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Inhibition of cAMP signaling recovers congenital heart defects in Pde2A deficient mice and reverts oxidative stress

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Statement of the Problem: Phosphodiesterases (PDEs) are the enzymes that hydrolyze cyclic nucleotides (cAMP and cGMP) playing a key role in the homeostasis of these two secondary messengers. PDE2A is a dual-specific PDE that breaks down both cAMP and cGMP and can be activated by cGMP. It appears peculiar that the Pde2A-knockout (KO) mouse model is embryonically lethal, likely due to a strongly reduced size of liver and to a severe anemia. In addition, the heart of Pde2A-KO embryos shows ventricular and atrial septum defects, hypertrabeculation, heart dilatation and non-compaction defect. We recently highlighted a direct relationship between Pde2A impairment, consequent increase of cAMP and the onset of mouse congenital heart defects (CHDs), however the molecular mechanisms underlined the heart defects remain unknown. Methodology: Here, we carried-out the transcriptome of Pde2A-KO embryonic heart by RNA sequencing. We also tested in Pde2A-heterozygous pregnant females two drugs, Metoprolol and H89, that acting on cAMP signaling, rescue CHDs in Pde2A-KO embryos. Findings: We found a significant modulation of more than 500 genes affecting biological processes involved in the immune system, cardiomyocyte development and contractility, angiogenesis, control of gene transcription and oxidative stress. The most altered genes common in different pathways were also analyzed by quantitative real time PCR confirming the RNA-seq data. Metoprolol and H89 were able to prevent heart dilatation and hypertabeculation. Metoprolol was also able to partially impede heart septum defect and oxidative stress at molecular levels. Conclusions: We identified specific biological processes, molecules and cell signaling that can be targeted by selected drugs with consequent beneficial effects for cAMP-dependent CHDs.

Biography

Manuela Pellegrini during her career had two main scientific interests, one on cardiac field and the other on DNA damage repair field. For several years she worked on the generation and characterization of several transgenic and knockout mouse models to study cardiogenesis and genomic instability. Among her works, the studies on cardiogenesis revealed the important role of c-Kit cardiac stem cells during heart rigeneration (Di Siena et al., CCDIS 2016), the cross-talk between Phosphodiesterase 5 and Phosphodiesterase 2A in the neonatal cardiomiocyte beta2 adrenergic response (Isidori et al., 2015) and the critical role of Phosphodiesterase 2A for the correct heart development (Assenza et al., Card Res 2018); the studies on genomic instability shed light on distinct events of Atm kinase activation and Atm kinase activity (Pellegrini et al., Nature 2006), revealed the essential role for Atm kinase activity during embryonic development (Daniel et al., JBC 2012) and documented the rescue of Atm deficiency following Atm restoration (Di Siena et al., CCDIS 2018)