrudes from the hydrophilic region to the nuclear plasma where it interacts with the nuclear lamina. It is speculated that emerin contributes to maintenance of the nuclear structure and stability, as well as nuclear functions. Genetic defects in emerin are linked to Emery-Dreifuss muscular dystrophy (EDMD)[29-30]. In addition to emerin, certain mutations in the *LMNA* gene can also result in clinical EDMD[11,19]. It was determined that several, but not all, disease mutations in emerin map to a central lamin A-binding domain, and that mutations in this region disrupt emerin-lamin A interactions[27]. Genetic defects of lamin A/C resulting in the same EDMD phenotype suggest the likelihood that certain mutations of *LMNA* gene interrupt the association of lamin A/C with emerin in the nuclear envelope. Indeed, mutation L530P of lamin A/C resulted in an assembly defect through a disassociation of lamin A/C from emerin[11]. In this study, emerin was shown not to associate with Mel18 in wild-type cells. However, it does associate with Mel18 in the HGPS cells. We propose that this is a part of the dominant negative effect of progerin. In the HGPS cells, the mutant progerin might be involved in bridging this association through the hnRNP E1. We have seen that the association between progerin and hnRNP E1 is very strong (Figure 4B, lane 1) and the association of hnRNP E1 with Mel18 is very strong (Figure 3, lanes 13 – 14; Figure 4D, lane 9). It is likely that progerin has an increased association with hnRNP E1, which is tightly associated with Mel18. When progerin associates with emerin in HGPS, the emerin, progerin, hnRNP E1, and Mel18 form a protein complex, which was pulled down by mAb anti-emerin and was probed by mAb of anti-Mel18, as seen in the Figure 3.

The newly formed progerin-contained protein complex may have been comprised of more than emerin, progerin, hnRNP E1, and Mel18. We have found that lamina proteins included in this study may have selectively associated with PIPPs (Table 1). The lamin B1 associates with UBC9, EGF, and hnRNP E1; the LAP2β with UBC9 and hnRNP E1 but not EGF and Mel18; the emerin with hnRNP E1 and EGF but not UBC9. These associations establish a meshwork, in addition to lamina structures, at the INM to participate in the complicated cellular functions as well as pathogenic mechanisms that underlie HGPS and other laminopathies. It is likely that hnRNP E1 plays a central role in this complex because it associates with all of the PIPPs and lamina proteins. HnRNP E1 is an RNA-binding protein with three KH domains[31]. Within the hnRNP complex, it regulates RNA processes[32]. Our recent study showed that hnRNP E1 regulates hundreds of transcripts and translations. Whether the PIPPs and lamina proteins involved in this study are the targets regulated by hnRNP E1 is an open question, and a subject for further investigation.



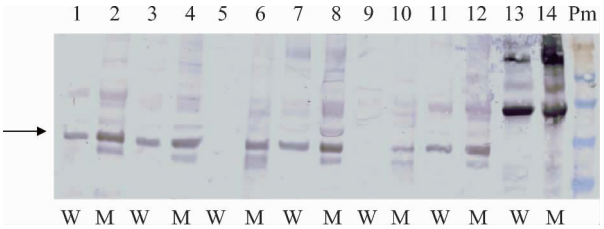
Immunofluorescent staining of hnRNP E1 showed endogenous hnRNP E1 (green) overlappes with lamina proteins (red) that include lamin A/C, lamin B1, and emerin in nuclei of both wild-type (WT) and progeria (HGPS) fibroblasts. Mitochondrial marker antibody was used as a non-nuclear control and shown there was no overlapping signal between nuclear hnRNP E1 and cytoplasmic mitochondria.

Figure 1 Co-localization of hnRNP E1 with lamina proteins



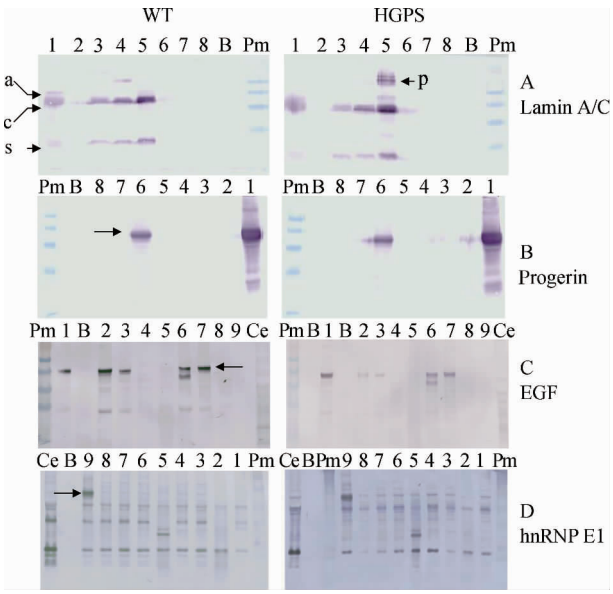
PIPPs (green) were shown to overlap with nuclear marker (red) of lamin A/C in both wild-type (WT) and progeria (HGPS) fibroblasts in panels A-C, except in panel B where the overlapped signal of Mel18 in WT cells were weak, compared to the signals stained by either anti-lamin A/C (HGPS) or anti-progerin (HGPS-P) antibodies in HGPS cells.

Figure 2 Localization of PIPPs at nuclei of wild-type (WT) or progeria (HGPS) fibroblasts



Mel18 was co-immunoprecipitated with lamin B1 (lanes 1 – 2), LAP2β (lanes 3 – 4), emerin (lanes 5 – 6), UBC9 (lanes 7 – 8), Mel18 (lanes 9 – 10), EGF (lanes 11 – 12), and hnRNP E1 (lanes 13 – 14). The Mel18 was probed by a mAb as a 40 000 band (arrow pointed). No signal was detected at lanes 5 and 9 from the wild-type (W) fibroblasts. Signals of HGPS (M) lanes were stronger than W lanes. Two heavier bands, which were about 53 000 and 98 000, stained by the mAb of anti-Mel18 in lanes 13 – 14 were detected, suggesting that protein complex was not disassociated with the current conditions. Pm is a protein marker.

Figure 3 Mel18 differentially associates with emerin



Specific antibody was used to immunoprecipitate hnRNP E1 (A, lane 1), lamin B1 (A – B, lane 5; C – D, lane 1), emerin (A – D, lane 2), LAP2β (A – B, lane 3; C – D, lane 4), SREBP (A – B, lane 4; C – D, lane 3), UBC9 (C – D, lane 6), EGF (C – D, lane 7), Mel18 (C – D, lane 9), progerin (A – B, lane 6; C – D, lane 5), and BI1 (A – D, lane 8) from wild-type (WT) or progeria (HGPS) cells. The immunoprecipitated protein complex was applied to a western blot that was probed by antibody against lamin A/C (A), progerin (B), EGF (C), and hnRNP E1 (D). Pre-lamin A (A, p) can be seen in lane 4 (WT) and lane 5 (HGPS), as pointed by an arrow. Bands of degraded lamin A/C with a smaller size are labeled by an arrow (A, s). Lane Ce refers to the cellular extract of total proteins without immunoprecipitation. Lane Pm is a protein marker. B refers a blank lane. a and c are the appropriate size for lamin A and lamin C. Arrows point to the specific PIPP band(s).

Figure 4 Co-immunoprecipitations of PIPPs with lamina proteins

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Progerin 作用的伴侣蛋白和核纤层蛋白间的相互作用:在早老症中 Me118 与 emerin 的相互作用

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