Myocardial overexpression of ANKRD1 causes sinus venosus defects and progressive diastolic dysfunction

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Aims: Increased ANKRD1 levels linked to gain of function mutations have been associated to total anomalous pulmonary venous return and adult cardiomyopathy occurrence in humans. The link between increased ANKRD1 level and cardiac structural and functional disease is not understood. To get insight into this problem, we have generated a gain of function ANKRD1 mouse model by overexpressing ANKRD1 in the myocardium.

Methods and Results: Ankrd1 is expressed non homogeneously in the embryonic myocardium, with a dynamic nucleo-sarcomeric localization in developing cardiomyocytes. ANKRD1 transgenic mice present sinus venosus defect, which originates during development by impaired remodeling of early embryonic heart. Adult transgenic hearts develop diastolic dysfunction with preserved ejection fraction, which progressively evolves into heart failure, as shown histologically and hemodynamically. Transgenic cardiomyocyte structure, sarcomeric assembly and stability are progressively impaired from embryonic to adult life. Postnatal transgenic myofibrils also present characteristic functional alterations: impaired compliance at neonatal stage and impaired lusitropism in adult hearts. Altogether, our combined analyses suggest that impaired embryonic remodeling and adult heart dysfunction in ANKRD1 transgenic mice present a common ground of initial cardiomyocyte defects, which are exacerbated postnatally. Molecular analysis showed transient activation of GATA4-Nkx2.5 transcription in early transgenic embryos and subsequent dynamic transcriptional modulation within titin gene.

Conclusions: ANKRD1 is a fine mediator of cardiomyocyte response to hemodynamic load in the developing and adult heart. Increased ANKRD1 levels are sufficient to initiate an altered cellular phenotype, which is progressively exacerbated into a pathological organ response by the high ventricular workload during postnatal life. Our study defines for the first time a unifying picture for ANKRD1 role in heart development and disease and
provides the first mechanistic link between ANKRD1 overexpression and cardiac disease onset.


Keywords: ANKRD1, cardiac development; diastolic dysfunction; hemodynamics.

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Website(s): http://www.biomed.unipd.it/research-areas/muscle-physiology-in-health-and-disease/pathophysiology-of-striated-muscles/people/