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Microtubule cytoskeleton regulates connexin 43 localization and cardiac conduction in cardiomyopathy caused by mutation in A-type lamins gene.

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Abstract

Mutations in the lamin A/C gene (LMNA) cause an autosomal dominant inherited form of dilated cardiomyopathy associated with cardiac conduction disease (hereafter referred to as LMNA cardiomyopathy). Compared with other forms of dilated cardiomyopathy, mutations in LMNA are responsible for a more aggressive clinical course due to a high rate of malignant ventricular arrhythmias. Gap junctions are intercellular channels that allow direct communication between neighboring cells, which are involved in electrical impulse propagation and coordinated contraction of the heart. For gap junctions to properly control electrical synchronization in the heart, connexin-based hemichannels must be correctly targeted to intercalated discs, Cx43 being the major connexin in the working myocytes. We here showed an altered distribution of Cx43 in a mouse model of LMNA cardiomyopathy. However, little is known on the molecular mechanisms of Cx43 remodeling in pathological context. We now show that microtubule cytoskeleton alteration and decreased acetylation of α -tubulin lead to remodeling of Cx43 in LMNA cardiomyopathy, which alters the correct communication between cardiomyocytes, ultimately leading to electrical conduction disturbances. Preventing or reversing this process could offer a strategy to repair damaged heart. Stabilization of microtubule cytoskeleton using Paclitaxel improved intraventricular conduction defects. These results indicate that microtubule cytoskeleton contributes to the pathogenesis of LMNA cardiomyopathy and that drugs stabilizing the microtubule may be beneficial for patients.

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