Sall1 marks non-Mesp1 derived new cardiac cell lineage. In addition, Sall1+Mesp1- cells labeled by DiO was detected differentiated cTnT+ cardiomyocytes in vivo heart. Amazingly, Sall1/Mesp1 DKO mice as loss-of-function study caused no cardiac field, and Dox inducible *Sall1*-Mesp1-overexpressed hiPS cells as gain-of-function study efficiently differentiate cardiomyocytes. These results indicate that *Sall1*-Mesp1 coordinately regulates cardiac cell lineages.

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SINOATRIAL NODE PACEMAKER CELLS GENERATED FROM HUMAN PLURIPOTENT STEM CELLS CAN FUNCTION AS BIOLOGICAL PACEMAKER

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The human heart rate is established by the sinoatrial node (SAN) that functions as primary pacemaker throughout life. Impaired SAN function due to congenital disease or aging is routinely treated by implantation of an electronic pacemaker that has disadvantages including limited adaption to growth in pediatric patients and lack of autonomic responsiveness. Biological pacemakers derived from human pluripotent stem cells (hPSCs) represent a promising alternative. Although hPSC differentiation cultures directed to a cardiac fate contain some pacemaker cells in addition to other cardiomyocytes subtypes, strategies for directed differentiation of SAN myocytes do not exist. Using developmental biology as a guide, we developed a differentiation strategy that promotes the generation of hPSC-derived populations that contain up to 35% SAN-like pacemaker cells (SANLP). These SANLP express typical SAN markers including TBX3, TBX18, SHOX2 and HCN4 at significant higher levels than found in control hPSCs-derived ventricular cardiomyocytes. SANLP do not express the ventricular markers MLC2V or IRX4, the atrial marker NPPA or the atrioventricular node marker TBX2. Furthermore, SANLPs display typical functional pacemaker properties including appropriate ion current profile and chronotropic responses to autonomic signals. In order to evaluate the potential of SANLPs for biological pacemaker applications we tested their ability to pace cardiac-tissue both in-vitro and in-vivo. To this end we show that coculture of SANLP

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EICOSAPENTAENOIC ACID ENHANCES DIFFERENTIATION OF EMBRYONIC STEM CELL INTO CARDIOMYOCYTE

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Embryonic stem cells (ESCs) offer a reliable means to produce acceptable number of functional cardiomyocytes to exploit in cell therapy, however low efficiency of differentiation hampers its therapeutic use. Although a vast number of chemical compounds have been tested on efficiency of cardiac differentiation, the effect of fish oil components like eicosapentaenoic acid (EPA) remained unstudied. EPA has been reported to have several cardioprotective effects, but there is no study about its contribution in cardiac differentiation. In the present study, mouse ESCs were induced to differentiate using hanging drops to form embryoid bodies and treatment with ascorbic acid, and in order to examine the effect of EPA, they were treated with different concentration of EPA simultaneously. Gene and protein expression and functional properties of cardiomyocytes derived from ESCs were evaluated. EPA at low concentration increased percentage of beating and beating area. It could also upregulate mRNA expression of Nkx2.5, Mef2c, α-MHC, cTnT and CX43 significantly. Flowcytometric analysis showed that the percentage of α-MHC positive cells in EPA-treated group was higher than control group. However, these findings have not been observed at higher concentrations of EPA. In conclusion, we have demonstrated that treatment of mESCs undergoing cardiac differentiation with low concentration of EPA enhanced cardiac differentiation and exhibited synergistic effects with ascorbic acid.

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NANOFIBROUS PATCHE LOADING Tβ4-MSCS WITH EPICARDIAL GRAFT ACCELERATE INFARCT MYOCARDIAL REPAIR BY ACTIVATING ENDOGENOUS REGENERATION MECHANISMS

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