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News and Views

Towards 'Eternal Youth' of cardiac and skeletal muscle

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INTRODUCTION

The dream of eternal youth, exemplified throughout history by several examples such as the Epic of Gilgamesh in ancient Sumeria (Figure 1) in which the King of Uruk searches for a plant to restore youth, and the story of Dorian Gray in Oscar Wilde's classical novel (Figure 2), has captured the imagination of mankind, and continues to be a major target for research. This is stimulated by the fact that the recent increase in life expectancy has resulted in a massive increase in the percentage of "ageing" individuals in the community (Figure 3). Ageing affects several organ systems, with two of the most crippling, involving cardiac and skeletal muscles. In this article we review the recent developments in these two areas.

REVERSING AGEING CARDIAC MUSCLE

Advancing age results in myocardial diastolic dysfunction, which can cause heart failure with preserved ejection fraction (HFpEF), currently thought to be as prevalent as heart failure with reduced ejection fraction (HFrEF). In stark contrast to the latter, where the use of beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists have resulted in remarkable reductions in mortality, no evidence-based therapies exist to treat HFpEF to date¹⁻⁷. Compared to HFrEF, HFpEF patients are older, more commonly women, and have a higher prevalence of hypertension, obesity, anemia, atrial fibrillation, and noncardiac comorbidities⁸. Among elderly women, HFpEF comprises almost 90% of newly diagnosed heart failure cases⁹. The prevalence of HFpEF has been rising steadily over the past two decades at a rate of approximately 1% per year, in contrast to that of HFrEF, which has remained unchanged over the same period¹. At this rate, and with the current population ageing trends, it is expected that HFpEF will represent the dominant heart failure phenotype in the near future.

The molecular pathogenesis of HFpEF has not been adequately defined, but it is now evident that diastolic dysfunction is not the only underlying abnormality^{10,11}. Other mechanisms including ageing¹², skeletal muscle dysfunction¹³⁻¹⁶, inflammation¹⁷, neuroendocrine and renal dysfunction¹⁸⁻²⁰, chronotropic incompetence²¹, right ventricular dysfunction²², abnormal ventricular-arterial coupling^{23,24}, and endothelial dysfunction^{25,26} have been implicated. Changes affecting the myocardium, namely impaired relaxation and increased stiffness, are cornerstone to the development of HFpEF. Recent experiments utilizing chronic parabiosis, where the circulations of two mice are joined (Figure 4a) have thrown new light on the mechanisms of HFpEF in old animals. Loffredo and colleagues, conducted a series of elegant experiments in mice with age related cardiac hypertrophy and failure, analogous to that in humans²⁷. When joined to young animals (heterochronic parabiosis) for a period of four weeks, the old animals showed regression of cardiac hypertrophy without influencing the structure of the joined young animal heart (Figure 4b). The structural and functional reverse remodeling observed in the older hearts exposed to heterochronic parabiosis was associated with decrease in the classical molecular markers of hypertrophy and wall stress such as ANP and BNP, with increase in sarcoplasmic endoplasmic reticulum Ca²⁺ a (SERCA 2a) known to be decreased in diastolic dysfunction^{28,29,30,31}.

<http://dx.doi.org/10.5339/gcsp.2015.12>

Submitted: 12 February 2015
Accepted: 26 February 2015
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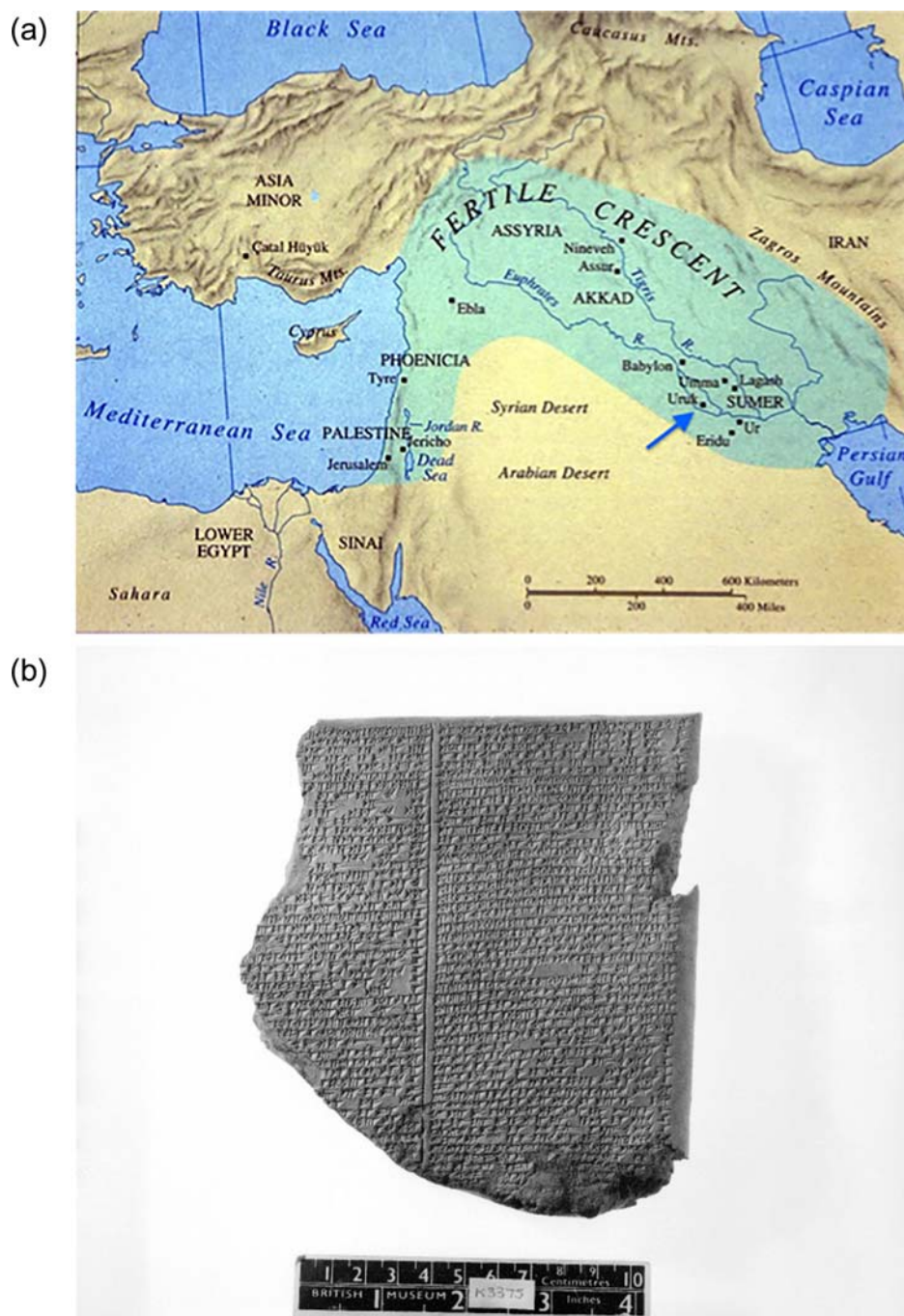


Figure 1. Map of Ancient Mesopotamia (a). The arrow points to the city of Uruk in Sumeria. Poem of the Epic of Gilgamesh – 11th tablet (British Museum) (b). The poem (circa 2100 BC), is often regarded as the first great work of literature. The second half of the epic describes the long and perilous journey of Giglamesh, King of Urik, in search of eternal life.

In an attempt to explore the mechanisms responsible and the possible therapeutic implications, the authors conducted an extensive search for the circulating substance or substances responsible for the observed changes. Utilizing broad-scale proteomics analysis using aptamer-based technology, they identified several candidate molecules, including growth-differentiation factor 11 (GDF11). This growth factor belongs to the transforming growth factor- β (TGF- β) superfamily of growth and differentiating factors, which includes the TGF- β s, activins and bone morphogenetic proteins. TGF- β superfamily is known to regulate cell growth and differentiation as well as cell death³². The actions and specificity of members of the TGF- β superfamily secreted proteins are transmitted to the nucleus



Figure 2. Actor Ben Barnes starring as Dorian Gray in a 2009 British movie based on Oscar Wilde’s classical novel “The Picture of Dorian Gray” (1891).

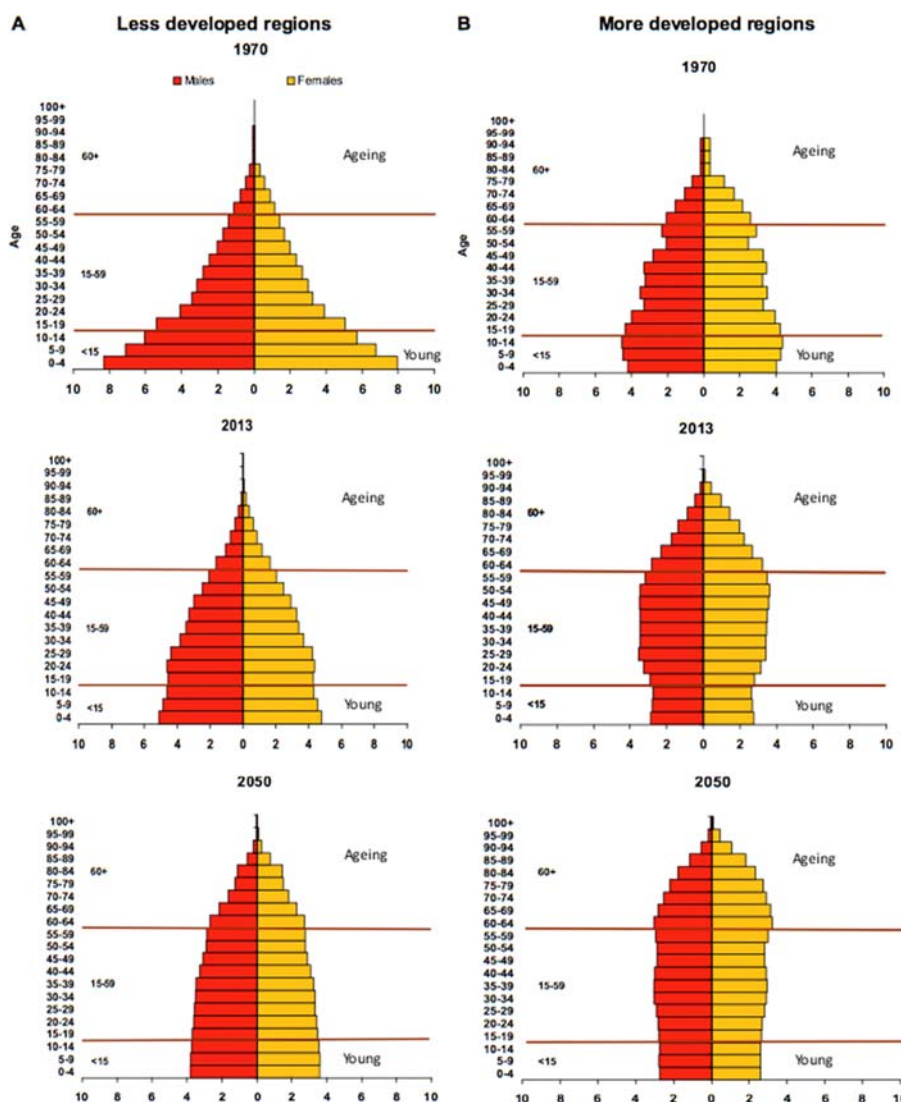
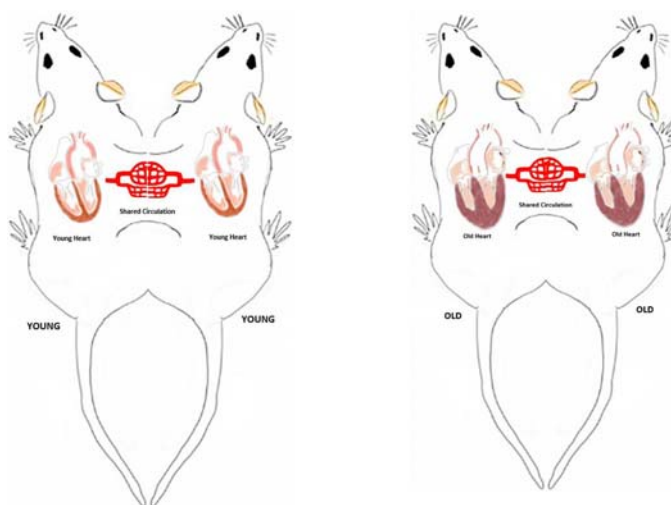


Figure 3. Population pyramids of the less and more developed regions: 1970, 2013, and 2050 [source: UN World Population Ageing 2013].

(a) Isochronic parabiosis



(b) Heterochronic parabiosis

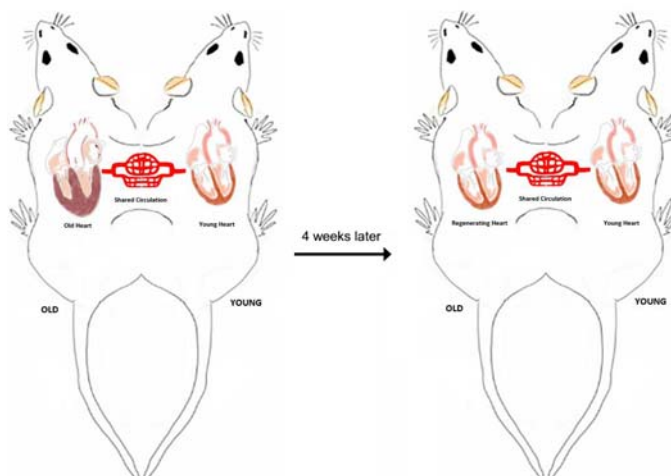


Figure 4. Chronic Parabiosis. a) Isochronic parabiosis where the circulations of two mice of similar age (young-young or old-old) are surgically connected together and b) heterochronic parabiosis where the pairing is done between a young and an old mouse. Heterochronic - but not isochronic parabiosis - is associated with gradual regression of age-related cardiac hypertrophy in the old mouse.

by the Smad pathway, which acts as depressor and stimulator of transcription of a large number of relevant genes (Figure 5).

Previous work in our lab, has shown that Activin/Follistatin (another member of the TGF- β superfamily) pathway could play an important role in remodeling associated with HF as well as reverse remodeling following left ventricular assist device (LVAD) combination therapy³³. Loffredo and colleagues demonstrated that the circulating levels of GDF11 decreased with age and were restored following heterochronic parabiosis. To investigate the physiologic relevance of their findings, they went on to show that GDF11 can prevent myocardial hypertrophy both *in vitro* and *in vivo* models, and that systemic administration of this substance in old animals with abnormal hearts resulted in reverse remodeling, similar to that observed following heterochronic parabiosis. As mentioned by Rando and Finkel³⁴, these experiments suggest that Galen was right when he stated that disease was due to “bad humor”; circulating blood in this case. Taken together, these findings might have very exciting implications with regard to developing novel therapies for the ageing myocardium.

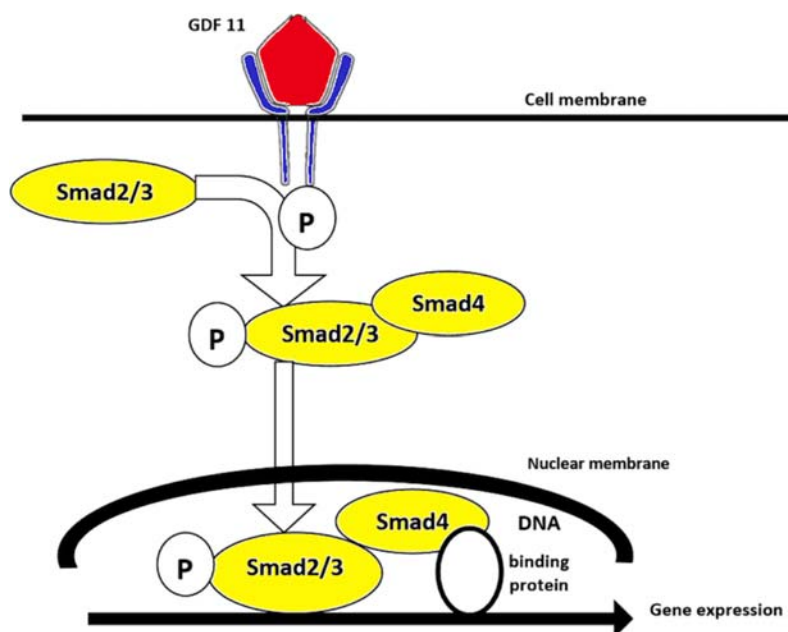


Figure 5. Mechanism of action of Growth Differentiating Factor 11 (GDF 11). GDF 11 – a ligand from the transforming growth factor β (TGF- β) superfamily – binds the extracellular domain of type I and II Ser/Thr kinase receptors. Phosphorylation of type I receptor leads to sequential phosphorylation of members of the intracellular Smad signal transduction pathway, ultimately resulting in changes to nuclear gene expression.

REVERSING AGEING SKELETAL MUSCLE

Old age is associated with diminution in skeletal muscle mass, which is crippling in more than one way, and has been shown to be associated with fractures due to falling, declining quality of life with loss of independence.^{35,36,37,38} In addition, it is hypothesized that it may influence heart function.^{39,40}

The extent of loss of skeletal muscle mass has been shown to correlate inversely with survival (Figure 6).^{41,42} Evidence from experimental models has shown that the age-related decline in skeletal muscle function is related to intrinsic changes in the skeletal myoblasts^{43,44} as well as circulating factors, both of which can be reversed in the animal models.^{45,46,47,48} Skeletal muscle homeostasis and regeneration is dependent on the existence of Pax7-expressing progenitor cells on the surface of each

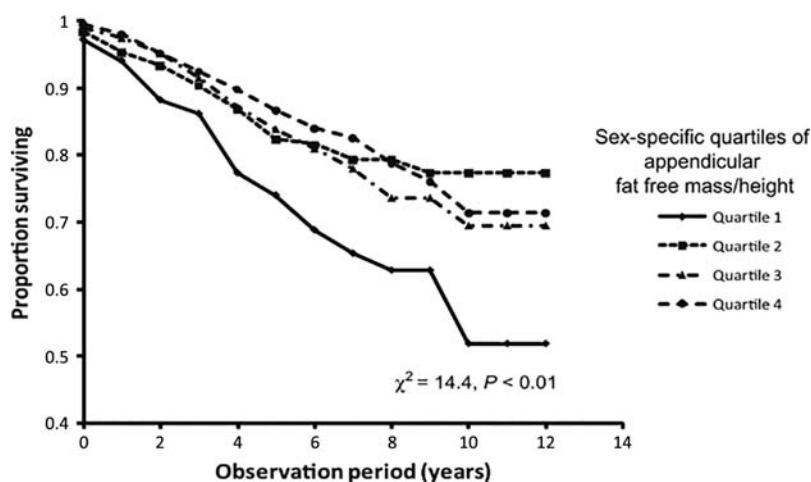


Figure 6. Association between muscle mass and survival. 12-year survival in 1413 healthy old individuals according to sex-specific quartiles of appendicular fat free mass/height. Fat free mass was measured using dual-energy X-ray absorptiometry. Sex-specific quartiles for appendicular fat free mass divided by height were calculated to account for sex differences in body composition. Quartile 1 corresponds to the lower quartile while 4 corresponds to the upper quartile. From Bunout D. et al.⁴¹.

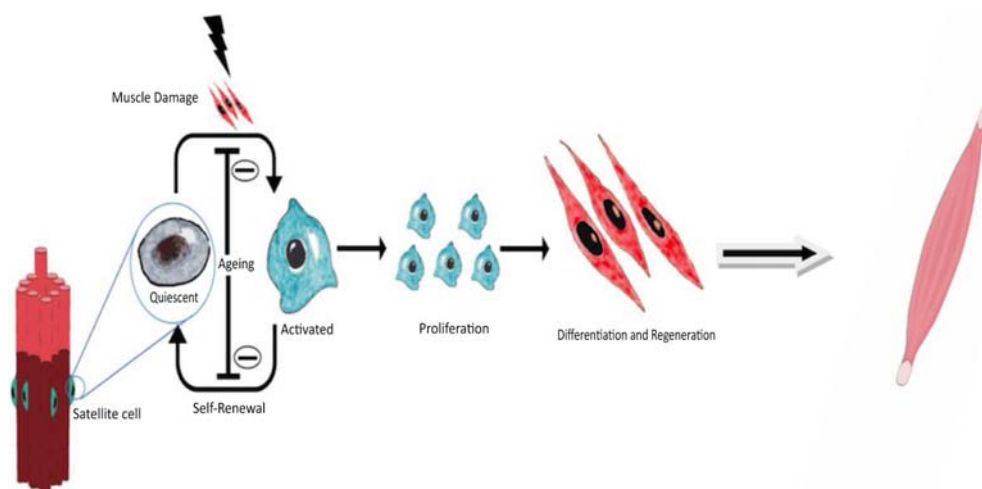


Figure 7. The effect of age on skeletal muscle regeneration. Quiescent progenitor cells (satellite cells) exist on the surface of skeletal muscle fibres. Following damage to the muscle, these cells are capable of proliferating into muscle progenitor cells - that eventually regenerate new muscle fibres - and self-renewal to replenish their own population. This capacity progressively declines with ageing.

normal muscle fibre. Skeletal myoblasts can be separated using single fibre cell culture technique, or cell sorter due to their unique expression of surface molecules Sca1⁻, CD45⁻, CD11B⁻, CXCR4⁺, Beta 1 integrin and other progenitor cells. Skeletal myoblasts can self renew and differentiate to myotubes which regenerate skeletal muscle (Figure 7). The number of skeletal myoblasts as well as their capacity to regenerate skeletal muscle decline with advancing age.³⁸

The mechanisms responsible for this decline have been shown to be due both to inherent changes of the skeletal myoblasts, as well as due to changes in circulating factors similar to those described for the aging myocardium.^{48,49} With regard to the intrinsic changes, Pedro Sousa and colleagues from Barcelona showed that the aging skeletal myoblasts lose the capacity for reversible quiescence and activation which was due to down regulation of p16 ink4a.⁴⁸ This loss of regenerative capacity of the aging myoblasts persisted even after transplantation in young rats, showing that these changes were independent of the environment. Silencing of p16 ink4a restored the functional regenerative capacity of the cells. Work by Price et al. and Tierney et al. implicated yet another pathway – JAK-STAT – and demonstrated an age-related increase in JAK-STAT signal transduction in mouse muscle suggesting

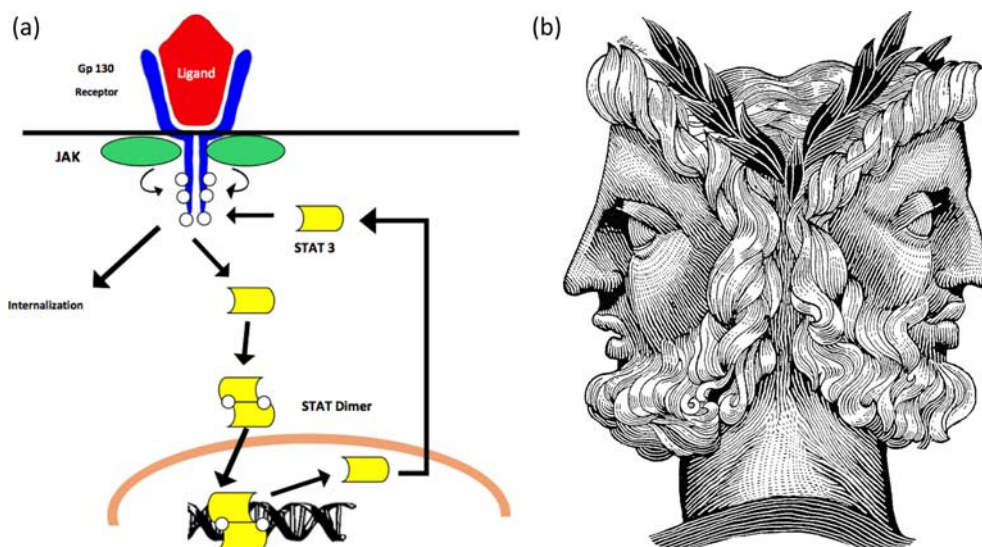


Figure 8. Janus Kinase Signal Transducer and Activator of Transcription (JAK-STAT) pathway (left; a) and Janus, the Roman God of gates, doors, passages and endings (right; b).

that it may suppress myogenic activity. The authors went on to demonstrate that JAK-STAT inhibition promoted satellite cell expansion and rescues muscle regeneration defects in elderly and dystrophic mice using a series of in-vitro and transplant-based siRNA inhibition of JAK kinase and Stat3 (Figure 8).^{50,51,52}

Recent work by Sinha, Richard Lee, and Amy Wagers from Harvard, using heterochronic parabiosis, showed that decline in circulating GDF11 levels is implicated in the age-related decline in skeletal muscle function.⁵³

CONCLUSIONS AND FUTURE DIRECTIONS

New experimental work has shown, in small animal models, that cardiac and skeletal dysfunction associated with ageing can be reversible, through different mechanisms. This opens the door for concerted research in the applicability of these or other methods to large animal models and ultimately humans, bringing the dream of “eternal youth “ nearer.

Acknowledgements

The authors would like to thank Dr. Hassan Kamel for producing the illustrations.

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