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Commentary

A small peptide possesses great potentials in myocardial infarction intervention

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Damaged myocardial tissue is difficult to recover after myocardial infarction (MI), and scars without systolic function formed on the heart put patients at risk of arrhythmia or cardiac failure. Common surgical and medical management mainly function to attenuate the associated symptoms, with fewer effects on promoting regeneration of the damaged myocardium [1]. New strategies to enhance the ability of myocardial regeneration need to be explored.

In recent years, cell therapy has been regarded as a potential means to repair the heart. Many studies and clinical trials have shown that the use of adult stem cell-secreted growth factors, chemokines, and other bioactive substances, can play a role in promoting myocardial angiogenesis, regulating local inflammatory response, and promoting extracellular matrix remodeling, thereby treating the damaged heart [2]. However, the clinical application of the cell therapy is restricted by several limitations: self-replication of transplanted cells may increase the risk of tumors; the large number of cells transplanted into the heart may also induce arrhythmias; and the implanted foreign cells may lead to immune rejection [3]. The extraction, culture, storage, and transportation of the cells are complex and time-consuming. This means it is difficult to meet the standardized requirements of mass production.

To solve the above limitations, scientists have recently developed two promising surgical strategies that use acellular biomaterials to improve post-infarct myocardial remodeling by promoting a pro-angiogenic and antifibrotic environment, which are nominated as artificial heart patches (also called "epicardial infarct repair", EIR) and intramyocardial injection(IMI) respectively [4-6]. New bioactive substances loaded for the repair have been investigated and some have achieved promising results. As one of the representative reports, Huang et al. [7] have utilized cell-free extracellular matrix from the pig heart as scaffold, and synthetic cardiac stromal cells generated by encapsulating secreted factors from isolated human cardiac stromal cells to fabricate an artificial heart patch. *In vivo* tests on rats and pigs, the EIR therapy has shown promising results in restoring cardiac function after MI [8,9]. However, there are some potentially relevant complications of the EIR method, involving calcification or local inflammation. With extensive consideration, our collaborators Zhang et al. selected a novel HDAC7-derived phosphorylated 7-amino-acid (aa) peptide (7Ap), injected it into the myocardium around the infarction zone, and rightfully demonstrated its efficacy in preventing adverse cardiac remodeling seen following infarction [10]. They highlight the potential role of 7Ap-loaded collagen in facilitating recovery from such ischemic changes by a composite mechanism of stimulating vascular progenitor cell recruitment and differentiation, restraining cellular apoptosis and fibrosis of the ventricular wall, and promoting cardiomyocyte cycle progression.

It is recognized that HDAC7 plays an essential role in the maintenance of endothelial homeostasis, smooth muscle cell differentiation and vascular integrity [11-13]. The transcript variant 2 of HDAC7 in both mice and human contains a short open reading frame (sORF) within the 5' non-coding area. In our previous work, the translation of the sORF was found to give rise to a 7aa-peptide in mice [14]. Employing sORFs and sORFs encoded peptides (SEPs) as biological therapies is evolving with increasing importance, as their new biological functions are emerging. one such identified clinical benefit is the muscle-specific long noncoding RNA, which encodes DWORF (a peptide). DWORF remains as the sole known endogenous peptide capable of activating the SERCA pump, to enhance the contractility of muscles [15]. It is therefore a future strategy to use likewise small peptides to regulate local resident stem cells, and this paper of Zhang et al. [10] paves the way to employ such sORFs in transforming the treatment approaches to patients following MI.

Our previous work revealed that the 7A peptide in mice can be alternatively translated from HDAC7 mRNA in cardiac progenitor cells in response to vascular injury [14], and modulates Sca1$^+$-VPC activation and its effects on vascular injury repair and angiogenesis in ischemic tissues. A functional analysis was further evaluated by using different disease and transplantation models and its translational potential in vascular repair and regeneration was confirmed [16]. In this study, sustained delivery of 7A, especially 7Ap, from tissue-engineered vascular grafts could attract Sca1$^+$-VPC cells into the grafts, contributing to endothelialization and intima formation in the vascular graft. These results suggest that this novel type of peptide possesses robust translational potential in vascular regenerative medicine.

As a professional in the field of biomaterials, Zhang et al. [10] further highlights the role of tissue grafting, in promoting cardiovascular outcome. They seek to maximize the effects of intramyocardial delivery of 7Ap. They selected a collagen-based hydrogel, due to its minimizing capability of degradation from endogenous peptidases and invasion; its ability to maintain cardiac structure and sustain a favorable microenvironment for cell survival and proliferation. Subsequently, they were able to provide local delivery of the 7Ap to the myocardium and sustain a conducive environment for cardiac regeneration. In doing so, further therapeutic effects of locally released 7Ap from the collagen hydrogel were established – as serving as a bioactive factor in promoting the recruitment of endogenous Sca-1$^+$ stem cell to the site of injury. Albeit previously, the mechanism of trafficking Sca-1$^+$ stem cell to the site of action in ischemic myocardium, remained largely unclear, the work of Zhang et al. functions to bridge the missing gap of such knowledge.

Alongside the role of 7A and 7Ap in Sca1$^+$ stem cell niche formation, the paper also discusses their ability to influence neo-angiogenesis and their contribution of blood reperfusion in ischemic tissue. Such angiogenic-effects, as translated by the formation of new blood vessels, have somewhat promising therapeutic benefits in salvaging the ischemic myocardium during the initial stages after MI [17,18]. despite numerous preclinical studies attempting to investigate proangiogenic therapies for MI, such as by administering stem/progenitor cells for example, the clinical translation of such studies in patients with acute MI, has demonstrated mixed results. Often, caveats have been applied to methodological planning, such as the way angiogenic growth factors are delivered. Hence, previous results suggested that employing a single growth factor or cell type may not adequately support angiogenesis [19]. The paper of Zhang et al., however, sheds light on the local intramyocardial delivery of 7Ap as being capable of supporting angiogenesis, whereby offering a scope of advancement in the development of pro-angiogenic therapies, following MI. Such angiogenic de-novo formation of blood vessels is of great clinical importance, when considering their ability to regulate cardiomyocyte hypertrophy and contractility, thereby ameliorating the adverse ventricular remodeling that is seen as a result of hypoperfusion-induced cardiomyocyte-death. The therapeutic benefits of such an impediment can be translated as a halt in the progression of eventual heart failure [19,20].

Another important finding in this research is that the 7A peptide repairs the damaged myocardial tissue by promoting the post-mitotic cardiomyocytes to re-enter the cell cycle. It is well-known that differentiated cardiomyocytes generally permanently exit the cell cycle, causing cardiomyocytes to be incapable of repairing via regeneration. A recent landmark study in this field showed that overexpression of four cell-cycle regulators, cyclin-dependent kinase 1 (CDK1), CDK4, cyclin B1, and cyclin D, which were screened from the proliferating fetal cardiomyocytes, efficiently induced cell division in post-mitotic mouse, rat, and human cardiomyocytes, with significant improvement in cardiac function after MI [21]. Though the specific molecular mechanism of the regulatory role of the 7A peptide needs to be further elucidated, the study of Zhang et al. undoubtedly enriches our understanding of the regulatory mechanism of cardiomyocyte cycle progression.

A limitation of the study design could however be the use of the left ventricular ejection fraction as an assessment parameter to determine the efficacy of the 7Ap. The subsequent increase in left ventricular ejection fraction secondary to the infusion of 7Ap-loaded collagen hydrogel may be useful at indicating the effects on systolic dysfunction [22]. However, relying on such an assessment parameter, the study sought to assess the left ventricle's systolic function solely, as diastolic dysfunction often presents with preserved ejection fraction [23]. This study might therefore have benefitted from investigating diastolic impairment also, as likewise diastolic, and systolic impairments do not often occur mutually exclusively, following MI.

Overall, this paper helps to deepen our understanding of the adverse functional and structural effects seen in the ischemic myocardium. Not only does it provide descriptive characteristics of such changes, but it also gives an insight into the role of a HDAC7-derived 7Ap peptide in overcoming such changes. It highlights the future direction of medical therapies as relying on likewise small peptides to regulate local resident stem cells, thereby transforming the approach of treating the likewise hypoperfused and adversely remodeled myocardium following an MI. The therapeutic use of such local resident stem cell activation in improving cardiovascular outcomes following myocardial infarction, could provide breakthroughs in improving the cardiovascular decline and high mortality commonly seen post-MI.

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