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p63 silencing overcomes barriers to human cardiac cellular reprogramming

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Nongestive heart failure (CHF) typically occurring as a result of myocardial infarction (MI) is the leading cause of cardiac mortality in the West. Recent CHF treatment research strategies have focused on exogenous stem cell administration to replenish cardiomyocytes in myocardial infarct zones and thereby enhance cardiac function, but the results of stem cell trials have largely been disappointing; likely due to inadequate implant phenotypes and/or poor implant survival and integration into the host myocardium. Despite some evidence of limited endogenous myocyte replication or regeneration from resident stem cells, native adult cardiac muscle does not effectively regenerate itself de novo after cardiomyocyte death. Strategies have therefore been devised which administer exogenous stem cells or reserve cells (e.g., embryonic stem cells, mesenchymal stem cells or skeletal myoblasts) into the infarct zone to enhance cardiac function. The seminal finding, that cellular reprogramming strategies could be used to produce induced pluripotent stem (iPS) cells from adult somatic cells was soon followed by findings of several groups that iPS cells could be re-differentiated into cells with a cardiomyocyte-like phenotype. The more recent discovery that "cardio-differentiating" transcription factors (e.g., GATA4, MEF2C and TBX5 ["GMT"]) generate "induced cardiomyocyte-like" (iCM) cells directly from somatic cells suggests that in situ cardiomyocyte regeneration could be used to completely bypass stem cell or (potentially immunogenic and/or tumorigenic) iPS staging. Notably, cellular reprogramming has been shown to significantly improve cardiac function in rodent MI models, yielding up to 30% increase in ventricular function. Low reprogramming efficiency in human cells remains, however, as a challenge to this new field. Given evidence that the resistance of human cells to reprogramming might be related to restraints on the cell "plasticity" of higher-order species, and given that the p53 family of genes appears to modulate such plasticity in induced pluripotent stem (iPS) cells, we have demonstrated that p53 downregulation enhances rodent cardiac fibroblast reprogramming into iCMs. Given the association of p53 mutations with human neoplasm, we refocused these investigations onto the p53 family member p63, which has been shown to have "anti-plasticity" effects similar to p53 in iPS models, but which possesses a negligible human oncogenic profile compared to p53. We have now shown that p63 silencing is even more effective than p53 downregulation in enhancing fibroblast transdifferentiation into iCMs, and that the combined administration of the cardio-differentiating factors Hand2 and Myocardin with p63 silencing induces iCM contractility in vitro. We have now also demonstrated that shRNA-mediated downregulation of p63 induces up to a 40-fold increase in expression of the cardiomyocyte marker cTnT in cardiac fibroblasts harvested from CHF patients compared to "classic" reprogramming with Gata4, Mef2c, and Tbx5. Taken together, these data suggest that cellular reprogramming may represent an encouraging new approach to treatment of post-infarct cardiomyopathy, and that *p63* silencing may be a compelling strategy for overcoming the resistances of human cells to reprogramming.

Biography

Todd K Rosengart is Professor and Chairman of the Michael E DeBakey Department of Surgery at Baylor College of Medicine (BCM). He also holds the DeBakey-Bard Chair of Surgery, and is Professor of Heart and Vascular Disease at the Texas Heart Institute. Amongst other institutional roles, he is Board Chairman of the Affiliated Medical Services, a 1000-Provider Medical Services Consortium of BCM and University of Texas Faculty for the Harris Health County Medical System, Vice-Chair of the BCM Faculty Group Practice, overseeing its 350-provider BCM Private Clinical Faculty, and he serves on the Joint Venture Board of Baylor St Luke's Medical Center. He also recently served as National Chairman of the CHI Cardiothoracic Surgery Clinical Standards Committee, with oversight of cardiovascular surgery activities for 20 institutions performing cardiac surgery as members of CHI, a national non-profit organization with 120 member hospitals.

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