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EDITORIAL

A novel signalling mechanism regulating telomere length in cardiomyocytes

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This editorial refers to 'Pim1 maintains telomere length in mouse cardiomyocytes by inhibiting TGFβ signalling' by D.E. Ebeid *et al.*, pp. 201–211.

Clinical management and treatment of human diseases are continuously improving, with a progressive elongation of life expectancy in Western countries. As a consequence of the elevation of the average age of the population, the incidence of ageing-related diseases will progressively increase in the next years. Among ageing-related diseases, cardiovascular diseases still represent the first of cause of death in the Western world. Ageing induces multiple cardiac abnormalities such as cardiomyocyte hypertrophy, mitochondrial abnormalities, calcium handling uncoupling, and contractile dysfunction. Therefore, the future task of medicine will be the discovery of new therapies for the attenuation of ageing process and ageing-related diseases, including cardiovascular diseases.

Telomere length is considered a marker of cellular age.[1] In proliferating cells, telomeres progressively shorten, finally arresting cell division and even triggering apoptosis. In addition, telomere length is significantly reduced in response to oxidative and metabolic stress. On the other hand, telomere length is preserved by telomerase enzyme.[1] Previous works demonstrated that telomere shortening is associated with the development of cardiomyocyte abnormalities and dysfunction, despite the fact that cardiomyocytes are terminally differentiated post-mitotic cells.[1] Shorter telomeres were found to be associated with the development of cardiac dysfunction and hypertrophy.[1] Mice with deletion of telomerase RNA component showed a dramatic loss of telomere length and progressively developed dilated cardiomyopathy and heart failure through the up-regulation of p53.[2] Conversely, cardiac overexpression of telomerase reverse transcriptase (TERT), the catalytic subunit of telomerase enzyme, preserved telomere length, reduced myocardial ischaemic injury, and attenuated chronic cardiac remodelling and dysfunction following permanent coronary artery ligation.[3,4] In addition, endogenous TERT expression in the heart progressively declines during ageing, suggesting that this mechanism contributes to ageing-induced cardiomyocyte abnormalities.[1]

Ebeid *et al.* provided compelling evidence demonstrating that the serine/threonine kinase Pim-1 promotes telomere elongation in adult cardiomyocytes, by inducing the up-regulation of TERT.[5] Mice with cardiomyocyte-specific overexpression of Pim-1 showed longer telomeres in cardiomyocytes, whereas mice with systemic Pim-1 gene deletion showed a significant reduction of telomere length. Pim-1 overexpression induced significant up-regulation of TERT, and TERT knockdown attenuated the effects of Pim-1 on telomere length. These results are in line with previous evidence showing that Pim-1 overexpression induces telomere elongation and promotes TERT expression also in proliferating cardiac interstitial cells.[6]

Mechanistically, Ebeid *et al.* showed that Pim-1 up-regulates TERT and preserves telomere length by inhibiting transforming growth factor-β (TGF-β) signalling. TGF-β expression was found to be progressively increased in cardiomyocytes in response to stress, and inhibition of TGF-β receptor preserved telomere length like Pim-1 overexpression. Although Pim-1 overexpression did not affect TGF-β expression in cardiomyocytes, it significantly reduced Smad2/3 phosphorylation, which is required for nuclear translocation of these transcription factors in response to TGF-β signalling activation and subsequent up-regulation of TGF-β target genes. Remarkably, TGF-β receptor inhibition attenuated telomere shortening in Pim-1 KO mice, whereas it did not induce additional effects on telomere length in cardiomyocytes with Pim-1 overexpression. Overall, these results would suggest that TGF-β promotes telomere shortening in cardiomyocytes through autocrine/paracrine effects, and Pim-1 activation blocks this process by inhibiting Smad2/3 activation.

Although the molecular mechanisms through which Pim-1 reduces Smad2/3 phosphorylation were not directly elucidated, the authors hypothesized that Pim-1 may elicit these effects like its upstream regulator Akt1. A previous study demonstrated that Akt1 interacts and sequesters Smad3 outside the nucleus, thereby reducing its phosphorylation.[7] The mechanisms through which Pim-1 increases TERT expression by inhibiting TGF-β signalling were also not clarified. Previous work showed that Smad3 binds to TERT promoter and reduces it expression in cancer cells.[8] Future studies are needed to test whether Pim-1 physically interacts with Smad2/3 in cardiomyocytes and extrudes them from the nucleus, thereby reducing their binding to TERT promoter. Of note, phosphorylation levels of Smad2/3 were not significantly different in the heart of Pim-1 KO mice with respect to WT mice. It is possible that Pim-1 and TGF-β signalling regulate telomere length also through other

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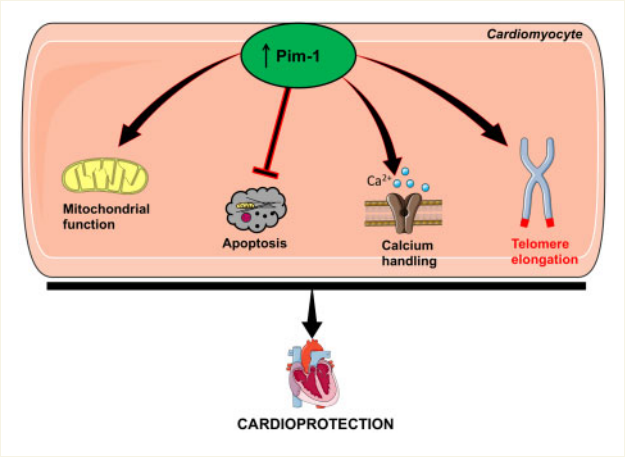

Figure 1 Pim-1 activation elicits multiple beneficial effects in cardiomyocytes. A schematic representation of the beneficial effects of Pim-1 activation in cardiomyocytes in response to stress. Telomere length preservation may contribute to the cardioprotective functions of Pim-1.

downstream targets, independently of Smad2/3. Future studies are needed to test this hypothesis.

Several important aspects regarding the crosstalk between Pim-1 and TGF-β signalling for the regulation of telomere length will need to be investigated in future studies. It will be important to test whether Pim-1 effects on telomere length are also exerted in endothelial cells. In fact, it was previously shown that TERT overexpression reduces ageing-induced endothelial dysfunction and increases NO production.[1] It will also be important to test whether Pim-1 can attenuate other deleterious effects of TGF-β signalling activation, such as fibrosis. Finally, previous studies demonstrated that Pim-1 overexpression in cardiomyocytes reduces myocardial damage in response to ischaemia/reperfusion injury and pressure overload, through multiple beneficial effects.[9,10]Pim-1 was shown to preserve mitochondrial function and structure; to inhibit apoptosis by increasing the expression levels of Bcl-2 and Bcl-XL; and to improve calcium handling through SERCA2a up-regulation. It is possible that the preservation of telomere length also contributes to the beneficial effects of Pim-1 in cardiomyocytes (*Figure 1*). In this regard, TERT localizes to nucleus and mitochondria. Mitochondrial TERT was previously shown to reduce stress-induced mitochondrial DNA damage and reactive oxygen species (ROS) generation and to improve mitochondrial function.[11]

Overall, the study from Ebeid *et al.* demonstrated that Pim-1 activation and TGF-β receptor inhibition may represent new potentially therapeutic strategies to preserve telomere length and reduce cardiac ageing and diseases. It will be important to develop pharmacological activators of Pim-1 and test their efficacy for the treatment of cardiovascular ageing and diseases. A possible limitation to the possible therapeutic use of Pim-1 activators is related to the fact that Pim-1 was firstly described as an oncogene, being associated with the development of different types of cancer, including leukaemia and lymphoma. Therefore, it will be important to test in the future whether Pim-1 activation may also predispose to cancer development, aside from its potential beneficial cardiovascular effects.

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