Stem Cell Reviews and Reports (2018) 14:627–628
https://doi.org/10.1007/s12015-018-9842-9

Circulating Stem Cells in Physiology and Pathology - Recent Studies Published in *Stem Cell Reviews and Reports*

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Published online: 7 August 2018

Hematopoietic stem cells (HSC) are untired travelers and a small number of these cells circulate under steady state conditions in peripheral blood (PB) for two main purposes i) to maintain a stem cell pool in remote bone marrow (BM) locations in the body and ii) to "patrol" peripheral tissues and organs and, when needed, to respond to organ injuries and infections. The number of these cells increases in stress situations related to infections, inflammation, organ injury as well as after strenuous exercise. Circulating stem cells also show a circadian rhythm of circulation with the peak in the morning hours and nadir at night. Recently, evidence has accumulated that not only HSC but also other types of stem cells including mesenchymal stem cells (MSC), endothelial progenitor cells (EPC), and very small embryonic like stem cells (VSELs) circulate at low level in PB under steady state conditions and a number of these cells increase in stress situations. The advance in flow cytometry allows us to identify and to enumerate these rare cells based on their phenotype [1].

However, circulation of stem cells in PB is a frequent topic of papers published in several journals, it has been also addressed in recent papers published in *Stem Cell Reviews & Reports* and thus it would be important to briefly highlight this interesting work for our readership. Firstly, despite several overlapping mechanisms that have been described in facilitating egress of stem cells from BM into PB, the crucial role plays an activation of innate immunity that is well known as the first responder to tissue/organ injury or infection. In a paper from Dr. Budkowska's group [1], it has been nicely confirmed that both activation of complement cascade and an increase in PB level of bioactive phospholipid spinhgosine-1 phosphate (S1P) regulates the egress of HSC from BM into PB, and moreover contributes to circadian circulation of HSC beside the circadian tension of beta-adrenergic system as elegantly reported by others. Next, two other papers from Drs Smadja's and Moniuszko's group demonstrated an increase in the number of circulating VSELs in patients with hypoxic lung disease and pulmonary hypertension (PH) [2] and the most frequent form of primary glomerulonephritis worldwide which is IgA nephropathy [3]. Both authors have concluded that the release of these cells into circulation could promote lung and kidney repair, respectively. This tempting conclusion however, requires further studies. Nevertheless, it is well known that the number of circulating HSC, EPC and VSELs increases in patients after heart infarct, liver damage, stroke, intestine inflammation and even in patients suffering from psychotic episodes. These cells released into PB could be involved in the regeneration of damaged organs by direct contribution to damaged tissues or by providing paracrine signals in i) soluble form or ii) in the form of regeneration promoting trophic extracellular microvesicles (ExMVs) [4]. These soluble factors pending the secretome profile of the stem cells include growth factors, cytokines, chemokines, bioactive lipids as well as extracellular nucleotides. On the other hand stem cell-derived ExMVs may also contain as a cargo mRNA, miRNA, proteins and even mitochondria. Many of these soluble factors or constituents of ExMVs may inhibit cell apoptosis in damaged tissues, stimulate angiogenesis, and promote cell proliferation. They may also activate dormant stem cells residing in damaged organs. To support this, it has been demonstrated that the number of circulating stem cells in PB may be of prognostic value, for example, in patients after heart infarct or stroke.

Another important question regarding circulating stem cells is if they are always beneficial or sometimes instead of being "friends', they may be a "foe" in some pathological situations. The rationale behind this is that circulating stem cells may falsely recognize a growing tumor as a "normal" damaged tissue and provide EPC for vasculogenesis and MSC for stromalization. Another possibility is that they could fuse (e.g, VSELs) in tissues affected by inflammation with differentiated cells and form heterokaryons. If such heterokaryons by chance survive fusion and successfully exclude additional chromosomes,

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they could grow polyploid tumors. These two possibilities however, also require better experimental evidence.

In conclusion, a profile of circulating stem cells in PB may be of diagnostic and prognostic value. Nevertheless, the physiological and pathological meaning of this phenomenon in particular for circulating MSC, EPC and VSELs requires further studies. More, work is also needed to better understand the molecular mechanisms and factors involved in orchestrating trafficking of these cells between tissues as they use PB and lymph as "trafficking highways" [5].

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