Senescence associated secretory phenotype exacerbates overload pressure-cardiac hypertrophy

Authors:
D.B. Nugroho¹, K. Ikeda², A. Haryono³, P. Rinastiti³, A.J. Barinda⁴, N. Emoto², ¹Gadjah Mada University. Faculty of Medicine, Public Health and Nursing, Department of Internal Medicine - Yogyakarta - Indonesia, ²Kobe Pharmaceutical University, department of Clinical Pharmacy - Kobe - Japan, ³Kobe University. Graduate School of Medicine, Department of Internal Medicine, Division of Cardiovascular Medicine - Kobe - Japan, ⁴Indonesian Medical Education and Research Institute - Jakarta - Indonesia.

Topic(s):
Basic Science - Cardiac Diseases: Cardiac Hypertrophy

Citation:
European Heart Journal (2019) 40 (Supplement), 1322

Background: Advanced age is a significant risk factor for cardiovascular diseases such as hypertension and cardiac hypertrophy. The vascular system forms an essential component of cardiac tissue, to provide routes for circulation and transportation of nutrients and oxygen throughout the cardiac muscle. In addition to its function in vascular biology such as vasodilation and neovessel formation, endothelial cell (EC) also provides many secreted angiocrine factors that are crucially involved in maintaining tissue homeostasis. Ageing induces cellular senescence in various cells including EC. Senescent cells produce senescence-messaging secretomes that have deleterious effects on the tissue microenvironment, referred to as the senescence-associated secretory phenotype (SASP). Because of the crucial roles of EC in tissue homeostasis, EC senescence is presumed to play significant roles in age-related cardiac dysfunction, however, whether and the mechanism by which EC senescence affects age-related cardiac dysfunction remains to be elucidated.

Purpose: We aimed to investigate the role of senescent ECs in cardiac hypertrophy and heart function.

Methods: To investigate a contribution of senescent EC in age-related cardiac tissue dysfunction in vivo, we generated EC-specific progeroid mice that overexpress the dominant negative form of telomeric repeat-binding factor 2 (TRF2), which play a central role in the protection of chromosome ends, under the control of the vascular endothelial cadherin promoter (VEcad-TRF2DN-Tg). To induce pathological cardiac remodeling, Transverse Aortic Constriction (TAC) was performed in mice at the age of 10–12 weeks old. Cardiac function was assessed using fractional shortening percentage and ejection fraction measured with echocardiography every week until sacrifice day. Mice were sacrificed 4 weeks after TAC, heart tissue was collected for histological analysis, cardiac morphometry analysis, gene expression and protein expression analysis. In vitro, H9C2 rat cardiomyoblast cells were incubated with conditioned medium derived from control or senescent EC in the presence or absence of angiotensin II to induce cardiac hypertrophy.

Results: The serial echocardiographic analysis after TAC revealed the exacerbated LV dysfunction in VEcad-TRF2DN-Tg compared to that in wild-type mice. Morphometric and histological analysis 4 weeks after TAC showed increased heart weight and aggravated cardiac fibrosis in VEcad-TRF2DN-Tg mice. In vitro studies demonstrated that conditioned medium derived from senescent ECs enhanced cardiomyocyte hypertrophy in H9C2 cells. Of note, we found that treatment with Y2762, a Rho Kinase inhibitor, canceled the exacerbated cardiac hypertrophy caused by endothelial SASP.

Conclusion: These findings demonstrate for the first time that senescent ECs play causative roles in age-related cardiac disorders through the SASP, potentially by activating Rho-ROCK pathway in cardiomyocytes.