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Human Very Small Embryonic Like (hVSEL) Stem Cells: Little Miracles

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Abstract

In this review we explore the clinical importance of human Very Small Embryonic Like (hVSEL) stem cells as a source of pluripotent stem cells for use in regenerative medicine procedures. Autologous pluripotent hVSEL stem cells are a valuable resource in regenerative medicine especially when activated with Strachan-Ovokiatys Node Generator (SONG) modulated laser light. The review provides an overview of hVSEL stem cell technology and some insights into the massive potential of SONG modulated laser activated hVSEL stem cells regenerative medicine.

Introduction

As my mind can conceive of more good, the barriers and blocks dissolve. My life becomes full of little miracles popping up out of the blue.

Louise L. Hay (1926–2017)

Tissues which undergo rapid physiological turnover, or are damaged by trauma or disease, need repair by a wide range of stem cells present in the human body[1]. These stem cells include haemopoietic stem cells[2], mesenchymal stem cells[3] and other more recently discovered stem cells such as neural stem cells in the Central Nervous System (CNS)[4] and bronchio-alveolar stem cells in the lungs[5]. In addition to these naturally occurring stem cells there are 'man made' stem cells such as human Embryonic Stem Cell (hESC)[6] and Induced Pluripotent Stem Cells (iPSC)[7]. Despite these discoveries and high levels of hype, only one stem cell type (the haemopoietic stem cell) is currently used in routine clinical practice in the treatment of haematological malignancy such as leukaemia[8]. The remainder of the stem cell types are still either at the basic research stage or at best in clinical trials[9].

There is, however, one stem cell type which mysteriously does not attract much interest in the scientific and medical literature and that is the hVSEL stem cell. Some authors suggest that hVSEL stem cells are totally inactive or dormant in normal physiology[10] which in our opinion as explained and evidenced below is highly unlikely. Other authors state that when hVSEL stem cells are activated they play an important reparative role during diseases such as stroke[11], in cases of trauma[12] and even in psychosis[13] and in other psychiatric disorders[14]. Some very influential authors in high impact journals even claim that hVSEL stem cells do not exist[15,16]. The rationale behind such claims is difficult to understand and it may even relate to the financial and political pressures in the complex and highly competitive world of stem cell technology[17]. Whatever the reason for these positive and negative views, it is fair to say that hVSEL stem cells do exist and that in the course of time they may be proven to be not only the most important stem cell in existence but also the stem cell of choice for regenerative medicine procedures.

The Ontogeny of hVSEL Stem Cells

Before we explore our thesis on hVSEL stem cells it is important to put the ontogeny of these important stem cells into context. The key to understanding the ontogeny and the overall importance of hVSEL

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stem cells is to understand a rarely discussed stem cell present in early embryonic development called the Primordial Germ Cell (PGC). PGC arise before gastrulation in the proximal epiblast[18] and find their way to the genital ridge (*via* extraembryonic tissue and the primitive streak) of the developing embryo whilst retaining broad, cross-germ-layer differentiation ability[19,20]. This migration of PGC results in the development of the first haemangioblasts which are the pre-cursors to haemopoietic stem cells (HSC) and endothelial progenitor cells (EPC) in the yolk sac of the developing embryo[21-25]. The next stage of development is that the PGS migrate to the genital ridges of the embryo and on through the aorto-gonado-mesonephros (AGM) where the first definitive HSC are found in the aortic endothelium[26,27]. In the light of this information several authors have suggested that hVSEL stem cells are produced by migrating PGC[28-31]. This concept is further supported by the fact that PGC and hVSEL stem cells have both been shown to be capable of producing HSC and EPC[32,33]. The concept of migrating PGC being the ultimate source of HSC, with a possible intermediary of hVSEL stem cells, still needs further research. Nevertheless, the current evidence appears to suggest that hVSEL stem cells may be precursors to HSC and if so then hVSEL play a critical part in haemopoiesis from early embryonic development and throughout normal life. It is equally possible that hVSEL stem cells, since they are pluripotent, could be the precursors of other stem cells in the body but once again further research is needed to confirm or refute these concepts.

Properties and Activation of Platelet Rich Plasma (PRP)

Properties of PRP

Platelet rich plasma (PRP) has attracted considerable attention and some success in many contemporary areas of medical practice including the treatment of musculoskeletal disease[34,35] and in the treatment of sports related injuries[36,37]. In terms of the concepts in this review it is important to clearly understand the constituents and properties of PRP. Traditionally, PRP was considered to be a blood product which had a platelet count higher than that in peripheral blood, making it an obvious basic treatment for thrombocytopenia[38]. Platelets are non-nucleated cells which are derived from the megakaryocyte located in the bone marrow[39] and they contain four types of granules:

- Alpha granules[40] containing the adhesive proteins fibrinogen, vitronectin, thrombospondin and von Willibrand Factor (VWF)[41]. In addition, alpha granules contain growth factors and cytokines which mediate wound repair, inflammation and angiogenesis[42].
- Dense (or delta) granules containing ADP, ATP, calcium, serotonin, polyphosphate and pyrophosphate[43,44].
- Lysosomes containing hexosaminidase, arylsulphatase, ß-glucuronidase, ß-galactosidase, acid phosphatase and cathepsins[45].
- T (or tubular) granules containing TLR9, PDI and VAMP-8[46] which are thought to be an alpha granule subtype[47].

The platelets in PRP clearly have a potential role in the anti-inflammatory[48] and regenerative[49] properties which have been observed when PRP is used clinically.

The plasma component of PRP is also extremely important in the overall potential therapeutic action of PRP. The plasma in PRP contains high concentrations of growth factors and cytokines such as a wide range of interleukins, RANTES, PDGF, VEGF, GM-CSF, MIP 1b and CXCL chemokine (IP-10)[50,51]. These are extremely wide-ranging cytokines and growth factors which when in concentrated form in PRP no doubt enable differentiation, proliferation, tissue morphogenesis and chemotaxis in tissue healing[52]. It is proposed that the mechanism of action of these cytokines and growth factors in PRP is by the autocrine and paracrine route[53]. There are also several reports on the use of autologous PRP in fertility treatment where the added component of possible endocrine action of PRP may be active[54,55].

PRP clearly contains a complex and interactive range of cytokines and growth factors and there may still be more to discover and many more mechanisms of action to be defined[56,57].

The third component of PRP, which is either ignored or dismissed as being present in PRP, are hVSEL stem cells. Our own research has clearly shown the presence of CXCR4+, SSEA4+, Oct 3/4+, CD45-, Lin- hVSEL pluripotent stem cells in PRP derived from human peripheral blood[58]. Other authors also describe hVSEL stem cells being present in human peripheral blood[59] whilst some suggest that the hVSEL stem cells found in umbilical cord blood are an 'aberrant and inactive' population of cells[60]. It is evident that there are conflicting reports in the scientific

and medical literature about the existence, viability and biological activity of hVSEL stem cells and more research is required to clarify this situation. Nevertheless, it is also clear that PRP contains hVSEL stem cells and that PRP is therefore a readily available source of functioning pluripotent stem cells which are currently ignored. The biological and therapeutic action of PRP does not currently include discussions on the importance of hVSEL stem cells in PRP in the overall efficacy of PRP treatments. The standardisation of the production of PRP is required to ensure homogeneity, safety and efficacy and carefully controlled clinic trials are needed using standardised preparations and methods to fully understand the full potential of PRP treatment[61].

The persistence of hVSEL stem cells throughout life, from young to old, has been reported[62] suggesting a potential homeostatic mechanism which maintains the hVSEL stem cell pool throughout life. This is supported by our unpublished observations of there being a constant availability of hVSEL stem cells in the PRP of patients who have undergone multiple PRP collections. The bone marrow is the likely source of the hVSEL stem cells to maintain the peripheral blood hVSEL stem cell pool. This is supported by the mobilisation of hVSEL stem cells into the peripheral blood following acute myocardial infarction[63]. In further support of this concept, hVSEL stem cells have been shown to be present in human bone marrow itself and also in human leukapheresis products[64]. This supports the hypothesis of migration of hVSEL stem cells from the bone marrow to the peripheral blood during physiological homeostasis and during pathological stimuli. Similar studies *in vitro* have suggested that hVSEL stem cells are the 'original embryonic stem cell' highlighting the critical importance of hVSEL stem cells in normal embryonic development and subsequent physiological homeostasis[65].

All stem cell types are subject to both intrinsic and extrinsic stress during normal physiology and in pathological states. Such stress can have detrimental effects especially on rapidly dividing stem cells[66]. There is a population of quiescent VSEL stem cells in murine bone marrow[67] which may be resistant to extrinsic heat stress in the same way as the quiescent population of MSC derived from desquamated endometrium of menstrual blood (eMSC)[68]. This raises the possibility that quiescent hVSEL stem cell residing in the bone marrow may be available for collection and SONG modulated laser activation even after high-dose chemotherapy. If this can be proven, then quiescent hVSEL stem cells may offer an alternative therapeutic route to patients who have undergone chemotherapy with the resultant damage to normal somatic cells[69]. Such an approach may have the ability to enhance somatic cell and tissue repair following high dose chemotherapy[70] and may even indicate a possible benefit of elective hVSEL stem cells harvest, SONG modulated laser activation and cryopreservation for later therapeutic application to restore somatic cells following high dose chemotherapy.

Activation of PRP

Most autologous PRP treatments involve the collection of peripheral blood into citrate dextrose anticoagulant, centrifugation at room temperature and then simple reinfusion of the room temperature PRP back into the patient. Such preparation of PRP may result in premature platelet activation which can be modulated by introducing thrombin into the PRP[71]. Other authors report that pulsed electrical fields can stimulate platelet activation and growth factor release in PRP[72] and more recently the voltage, pulse width and calcium concentration has been shown to modulate the release of growth factors, serotonin and haemoglobin[73]. It has also been reported that PRP may be activated by carrying out the processing at 4°C which promotes wound healing. The current evidence seems to indicate that PRP can be 'improved' by activation interventions of various types, the focus of which is to activate platelets which in turn increases the efficacy of PRP. Whilst this may all be very true and relevant it is interesting to note that none of these publications mention the most important component of PRP: pluripotent hVSEL stem cells. The activation technologies described above may well also activate hVSEL stem cells but no one, apart from the authors of this paper, has thought to assess this possibility.

Our ground-breaking research has clearly shown that Strachan-Ovokaitys Node Generator (SONG) modulated laser light interacts with hVSEL in PRP to upregulate the expression of CXCR4, Oct 3/4 and SSEA4[58]. Very briefly, 66 mL of peripheral blood is collected and centrifuged using validated PRP tubes and centrifuge. The resultant PRP is then exposed to the SONG modulated laser for 3 minutes and then re-infused back into the patient intravenously. The increased expression of the key surface antigens above on hVSEL stem cell may have a significant effect on the biology and physiology of SONG modulated laser activated hVSEL stem cells.

These changes are important, for example, in terms of cell locomotion, chemotaxis, signalling and adhesion where CXCR4 expression is increased in SONG modulated laser activated hVSEL stem cells[74]. The increased expression of Oct 3/4 in response to the SONG modulated laser is equally interesting. Oct 3/4 is not only a marker of pluripotent stem cells, but it is also important in driving cell differentiation towards the cardiac lineage and to the development of the mesoderm from the embryonic epiblast[75]. More recently Oct 4 has been further implicated in the reprogramming of somatic cells[76] making increased expression desirable in regenerative medicine protocols. SSEA-4 is a stage specific glycolipid cell surface antigen[77] thought to be involved in cellular signal transduction, cell recognition and cell adhesion[78] which are extremely important in pluripotent stem cell biology[79].

The use of laser light as a method of activation of stem cells, using the terminology photo-biomodulation, has been reported recently[80] and it has also been shown that photo-biomodulation may improve tissue regeneration and the proliferation, migration and differentiation of stem cells[81].

This is clearly a new and rapidly expanding field of study with many possible applications. Nevertheless, the SONG modulated laser seems to be ahead of these reports of laser technology in terms of understanding and applications. We have recently published a paper proposing a theoretical mode of action for SONG modulated laser hVSEL stem cell activation using concepts taken from quantum physics[82]. Here we propose that the SONG modulated laser light can remove blocking proteins from hVSEL stem cell surface antigens and thus induce the biological processes required for the hVSEL stem cells to have maximum effectiveness in tissue repair and regeneration.

We have termed the use of a SONG modulated laser to activate hVSEL stem cells in PRP as Nano-bioelectronic Photo-acoustic Therapy (NPT). In our clinical discussion below the SONG modulated laser was also applied to the patient as part of the treatment, to the areas where the stem cell repair is needed e.g. to the head in the case of neurodegenerative disease. This is supported by other authors who propose that enhanced homing of stem cells may be improve the efficacy regenerative medicine procedures[83]. When we refer to NPT we include SONG modulated laser being applied to stem cells *in vitro* and directly to the patient. The SONG modulation of the laser light ensures that no physical damage is caused when the laser is applied to the patient.

Clinical Application of Nano-bioelectronic Photo-acoustic Therapy (NPT)

The preliminary clinical studies and individual case studies described below were all undertaken following informed consent from the patients and with ethical committee approval where appropriate. The stem cells used in one of these studies were allogeneic umbilical cord blood derived mesenchymal stem cells (MSC) but the most data have now been collected using autologous hVSEL stem cells in PRP.

Our most recent publication in this field is a preliminary clinical study on the use of allogeneic NPT treated cord blood derived expanded MSC in the treatment of end-stage heart failure[84]. In this study 10 patients, who were all considered candidates for heart transplantation, received a single dose of intravenous NPT treated cord blood derived MSC and NPT to the cardiac region. All patients showed a statistically significant increase in their Left Ventricular Ejection Fraction (LVEF) and 8 of the patients remain alive and well with improved LVEF at the time of writing. Two patients subsequently died but these deaths occurred after the study was complete. An 80% survival rate in such a cohort of patients represents exceptionally high safety and efficacy. Further to this study we have case study data (included in the citation above) on the use of NPT treated autologous hVSEL stem cells in the treatment of end-stage heart failure. These patients also showed significant enhancement of LVEF function, including to normal and stable LVEF following treatment.

The two features of NPT treatment which we have seen in almost all patients are:

1. A rapid reduction, immediately following the intravenous infusion of SONG modulated laser activated hVSEL stem cells in PRP, of some of the symptoms being treated
2. A slower and sustained reduction in symptoms and recovery from disease

We hypothesise that the rapid effects seen in some patients may be due to the concentrated cytokines and growth factors present in PRP and also to the fact that those cytokines and growth factors have been exposed to SONG modulated laser light. In addition, we hypothesise that the slower but sustained reduction in symptoms is due to the actions of SONG modulated laser activated pluripotent hVSEL stem cells in the patient. This mechanism here is proposed to be by 2 distinct routes:

1. The creation of new tissue specific stem cells (e.g. cardiac stem cells) derived from laser activated hVSEL stem cells

2. The repair of the diseased or damaged stem cell niche by cells derived from laser activated hVSEL stem cells

Further research is needed to confirm or refute these hypotheses. This thinking is different to current ideas that stem cells may directly repair damaged tissue. In this hypothesis treatment is achieved by a repaired, restored and fully effective stem cell population and a repaired stem cell niche. These ideas are in parallel to what is known about bone marrow stem cell transplantation where both the stem cell compartment and bone marrow stem cell niche are repaired by the intravenous infusion of donor bone marrow stem cells[85,86]. The aim should be to repair the relevant stem cell compartment *and* the stem cell niche which will in turn result in the development of new healthy tissue in any system or organ.

We have seen similar benefits of NPT to patients suffering from neurodegenerative disease and neurological trauma, reflecting the pluripotency of hVSEL stem cells and their ability to cross the blood brain barrier[87] following intravenous administration.

Conclusions

This review has considered the properties of PRP with a specific focus on hVSEL stem cells and the clinical application of SONG modulated laser activated pluripotent hVSEL stem cells. This a new and exciting field of study. This technology may have wide ranging safety and efficacy in the treatment of diseases including cardiac disease[88], neurodegenerative disease[89], neurological trauma[90], musculoskeletal disease[91], type 1 diabetes[92], liver disease[93], lung disease[94], pancreatic disease[95] and psychosis and psychiatric disorders[13,14]. The pluripotent nature of hVSEL stem cells suggests that they may be useful throughout the body as a therapeutic procedure. Perhaps the most exciting potential application of hVSEL stem cells is to modulate the ageing process[96-98]. Such an intervention into the ageing process could significantly decrease the morbidity and mortality of age related disease[99].

The source of the hVSEL stem cells in the current studies described above is autologous PRP. Work is already underway on the possibility of using young allogeneic hVSEL stem cells to optimise treatment in older diseased patients where autologous hVSEL stem cells may be sub-standard. Such young hVSEL stem cells may be obtained from donated umbilical cord blood[100] or peripheral blood PRP of young healthy adult donors. These young hVSEL stem cells may be more biologically 'active' than older hVSEL stem cells obtained from old diseased patients based on current epigenetic concepts[101] and senescence studies[102,103].

Such an approach would of course require infectious disease screening[104] ABO Rh type matching and HLA matching[105] to the recipient. The allogeneic donor PRP could be collected and used fresh, or it might be possible to create a frozen HLA typed allogeneic PRP donor bank[106]. Our current data suggest that SONG modulated laser activation of hVSEL stem cells in PRP enhances the overall efficacy of intravenous PRP treatment[107] in a wide range of scenarios. We hypothesise, based on the literature, that the SONG modulated laser interacts not only with hVSEL stem cells but also with platelets[108], growth factors and cytokines[109,110] in PRP resulting in the very rapid effects seen in some of our clinical scenarios[111]. In our opinion, there is no doubt that hVSEL stem cells are indeed 'little miracles' and ongoing scientific and clinical research may soon bring these little miracles to all patients in need.

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Conflict of Interest:
Professor P. Hollands is CTO of Qigenix.
Dr T. Ovokaitys is CEO of Qigenix.

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