Neonatal and Adult Cardiovascular Pathophysiological Remodeling and Repair: Developmental Role of Periostin

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ABSTRACT: Heart development is not completed during the intrauterine life. The neonatal heart undergoes normal hypertrophy or compensation to complete the development and adapt to increased systolic pressures. Hypertrophy and increased neonatal wall stiffness are associated with a doubling of the number of fibroblasts and *de novo* formation of collagen. Postnatal remodeling normally is completed within 3-4 weeks after birth. However, it can be rekindled again in adult life in response to environmental signals that lead to pathological hypertrophy and fibrosis and, possibly catastrophic heart failure. The signals that trigger fibroblast and collagen formation (fibrosis) are not known, partly because the origin and differentiation of the cardiac fibroblast lineage is not well understood. Using Wilm's Tumor Green Fluorescent Protein (GFP) reporter mice and a single cell engraftment model we have shown that cardiac fibroblasts are derived from two extracardiac sources: the embryonic proepicardial organ (PEO) and the recruitment of circulating bone marrow cells of hematopoietic stem cell (HSC) origin. Periostin, a matricellular protein, is normally expressed in differentiating fibroblasts but its expression increases 4 to-64 times in pathological remodeling and heart failure. Thus, we hypothesized that periostin is profibrogenic, i.e. it promotes differentiation of progenitor cells into fibroblasts and secretion of collagen. To test this hypothesis we isolated and cultured neonatal wild type (WT) and periostin null, non-myocyte populations. Compared to WT cells, a third of the isolated null non-myocyte cells did not express any cardiac lineage markers, but if forced to express periostin, they became fibroblasts. To test the periostin profibrogenic hypothesis in vivo, we have combined a cryoinjury model with our single cell engraftment model in which a single GFP^+ HSC is injected into a lethal irradiated adult WT or periostin null host, followed by a 100µm circular (half-wall thickness) cryoinjury. In cryo-injured WT hearts, fibrosis and elevated wall stiffness were observed after four weeks, which correlated with increased recruitment of GFP^+ HSCs into the wound site that expressed periostin and fibroblast markers. Conversely, in cryo-injured nulls, after four weeks, the wound site was reduced in diameter; there was less fibrosis and significantly lower wall stiffness. If null mice had been engrafted with null GFP^+ HSC before cryo-injury, the wound site uniquely contained GFP^+ cardiomyocytes, but if transplanted with WT GFP^+ HSC before cryo-injury, the wound site contained GFP^+ fibroblasts that expressed periostin, but not myocyte markers. There was evidence of fibrosis and increased wall stiffness. We interpret these findings as supporting the notion that periostin is a profibrogenic matricellular protein that can also inhibit differentiation of progenitor cells into myocytes. Supported by NIH grants HL19136 and HL33756.

KEYWORDS: Neonatal heart, development, hypertrophy, fibroblasts, Periostin, progenitor cells, hematopoietic stem cells, cryo-injury

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