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Sequence variation in *PPP1R13L* results in a novel form of cardio-cutaneous syndrome

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Dilated cardiomyopathy (DCM) is a life threatening disorder whose genetic basis is heterogeneous and mostly unknown. Five Arab-Christian-infants, ages 4-30 months from four families were diagnosed with DCM associated with mild skin, teeth and hair abnormalities. All passed away before age 3. A homozygous sequence variation creating a premature stop codon at *PPP1R13L* encoding the iASPP protein, was identified in three infants, and in the mother of the other two. Patients' fibroblasts and *PPP1R13L*-knocked down human fibroblasts presented higher expression levels of pro-inflammatory cytokine genes in response to lipopolysaccharide, as well as *ppp1r13l*-knocked down murine cardiomyocytes and hearts of *ppp1r13l*-deficient mice. The hypersensitivity to Lipopolysaccharide was NF-kB-dependent, and its inducible binding activity to promoters of pro-inflammatory cytokine genes was elevated in patients' fibroblasts. RNA-sequencing of *ppp1r13l*-knocked down murine cardiomyocytes and of hearts derived from different stages of DCM development in *ppp1r13l*-deficient mice revealed the crucial role of iASPP in dampening cardiac inflammatory response. Our results determined *PPP1R13L* as the gene underlying a novel autosomal recessive cardio cutaneous syndrome in humans, and strongly suggest that the fatal DCM during infancy is a consequence of failure to regulate transcriptional pathways necessary for tuning cardiac threshold response to common inflammatory stressors.

Biography

Orly Avni is expert in gene regulation in the immune system. She has published many articles in reputed journals.

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