CD45+ fibroblast in maladaptive cardiac fibrosis and its suppression by a caveolin-1 surrogate peptide

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In response to pathological stimuli such as hypertension, myocardial infarction (MI) and valvular defects, the heart undergoes both qualitative and quantitative changes that contribute to the progression of congestive heart failure (CHF), which develops in concert with myocardial fibrosis. We have used two independent models (transverse aortic constriction and angiotensin II infusion) of pressure overload (PO) to induce cardiac fibrosis that results in compromised ventricular function. Based on the idea that caveolin-1 deficiency in fibroblasts and monocytes contributes to fibrosis, we explored the role of caveolin-1 in the fibrotic processes using the caveolin-1 scaffolding domain peptide (CSD, a 20-amino acid segment of caveolin-1 that acts as a functional surrogate). While it is accepted that bone marrow (BM)-derived cells play a key role in cardiac fibrosis, it is controversial whether this is solely due to monocytes differentiating into macrophages that secrete factors that activate resident fibroblasts, or whether BM monocytes also differentiate into a major portion of the fibroblasts that overexpress collagen I (Col I) in PO myocardium. Our recent studies support the latter idea that PO causes a major increase in the levels of CD45+/ HSP47+ cells in the fibrotic heart which could be blocked by treating mice with CSD. Suppression of fibrosis by CSD was accompanied with improved ventricular function. Moreover, when fibroblast cultures are initiated using cells from fibrotic heart, the fibroblasts continue to express CD45, strongly suggesting that CD45+ cells are indeed fibroblast precursors. Our results strongly suggest that monocytes differentiate into a major portion of the fibroblasts that overexpress Col I in the fibrotic heart and that the recruitment of monocytes, their differentiation into fibroblasts, and the overexpression of Col I by fibroblasts are all potential points of regulation of fibrosis by CSD. Our ongoing studies are focused to validate the importance of caveolin - 1 and CD45+ BM-derived cells in heart fibrosis so that they set the stage for developing CSD as a treatment for cardiac fibrosis.

Biography

Dhan Kuppuswamy is an Associate Professor of Medicine, Cardiology Division at the Medical University of South Carolina (MUSC), Charleston, South Carolina. As a faculty member for the past 23 years at MUSC, he has been studying cellular and molecular mechanisms involved in cardiac hypertrophy that often leads to congestive heart failure. He got his Masters and PhD degrees at the University of Madras, India and moved to US as a postdoctoral fellow in 1984. After joining as a faculty at MUSC, he employed much of his expertise into cardiology on how integrin-mediated tyrosine kinase signaling promotes growth, survival and differentiation of cardiac muscle cells and fibroblasts. Studies from his lab show that β3 integrin mediated signaling mechanisms activate nonreceptor tyrosine kinases that contribute to cardiomyocyte growth and survival on one hand and promote cardiac fibroblast proliferation and extracellular matrix accumulation on the other hand. His recent collaborative studies shows very compelling data that ventricular pressure overload in mice can cause increased levels of CD45+ cells (monocyte-derived cells) in the heart that express fibrogenic markers and that treating these mice with the caveolin-1 scaffolding domain (CSD) peptide can suppresses recruitment and differentiation of CD45+ cells into fibrogenic cells, decrease cardiac fibrosis, and improve ventricular function. He has trained several PhD students and postdoctoral fellows and he is actively involved in graduate school.

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