

Mini Review

Myocardial Regeneration: A Novell Multifaceted Strategic Approach

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Abstract

Myocardial infarction and cardiac failure is a major source of morbidity and mortality globally. Current treatment strategies are mostly palliative and suboptimal. Stem cell based treatment strategy for tissue regeneration has proven value in the treatment of some conditions. The optimal treatment of myocardial infarction/heart failure lays in restoration and maintenance of adequate functional myocardial syntitium. Mature myocardium has limited capacity for regeneration. The limitations for a successful myocardial regeneration include identification of an ideal stem cell line, exclusion of the scar tissue that follows myocardial injury, revascularisation and secondary preventive measures. This manuscripts outlines measures and provides the theoretical bases for addressing these significant challenges.

Introduction

Coronary heart disease and heart failure is a significant cause of morbidity and mortality globally. About 21 million adults worldwide are living with heart failure and the number is expected to rise. In Europe about 15 million people are living with heart failure and the incidence is expected to rise by 25% in 2030 [1]. Heart failure is characterised by frequent hospitalisation and high risk of mortality. An estimated 2% of most countries' health budget is spent on treatment of heart failure and 70% of this amount is spent on hospitalisation [1]. A person at age of 40 has a 1 in 5 lifetime risk of developing heart failure. More than 1million hospitalisation due to heart failure are reported annually in Europe [2]. According to the latest WHO data published in May 2014 coronary heart disease is the leading cause of death in the United Kingdom responsible for 75, 014 or 17.2% of total deaths. The in hospital mortality for patients admitted with heart failure is 1-4% while mortality 1 year after discharge from hospital is 20% [3]. In the United States of America coronary heart disease was the cause of 1 in every 7 deaths in 2011. Each year about 635 000 Americans have a new coronary heart attack. Every 34 seconds one American has a coronary event and approximately every One minute 24 seconds an American will die of heart attack. In the year 2011 every 1 in 9 death certificate in America mentioned heart failure [4].

Heart failure and coronary heart disease is a growing pandemic that demands a paradigm shift in the current strategies for management. Successful stem cell based myocardial regeneration is potentially the most promising approach but there are significant hurdles to cross before this is realised.

Identifying the challenges

The myocardium is a syntitium of very highly differentiated

cells, specialised for electrical and pump function. Myocardial infarction and consequent cardiac failure is a significant source of morbidity and mortality in contemporary society. The human adult myocardium is made predominantly of highly specialised/permanent or stable cells with limited capacity for regeneration [5,6].

The consequence of myocardial infarction is the loss and replacement of this functional syntitium with non-functioning scar and fibrous tissue.

The optimal management of myocardial infarction and cardiac failure has remained a significant challenge to science and medicine.

The management of myocardial infarction has evolved from pharmacological, surgical and percutaneous revascularisation, pump support device and more recently cell therapy. Except for cell therapy all existing cardiac therapy can best be described as palliative optimisation of residual function. The future management of myocardial infarction lays with stem cell based myocardial regeneration. This is the treatment strategy with significant potential for a cure. A lot of work has been done towards identification of a viable stem cell sources and their integration into the infarcted myocardium with variable results [5, 7].

Our aim and objective is to identify the current constrains and challenges of myocardial regeneration and to profound an all-encompassing strategy/hypothesis to address these issues with a view to achieving a functional, viable and sustainable myocardial regeneration as the goal standard of care for myocardial infarction and heart failure.

Multifaceted strategy for regeneration

The principles of achieving a viable myocardial regeneration lies in:-

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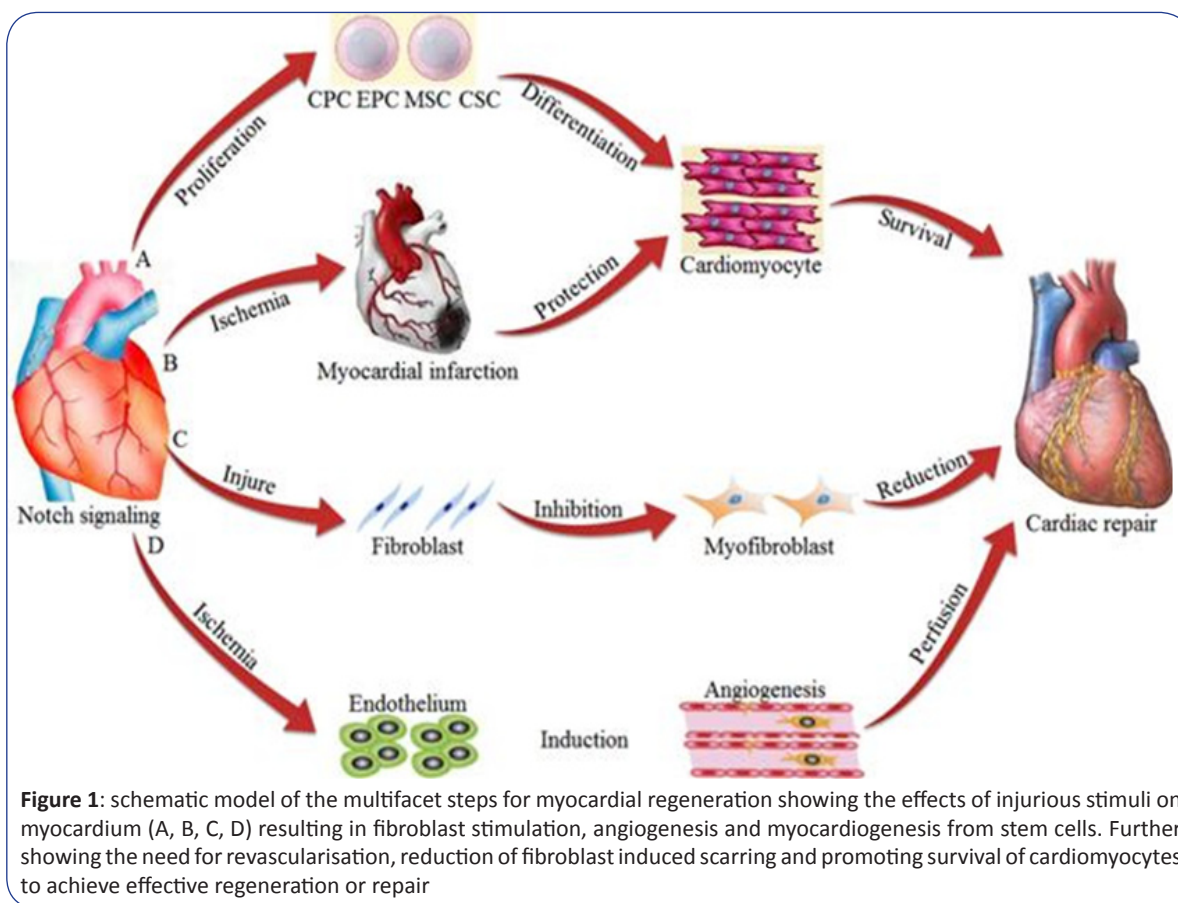
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Reversal of the initiating stimulus by revascularisation, inhibition of the process of repair by fibrosis, facilitation of regeneration of myocardial syncytium by stem cells and a maintenance strategy by secondary prevention.

1. The initiating stimulus for myocardial infarction is ischemia the first step towards achieving myocardial regeneration is the removal of the initiating injurious stimulus by revascularisation. As this will halt further myocardial damage and loss. This can be achieved both microscopically and macroscopically. Macroscopic revascularisation can be achieved by percutaneous angioplasty or surgical grafting while microscopic revascularisation refers to stem cell induced angiogenesis. Bone marrow stem cells have demonstrated significant capacity to achieve this goal [8].
2. It is essential to halt the process of healing by fibrosis in order to preserve room for the laying of new functional myocardial syntitium. The process of fibrosis refers to the replacement of infarcted myocardium by scar tissue. Scar tissue is not a suitable substrate for the laying of a functional myocardial syntitium. The requirement for laying a functional myocardial syntitium is to mimic the embryonic cardio- genesis milieum which is a highly vascularised vacuum with the required cytokines/hormones. It is therefore essential to inhibit fibrosis or scarring which is predominantly a fibroblastic activity. A prompt strategy of

fibroblast inhibition should be a requisite treatment of myocardial infarction in anticipation of subsequent regenerative treatment. There are various fibroblast inhibitors that could be explored. Recent evidence suggest that this can be achieved with agents' apelin and relaxin [9,10].

3. A carefully selected stem cell committed to the generation of myocardial syntitium can then be laid in the favourably generated substrate [7,11]. The adult human resident myocardial stem cells have limited proliferation and regeneration capacity. The need to circumvent this limitation is crucial to successful regeneration (figure 1) [12].
4. The activity of the stem cells can then be facilitated by required proteins such as neuregulin, periostin and IGF-1 which have been shown to stimulate stem cell propagation and differentiation [13-15]. Identification and modulation of the genetic loci responsible for the limited proliferation and regeneration capacity of the human resident myocardial stem cells calls for a very strong consideration.
5. Secondary prevention strategy with statins, ACE inhibitors, and antiplatelet with life-style changes like cessation of smoking will be essential to prevent further recurrence of ischaemic event and loss of myocardium.



Conclusion

An initial animal model to demonstrate this all-encompassing approach could provide the long awaited answer to a viable myocardial regeneration as the standard treatment for myocardial infarction and heart failure.

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