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The truncated plakophilin-2 protein localizes in the intercalated disc and induces cardiac fibrosis in a transgenic mouse model

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Objective: Plakophilin-2 (PKP2) mutations represent 50% of desmosomal mutations associated to Arrythmogenic Right Ventricular Cardiomyopathy (ARVC) in humans. Many of these mutations cause a truncated protein PKP2. However, the mechanism whereby truncated PKP2 causes disease is unclear. The aim of this study is to unravel the molecular and cellular mechanism of truncated PKP2 in ARVD pathogenesis.

Methods: For this study, we developed a transgenic mouse model containing a truncated PKP2 (329 of 837aa native protein) under specific cardiac promoter (α-MHC). We have studied alterations in the expression and the localization of different desmosomal proteins. In addition, we have studied alterations in cardiac morphology and size. We have also analyzed the histological phenotype using hematoxylin-eosin and Masson trichrome staining and oil red and Sirius red methods to detect the fatty and fibrous tissue. The level of cardiomyocytes early apoptosis has been analyzed by TUNEL. Finally, the ultrastructure of the intercalated disc has been analyzed using a transmission electronic microscopy.

Results: The truncated PKP2 was localized in the intercalated disc and a small fraction in the cytoplasm of cardiomyocytes. Interestingly, an intense signal of truncated protein was found in the nucleus of some cardiomyocytes. The expression and localization of distinct desmosomal proteins was similar in hearts from wildtype and transgenic mice. We do not detect any cardiac hypertrophy in the transgenic mice when it was compared with wildtype mice (0.65 ± 0.11 vs 0.71 ± 0.15; respectively). We have observed fibrosis in cardiac tissue in 2 of 30 total transgenic mice analyzed (7%). This is characterized by the presence of fibrous tissue with absence of adipocytes and apoptosis. Ultrastructure of desmosome reveals micro-breakages in the intercalated discs of cardiomyocytes from transgenic mice including the ones without fibrous tissue replacement.

Conclusions: Although a low frequency of fibrosis was found, the presence of micro-breakages suggests that the truncated PKP2 reduces the cardiomyocytes adhesion/viability and increases the predisposition to the development of fibrosis. We can hypothesize that presence of truncated PKP2 in the intercalated disc could compete with the endogenous PKP2 binding sites, affecting the cardiac tissue integrity.