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Novel nesprin-1 mutations associated with dilated cardiomyopathy cause nuclear envelope disruption and defects in myogenesis

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Nesprins-1 and -2 are highly expressed in skeletal and cardiac muscle and together with SUN (Sad1p/UNC84)-domain containing proteins and lamin A/C form the linker of nucleoskeleton and cytoskeleton (LINC) bridging complex at the nuclear envelope (NE). Mutations in nesprin-1 and -2 have previously been found in patients with autosomal dominant Emery-Dreifuss muscular dystrophy 4 (AD-EDMD 4, OMIM 612998) and 5 (AD-EDMD5, OMIM 612999) as well as dilated cardiomyopathy (DCM). In this study, three novel rare variants (R8272Q, S8381C and N8406K) in the C-terminus of the *SYNE-1* gene (nesprin-1) were identified in 7 DCM patients by mutation screening. Expression of these mutants caused nuclear morphology defects and reduced lamin A/C and SUN2 staining at the NE. GST-pull down indicated that nesprin-1/lamin/SUN interactions were disrupted. Nesprin-1 mutations were also associated with augmented activation of the ERK pathway *in vitro* and in hearts in vivo. During C2C12 muscle cell differentiation, nesprin-1 levels are increased concomitantly with kinesin light chain (KLC-1/2), and immunoprecipitation and GST-pull down showed that these proteins interacted via a recently identified LEWD domain in the C-terminus of nesprin-1. Expression of nesprin-1 mutants in C2C12 cells caused defects in myoblast differentiation and fusion associated with dysregulation of myogenic transcription factors and disruption of the nesprin-1 and KLC-1/2 interaction at the outer nuclear membrane. These findings support a role for nesprin-1 in myogenesis and muscle disease, and uncover a novel mechanism whereby disruption of the LINC complex may contribute to the pathogenesis of DCM.

Biography

Qiuping Zhang has her expertise in "Nesprin family research in Cardiovascular Biology field, specifically on understanding the complex roles of nesprin-1 and -2, family members of multi-isomeric scaffolding proteins, in regulating normal and pathological processes in the heart and muscle". She has studied extensively the role of nesprins in myoblast differentiation and function as well as mutations in nesprin-1 or -2 in associations with Emery Dreifuss muscular dystrophy and dilated cardiomyopathy. Her current research focuses on "Defining the roles of nesprins in cardiac cell function by determining the functional significance of novel nesprin-1 and -2 mutations on the linker of nucleoskeleton-and-cytoskeleton complex that connects the nuclear envelope to the actin cytoskeleton, and also identifying novel roles for nesprins in the sarcomere". This may reveal novel pathways that contribute to the development of cardiac cell dysfunction and cardiomyopathy.

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