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Commentary

Tissue non-specific alkaline phosphatase (TNAP): A player in post-MI cardiac fibrosis

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Heart disease with attendant cardiac fibrosis is a chronic economic and social burden in developed countries, killing more patients in developed countries than any other disease [1]. One of the major etiologies for cardiac fibrosis includes the chronic pathology associated with post-myocardial infarction, which can lead to activation and maintenance of profibrotic myofibroblasts in the heart that persist well after expansion and activation phases to then influence the accumulation of extracellular matrix in the noninfarcted regions of the heart [2]. Myofibroblasts contribute to cardiac fibrosis, and cardiac fibrosis has been identified as a primary contributor to heart failure for more than a decade [3]. Normally, in other tissues such as skin, myofibroblasts go through a phase of apoptotic cell death that removes them from the healed wound [4]. After myocardial infarction, there is growing evidence to suggest that myofibroblasts in the cardiac infarct scar receive the signal to undergo apoptosis eg, apoptotic priming, however other factors are activated to allow them to evade apoptosis, and this is suggested to be biomechanical and poorly understood paracrine growth factor signals [4]. Thus, myofibroblasts are seemingly locked in apoptotic priming, wherein senescence dominates [2]. Fibroblasts and myofibroblasts continue to populate the infarct scar and continue to add matrix not only to the infarct scar but also to the otherwise healthy adjacent bordering myocardium. This “spilling over” effect may be due to the persistence of the senescent myofibroblast phenotype(s) [4]. To date, there is no specific small molecule drug for the treatment of progressive cardiac fibrosis following myocardial infarction and thus a knowledge gap for quelling heart failure in tandem with interstitial fibrosis continues to exist. The requirement for the identification of novel molecular targets to generate novel targets for therapeutic development is needed, to provide the clinician with a novel drug therapy to address this form of heart failure. Extension of this idea may allow clinicians to address the balance of signals that allow for the propagation of signals that promote the survival of senescent myofibroblasts in the post myocardial infarct heart.

In the current issue of this journal, Cheng et al. [5] present data to link clinical and experimental cardiac fibrosis by tissue non-specific alkaline phosphatase, or TNAP. This molecule has been previously identified as a potential prognostic marker for cardiac fibrosis in patients with myocardial infarction [6]. However, the causality of TNAP in the pathogenesis of cardiac fibrosis is unknown. Cheng et al. present data examining patients with human fibrosis and murine fibroblast behaviour in response to forced overexpression of TNAP [5]. They found that post-myocardial infarction patients exhibited a consistently high serum TNAP levels, and that this was associated with increased risk of mortality in patients with ischemic heart disease. Further, high TNAP was positively correlated to elevated PICP/PIIINP in patients with MI. Thus elevated TNAP seems to hold promise as a biomarker and clinical relevance to link its participation in post-MI related cardiac fibrosis. Whether this molecule is an important driver of fibrosis, these investigators found that in mice with myocardial infarction, TNAP is elevated, and TNAP knockdown was associated with improved cardiac function and reduced fibrosis. They also report that exogenous TNAP treatment was associated with fibroblast proliferation [5]. Does TNAP provide a pro-survival signal that contributes to the maintenance of senescent myofibroblasts in the infarct scar of post myocardial infarct patients? The answer to this question is currently unknown, but this is only one possible line of investigation that the current data by Cheng et al. has generated and facilitated. Perhaps the answers to these questions are forthcoming in the not-to-distant future, and the integration of these future studies will bring us another step further to devising an effective therapy for cardiac fibrosis and heart failure associated with myocardial infarction.

Contributors. IMCD is the principal investigator in the Molecular Cardiology laboratory at the Institute of Cardiovascular Sciences at the University of Manitoba, Winnipeg, Canada. This laboratory group carries out investigation of the regulation of fibroblast activation and deactivation in heart disease and the molecular basis for cardiac fibrosis after myocardial infarction and left ventricular overload, and is supported by operating grants from the Canadian Institutes for Health Research (PJT-162,163) and the Heart and Stroke Foundation of Canada (G-17−0,018,631).

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Declaration of Competing Interest

The author has no competing interests.

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