NUCLEOCYTOPLASMIC TRANSPORT IN CELLS WITH PROGERIN-INDUCED DEFECTIVE NUCLEAR LAMINA

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The nuclear lamina (NL) is a fibrillar network located between the inner nuclear membrane of eukaryotic cells and chromatin-containing nucleoplasm. Recent data indicate that NL plays a relevant role in many fundamental cellular functions [1]. The principal components of NL are lamin A/C and laminB, which are encoded by the LMNA and LMNB genes, respectively [2,3]. Each LaA molecule undergoes a complex post-translational processing from the precursor prelamin A (pre-LaA) [4]. Yet, a specific single point mutation in LMNA leads to the internal deletion of 50 aminoacids preventing the post-translational processing of pre-LaA. The deletion mutant, called **progerin**, remains farnesylated and accumulates at NL leading to nuclear architectural defects such as blebs and herniations of nuclear envelope (NE) and thickening of NL [4]. This LMNA mutation is at basis of an extremely rare genetic disorder that causes premature, rapid aging shortly after birth names Hutchinson-Gilford progeria syndrome (HGPS) [1,4].
Owing to the close structural relationship between NL and the Nuclear Pore Complex (NPC), we tested whether HGPS affects passive and active nucleo-cytoplasmic shuttling of cargoes by means of an established model based of Fluorescence Recovery After Photobleaching [5]. We carried our experiments on cultured U2OS human cells, transiently co-transfected with progeria ($HGPS^+$) or wild-type ($HGPS^-$) LaA linked to fluorescent reporter DsRed, and NLS-EGFP or NES-EGFP fusion proteins. The use of $HGPS^+$ and $HGPS^-$ LaA-DsRed established cellular models where LaA correct fold or misfold into NL were easily visible by optical microscopy. Our findings clearly point out that dysmorphic NL affected neither active, nor passive nucleocytoplasmic translocation features of NLS-EGFP or NES-EGFP. Also, we found out that passive diffusion does not interfere with nuclear import or export, analogously to what reported by us [5]. Our results provide a complete picture of nucleocytoplasmic transport in progeria cells and can be easily reconciled with previous findings of impaired RanGTP gradient between nucleus and cytoplasm, given the small size of shuttling cargo [6].

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