CARDIAC LYMPHATIC VESSELS: A NOVEL TARGET FOR TREATMENT POST-MYOCARDIAL INFARCTION

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Abstract

In the UK 170,000 people a year suffer from a myocardial infarction (MI). During an MI immune cells are recruited to help repair the heart, however, prolonged inflammation can cause further damage leading to heart failure. We propose that lymphatic vessels, which transport immune cells may be important in resolving inflammation. We discovered that administration of the lymphatic growth factor, VEGF-C, following MI in rodents resulted in improved cardiac function. Translation of this work into clinical medicine could provide a novel therapeutic for humans post-MI which would offer treatment to reduce the severity of heart failure for millions of individuals.
During the time it takes you to read this essay one person in the UK will suffer from a myocardial infarction (MI). That is one MI approximately every three minutes, culminating in 175,000 per year [1]. During MI, stenosis of a coronary artery results in a region of the heart being starved of oxygen and metabolites, leading to extensive cardiomyocyte death. Consequently the function of the heart is impaired which can result in sudden death, cardiac rupture or the formation of scar, leading to progressive contractile dysfunction and ultimately heart failure [2]. An extensive immune response takes place during MI which is critical for healing, however, chronic inflammation leads to scarring [3]. Due to rapid intervention and early treatment an ever increasing number of people are now surviving MIs, meaning there is an increased population of people in the UK living with heart failure. Heart failure is a debilitating disease which can leave individuals struggling to carry out their daily activities as they suffer from breathlessness, fatigue and fluid accumulation. There is currently no treatment available to repair the damaged heart muscle. In fact the only cure for heart failure is a heart transplant, an impractical or unavailable option for many people. I am currently studying the response of lymphatic vessels within the heart to MI in a murine model and believe that in the future we may be able to reduce the incidence and severity heart failure by pharmacologically targeting cardiac lymphatic vessels.

The lymphatic vasculature is an extensive network present in all mammals [4] which is responsible for immune surveillance, tissue fluid regulation and absorption of lipid-containing chylomicrons into the gut. Lymphatic vessels have a critical role during inflammation. Their branched network covers almost the entire body and provides the main transport route for soluble antigens and antigen-presenting cells. Soluble antigens and antigen-presenting cells travel from peripheral tissues to lymph nodes, which are hotspots where immune responses are elicited. In various disease states, increased demand is imposed on the lymphatic network. In order to cope with this new lymphatics begin to grow through the process of lymphangiogenesis [5, 6]. Whilst systemic lymphatics have been well studied with regard to their development and response to disease states, little attention has previously been given to cardiac lymphatic vessels.

We hypothesized that cardiac lymphatics play an important role in clearing the inflammatory infiltrate post-MI. The response of monocytes and macrophages to MI can be divided into two phases. During the first few days following injury, pro-inflammatory Ly-6C^{high} monocytes are mainly recruited [7].
When inflammation begins to resolve, from 4 to 5 days post-MI, the number of Ly-6C\textsuperscript{high} monocytes falls and the monocyte population shifts towards more fibrotic/reparative and anti-inflammatory Ly-6C\textsuperscript{low} monocytes \cite{8}. The two phases of monocyte infiltration mark the two stages of healing which are essential for scar-formation. Lymphatic vessels are essential for the transport of immune cells to and from sites of inflammation \cite{9} and it has been established in other disease states that stimulation of lymphangiogenesis via addition of vascular endothelial growth factor proteins VEGF-C and VEGF-D which bind to and activate vascular endothelial growth factor receptor-3 (VEGFR3), can result in enhanced clearance of infiltrate and a reduction in chronic inflammation \cite{10-15}. We proposed that delivery of recombinant human VEGF-C protein post-MI would enhance the growth of new lymphatics, therefore improving the clearance of the inflammatory infiltrate from the region of injury and reducing the level of subsequent chronic inflammation, resulting in improved tissue repair and wound healing and an improvement in cardiac function post-MI.

In order to test the above hypothesis, MI was induced in adult mice by permanent ligation of the left-anterior descending coronary artery. Mice were then injected with either recombinant human VEGF-C or vehicle five times over one week post-MI. The response of the cardiac lymphatic vessels was assessed using histology and revealed an enhanced lymphangiogenic response in VEGF-C treated mice (Figure 1). Cardiac cine-magnetic resonance imaging (MRI) was performed, in collaboration with Dr Carolyn Carr, at 7 day intervals over 28 days to assess changes in cardiac function. Interestingly, the study revealed that VEGF-C treated mice displayed a significant improvement in cardiac function with regard to left ventricular ejection fraction at 14 and 21 days post-MI.
Figure 1: Treatment with recombinant VEGF-C following MI in a murine model leads to enhanced lymphangiogenesis and improved cardiac function. Treatment with VEGF-C post-MI induces an enhanced lymphangiogenic response which may improve the resolution of chronic inflammation, which reduces scarring. Results from cardiac cine-MRI revealed that treatment with recombinant VEGF-C improves cardiac function post-MI.

These promising results suggest that treatment with pro-lymphangiogenic growth factors such as VEGF-C may provide a basis for novel therapies which could, in future, be used to treat humans post-MI. Translation of the results from this study into a clinical setting would be extremely valuable and have the potential to lead to treatment options to reduce the severity of heart failure for millions of individuals who suffer from MI.

In order to take this research forward towards the goal of offering a clinical therapy, a collaborative, multi-disciplinary approach at the interface of basic medical science, chemistry and clinical medicine would be required. Further work will be carried out during this DPhil in order to further assess the impact of VEGF-C treatment on clearance of inflammation post-MI. Future work should also involve collaboration with medicinal chemists in order to discover and design alternative drugs which act in the same manner as VEGF-C but offer benefits in terms of route of administration and cost of
synthesis. Translation of VEGF-C or a similar therapy into the clinic would require the initiation of a clinical trial in order to test safety and efficacy in human patients.

Multidisciplinary collaboration to translate this project into a clinical therapy would require the identification of potential collaborators, the establishment of strong working relationships, a high level of organisation and an understanding of multiple disciplines. Having been involved in a collaboration with Dr Carr for the MRI study I have already experienced the process of acquiring new skills from outside my field and applying them. Furthermore, I have a strong understanding of the science underpinning this project and believe I have the capability to understand the other scientific disciplines which will benefit this work. This is illustrated by the work I have undertaken so far and by my joint first authorship on a paper reporting work from this project which is currently undergoing a second round of revision experiments for *Nature*. 
References

1. BHF, British Heart Foundation Cardiovascular Disease Statistics Factsheet. 2015.