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Characterization of emerin missense LEM-domain mutations present in patients with exclusive atrial cardiac defect

Summary

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Emery-Dreifuss Muscular Dystrophy (EDMD) is among the most widely common human genetic muscular dystrophies. The cardiac involvement in the disease is the most lifethreatening symptom and the major cause of mortality. The majority of cases of its X-linked type are due to mutations in a gene encoding for the nuclear envelope protein, emerin. Despite the considerable advances that have been achieved in terms of the characterization of emerin structure, various binding partners, and functions in the human body, the picture is still rather incomplete. Fifty years now after EDMD had been first documented, researchers still fall short of understanding the pathophysiology of the disease. Thereby, it comes as no surprise that, to date, there is no described treatment of EDMD. Accordingly, this thesis is an initial attempt to characterize three emerin LEM-domain missense mutations (P22L, DK37, and T43I) present in patients with exclusive cardiac defects. The main objective of this thesis is to investigate the effect of the three mutations on: emerin structure, its self-assembly, and interactions with some of its well-described binding partners.

The presented work highlights that albeit the localization of the three mutations in the only folded region of emerin, the variants show no global defect in their structure, except for the destabilization of the LEM-domain of the variant DK37. Importantly, the mutants are able to self-assemble, yet with astonishing fast polymerization kinetics. In addition, the investigations have illustrated that the three variants, despite the presence of the mutations in the BAF-binding domain, are surprisingly capable of binding BAF. The analysis did not reveal any differences in the mutants binding to Ig-fold domain of lamin A/C. Further, there is no defect in DK37 phosphorylation by Src kinase. Also, preliminary characterization of the DK37 mutation in immortalized human fibroblasts has featured no overt defects in mechanobiology, and in the expression of nuclear envelope or cytoskeletal proteins.

Taken all together, the presented work outlines that the three emerin missense

mutations display no defects in several prominent emerin properties, which are questioned in this thesis. On the basis of the results of the conducted research, considerable insight has been gained with regard to the consequences of the mutations of interest. In other words, the presented work lends support to following investigations in order to explore other unquestioned properties or functions of emerin that might be associated with the pathophysiology of EDMD.