Published Ahead of Print on July 5, 2016 as 10.5966/sctm.2016-0066.

STEM CELLS TRANSLATIONAL MEDICINE®

TISSUE-SPECIFIC PROGENITOR AND STEM CELLS

Concise Review: Functional Definition of Endothelial Progenitor Cells: A Molecular Perspective

JATIN PATEL,[a] PRUDENCE DONOVAN,[b] KIARASH KHOSROTEHRANI[a,b]

Key Words. Endothelial • Progenitor • Vascular • Angiogenesis

[a]University of Queensland Centre for Clinical Research, Herston, Queensland, Australia; [b]University of Queensland Diamantina Institute, Translational Research Institute, Woolloongabba, Queensland, Australia

Correspondence: Kiarash Khosrotehrani, M.D., Ph.D., Centre for Clinical Research, Building 71/918, University of Queensland, Herston Campus, Brisbane, Queensland 4029, Australia. Telephone: 61-7-3346 6077; E-Mail: k.khosrotehrani@uq.edu.au

Received February 2, 2016; accepted for publication April 25, 2016.

1066-5099/2016/$20.00/0

http://dx.doi.org/10.5966/sctm.2016-0066

ABSTRACT

Since the discovery of endothelial progenitor cells (EPCs) almost two decades ago, there has been great hope in their use in treating chronic ischemic disease. Unfortunately, to date, many of the clinical trials using EPCs have been hampered by the lack of clear definition of this cell population. Attributes of a progenitor population are self-renewal and multipotentiality. Major progress has been achieved moving from a definition of EPCs based on a candidate cell surface molecule to a functional definition based essentially on self-renewal hierarchy of endothelial colony-forming cells (ECFCs). More recent work has seized on this functional characterization to associate gene expression signatures with the self-renewal capacity of ECFCs. In particular, Notch signaling driving the quiescence of progenitors has been shown to be central to progenitor self-renewal. This new molecular definition has tremendous translational consequences, because progenitors have been shown to display greater vasculogenic potential. Also, this molecular definition of EPC self-renewal allows assessment of the quality of presumed EPC preparations. This promises to be the initial stage in progressing EPCs further into mainstream clinical use. STEM CELLS TRANSLATIONAL MEDICINE *2016;5:1–5*

SIGNIFICANCE

The development of a therapy using endothelial progenitor cells provides great hope for patients in treating cardiovascular diseases going forward. For continual development of this therapy toward the clinical, further understanding of the fundamental biology of these cells is required. This will enable a greater understanding of their stemness capacity and provide insight into their ability to differentiate and drive tissue regeneration when injected into a host.

INTRODUCTION

Cardiovascular diseases remain a leading cause of morbidity and mortality worldwide, accounting for approximately 25% of all deaths. Of these, ischemic heart disease contributed the greatest burden of mortality in the developed and developing worlds [1]. To this end, there have been significant research efforts made to understand the biology of the circulatory system, determining the process of vessel development during embryogenesis to tissue regeneration and repair for maintenance in the adult system. Angiogenesis, the sprouting of blood vessels from pre-existing vessel structures, has been the most widely studied process during situations of tissue regeneration and cancer formation [2]. This paradigm is driven by angiogenic factors secreted by endothelial cells and their surrounding cells, resulting in elongation of the vessel structure and repair. However, it is also well known that mature endothelial cells are terminally differentiated and possess limited proliferative capacity [2, 3].

In 1997, a seminal article was published by Asahara et al., demonstrating the existence of a circulating vascular stem cell. These were termed "endothelial progenitor cells" (EPCs) [4]. EPCs could be isolated directly from blood and reinjected into an ischemic situation in which they formed chimeric vessels in the host, contributing to neovasculogenesis, a developmental process in which a stem cell will form an entirely new vascular structure that then connects to the existing circulatory system [4, 5]. The discovery of EPCs has since initiated a large body of research during the past two decades that has brought substantial hope to patients with chronic ischemic disease who have limited medical and surgical therapeutic options.

In these numerous clinical trials, mostly in myocardial infarction and critical limb ischemia, various cell types with presumed progenitor activity were used to promote vascular repair. Improvement was observed after treatment of critical limb ischemia, such as increased pain-free walking distance and reduced leg ulcer size [6, 7], but positive effects were temporary and