Cardiovascular Research Supplements (2012) **93**, S52–S87

Frontiers in CardioVascular Biology, London 30th March – 1st April 2012
Second Congress of the ESC Council on Basic Cardiovascular Science

POSTER SESSION 2
31 March 2012

doi:10.1093/cvr/cvr334

Developmental biology

P263
Embryonic epicardial-derived cells: pioneering roles in building the adult cardiac interstitium

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The cardiac interstitium comprises a heterogeneous population of cells relevant to adult heart muscle homeostasis. The detailed embryonic origin, quantitative and qualitative composition of cardiac interstitial cells remains unknown. By means of cell lineage tracing technologies, we have mapped the cellular components of the murine developing interstitium from the embryo to postnatal stages. Our results demonstrate that embryonic epicardial-derived cells (EPDC) pioneer the colonization of the interstitial space in the developing heart, displaying a typical transmural patterning across cardiac chamber walls. This study indicates that most EPDC remain at the cardiac interstitium in the form of fibroblastic(-like) cells, dynamically interacting with other non-epicardial-derived cells (e.g. bone marrow-derived cells). Using a variety of in vitro assays, we have characterized subpopulations of EPDC following criteria related to their molecular profile and mobilization properties (cell adhesion; proteolytic activity).
From our data we conclude that:
1) EPDC are the first cells that populate the cardiac interstitium, where they home and remain along adulthood; 2) EPDC display a unique proteolytic program from early stages of cardiac development and 3) these cells might be instrumental to the homing of other cell types late in development/postnatal life.
In summary, our work provides new information on the biology of cardiac interstitial cells (most specially cardiac fibroblasts), offering clues to understand paracrine and/or autocrine signals, as well as the ECM-related mechanisms (protein deposition and proteolysis), involved in clinically relevant patophysiological phenomena like ventricular remodeling after myocardial infarction.

P264
Sodium channel remodelling leads to cardiac conduction system dysmorphogenesis

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Purpose: Several previous studies have revealed that increases of sodium currents (INa) seems to be an important factor in the prolongation of action potential duration and the generation of polymorphic ventricular tachycardia in repolarisation disorders, such as the long QT syndrome (Cardona K , 2010) which has been related to cases of sudden death in newborns (Roberts JD, and Gollob MH; 2010). Recently we have demonstrated that early sodium channel remodelling secondary to IKs blockage in a mouse model of long QT syndrome leads to morphological and functional anomalies of the ventricular conduction system during development which might further lead to cardiac hypertrophy (de la Rosa , in preparation).
Methods: To further assess the relationship between cardiac sodium currents remodelling and the conformation of the cardiac conduction system during development, we are currently designing and ex vivo system to increase INa current in Cx40-GFP embryos.
Results: We found that Cx40-GFP embryos treated with ATX-II toxin (which increases INa current,) display a significant decrease in the number of green ventricular trabeculations in the compared to control embryos indicating that increases in INa current in the developing heart leads to an abnormal ventricular conduction system configuration.
Conclusions: Here we provide the first direct evidence for a relationship between early sodium ion channels remodelling and the presence of morphological and/or functional anomalies of the ventricular conduction system in the developing heart. This study might shed new insights into understanding the mechanisms underlying cardiac electrophysiological disorders in newborns and may open new ways to better understand clinical pathologies such as cardiac congenital anomalies, arrhythmias and perinatal sudden death.

P265
Cardiac microhemocirculation in experimental myocardium necrosis

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Experimental necrosis of cardiac muscle is used as the model of myocardium infarction for the studies, aimed to the investigation of heart remodeling and pre-clinical trials of preparations with cardiotropic effect. The research aim is to examine heart microcirculatory channel under experimental necrosis of myocardium. The research is performed in 110 breedless male rats of 180-250g. Experimental necrosis of cardiac muscle was modeled by two ways: ligature of left coronary artery (group 1) and cryoeffect on left ventricle wall for 15 sec (group 2). Cryoeffect was done by nitrogen cryoinstrument with 3 mm's applicator diameter at temperature of its operating surface of -196°C. Vital microscopy of heart was performed by means of contact microscope LUMAM K-1 (LOMO, Russia) in luminescence regimen after intravenous introduction of sodium fluorescein. Myocardium necrosis in rats was recorded with electrocardiographer (Polyspektr-8/B, Russia). The most manifested differences in hemodynamics and microstructure of animals' myocardium of the groups 1 and 2 were found to the 14th day. In a central zone of myocardium necrosis in animals of the group 2 there were observed single vessles of small diameter, forming atypical picture for the heart. Along the perimeter the necrosis zone was surrounded by microvessels of bigger diameter versus the norm. In the animals of group 1 the zone of ischemic necrosis was surrounded by the net of newly formed microvessels with chaotic architecture. In the animals of group 1 the diameter of myocardium capillary of right ventricle in 1 hr after surgery reduced by 17% and in animals of the 2nd group it decreased by 36% if compared with the norm (8.49 + /-0.09 micron). To the 14th day the animals of group 1 versus to the rats of group 2 the diameter of microvessels and relative area of vascular channel (0.48 + /-0.11) returned to initial values. Conclusion. In microhemocirculatory channel of heart during all observation terms after myocardium necrosis remodeling there were observed significant changes. Remodeling of vascular channel of heart depends on the way of myocardial injury.

P266
DOCA/salt-induced hypertension + high-cholesterol/high-lipid diet: A large animal model of concentric LV hypertrophy with increased LV stiffness

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Background: Heart failure with preserved ejection fraction (HFPEF) is of increasing importance in the aging population. Although clearly associated with cardiac risk factors, the pathophysiology of HFPEF remains poorly understood, and pharmacological strategies established in systolic heart failure do not improve prognosis in HFPEF. This in turn is largely related to the lack of animal models for this disease.
Methods: Pigs were subjected to subcutaneous DOCA-pellet (deoxycorticosterone acetate, an aldosterone analogon) implantation and a high-lipid/high-salt feeding to mimick a cardiovascular risk profile of arterial hypertension and hyperlipidemia.
Results: After 3 months, DOCA-treated animals (n=3) versus time controls (n=3) developed persistent hypertension (tail-cuff systolic blood pressure during light sedation: 138 ± 5 vs. 93 ± 12 mmHg, $p < 0.05$) and had 8-fold increased plasma cholesterol levels. Echocardiography revealed concentric LV hypertrophy (septal wall thickness 16 ± 1 vs. 12 ± 1 mm, $p < 0.05$) at a preserved ejection fraction (72 ± 7 vs. $63 \pm 10\%$, p=NS). LV pressure-volume analysis demonstrated a leftward shift and a steeper slope of end-diastolic pressure-volume relationships (EDPVR) compared to a weight- and age-matched historic control group (n=13).