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Blood as a Source of Youth

Loffredo FS, Steinhauser ML, Jay SM, Gannon J, Pancoast JR, Yalamanchi P, et al. Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. **Cell 2013; 153:828-39. http://doi.org/q2f**

One of the presentations of heart failure with preserved systolic function is associated with age. Hypertrophy is typical in aging, but the mechanisms underlying diastolic dysfunction are not well known. To clarify some of the biological pathways involved in the development of cardiac hypertrophy with aging, Loffredo et al. assessed the influence of several blood circulating factors using heterochronic parabiosis. Parabiosis is a surgical technique, described over 150 years ago, by which two animals are joined to share blood circulation. The tissue growing in incisions made along the opposing flanks of each animal is sutured; and as result both circulations are anastomosed.

Loffredo et al. used young and old mice, which underwent parabiosis to form pairs: young-young, young-old, and old-old. After 4 weeks of exposure to young-old mice circulation, the hearts of old mice weighed less, accompanied by a reduction in cardiomyocyte size, compared to old-old control pairs. In addition, the expression of hypertrophy markers –such as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)– dramatically regressed in the hearts of heterochronic parabiosis (young-old) compared to isochronic parabiosis (old-old and young-young). Conversely, the expression of SERCA-2 (sarcoplasmic/endoplasmic reticulum calcium ATPase), an enzyme mainly associated with sarcoplasmic reticulum Ca2+ reuptake, contributing to the relaxation process, was increased in the young-old and young-young pairs. All these changes could not be explained by hemodynamic modifications.

In order to describe the mechanism of heterochronic parabiosis (young-old), the authors studied the expression of the growth differentiation factor 11 (GDF11). They observed an increased plasma expression in individual young mice compared to old mice, and in young-young and young-old pairs compared to old-old pairs. The effect of intraperitoneal administration of GDF11 in old mice was then assessed, with equally satisfactory results. Finally, parallel studies revealed that GDF-11 prevented neonatal myocyte hypertrophy induced by phenylephrine, but had no effect on ventricular hypertrophy caused by aortic constriction.

This study shows that shared circulation in young and old mice reverses age-related cardiac hypertrophy through GDF11 expression. The results are original and scientifically interesting, contributing to a better understanding of the aging processes and how they affect the heart. However, they cannot be extrapolated directly to patients. In this regard, it is not known whether increased blood levels of this growth factor in subjects with this type of heart failure could reverse the whole remodeling process. In addition, the impact on heart failure of different etiology is even more unclear, since no effects were observed in mice with hypertrophy due to aortic constriction. Moreover, changes observed in old mice did not result in functional improvement assessed by echocardiography.

However, the study by Loffredo et al. reveals a new signaling pathway that could become a potential target not only to slow but also to possibly reverse other organ disorders associated with aging.

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