The endothelium: a therapeutic target in cardiomyopathy?

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Abstract:

The endothelium is a critical component of the cardiovascular system that forms a protective barrier for CMs and releases paracrine factors to maintain CM health and function. Despite impressive progress, little attention has been given to the potential importance of cell-to cell signaling between ECs and CMs, even though ECs serve a paracrine function to enhance signaling in CMs, especially in context to pharmacological stimulation. This knowledge gap impedes our comprehensive understanding of organ dysfunction at a multi-cellular level. Mutations in LMNA, the gene that encodes lamin A/C are the most common cause of familial dilated cardiomyopathy (DCM), often referred as cardiolaminopathy. Despite LMNA being ubiquitously present, the mechanisms that underlie cardiolaminopathy remain elusive. Using induced pluripotent stem cell (iPSCs)-derived endothelial cells (iPSC-ECs), we recently showed that LMNA-induced DCM, due to a frameshift variant caused endothelial dysfunction. Next generation sequencing identified Krüppel-like Factor 2 as the transcription factor responsible for the EC dysfunction, which was reversed by a subset of statins, including lovastatin both in vitro and in vivo. Importantly, iPSC-cardiomyocytes (iPSC-CMs) from LMNA-DCM patients showed improvement in their function when co-cultured with iPSC-ECs and lovastatin, indicating an intricate crosstalk between the ECs and CMs in LMNA cardiomyopathy. By leveraging human iPSCs, bioengineering tools, genome editing, and NGS we propose to decipher the impaired cross-talk between ECs and CMs in LMNA cardiomyopathy and elucidate the

beneficial class effects of statins in improving the EC-CM signaling as a key factor in regulating cardiac function.