Characterisation of lamin A/C interaction with phosphoinositides

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Lamins are intermediate filaments found in the nuclei of eukaryotes where they are essential for a range of molecular events. While the role of lamins at the nuclear periphery is well studied, less is known about their assembly, dynamics and interactions in the interior. Recent studies suggest a role of the nucleoplasmic pool in chromatin organization, motion and in its accessibility by regulating epigenetic modifier complexes. The localization and interactions of lamins is proposed to be regulated by their complex post-translational modifications. Importantly, depletion of the nucleoplasmic lamin A is correlated with disease phenotypes like Hutchinson-Gilford progeria.

Preliminary data from the Laboratory of Biology of the Cell Nucleus show lamin A in a complex with nuclear myosin I and a phosphoinositide phosphatidylinositol 4,5-bisphosphate, PIP2. Phosphoinositides have recently been reported in the nuclear interior and implicated in transcriptional regulation (Sobol et al). Many nuclear proteins have been shown to associate with phosphoinositides via lysine/arginine-rich areas in their sequences (K/R-rich motifs) (Jungmichel et al 2014).

We aim to elucidate which domain of lamin A directly binds to PIP2. The lamin A gene was first screened for putative K/R-rich motifs, and four lamin A truncation mutants bearing clusters of those regions were purified from bacteria. The mutants will be tested for direct binding to PIP2 and other phosphoinositides in vitro.

Elucidating the binding domain of lamin A to PIP2 would allow us to disrupt the interaction and address the question of its biological relevance in the context of the lamin A/NMI/PIP2 complex.