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ARTICLE

Cord blood: the future of regenerative medicine?

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Abstract Cord blood stem cells have been in routine clinical practice for the past 20 years. The development of new therapeutic protocols in regenerative medicine require the use of stem cells and umbilical cord blood is an important and readily available source of cells for these applications. The latest concepts in routine transplantation of cord blood are reviewed followed by the critical role of cord blood stem cells in regenerative medicine research and novel approaches using cord blood as a source of whole blood for transfusion.

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Introduction

Since the first successful transplantation of umbilical cord blood in 1988 (Gluckman et al., 1989), cord blood has become an accepted source of haemopoietic stem cells for the treatment of leukaemia, haemoglobinopathy and for the repair of bone marrow following high-dose chemotherapy for solid tumours (Laughlin et al., 2004). Recent research has revealed that the cord blood mononuclear fraction is not only a readily available source of haemopoietic stem cells but also neuronal progenitors. A subpopulation of cells within the cord blood mononuclear fraction has been shown to have the potential to become neural cells (Chen et al., 2005). Endothelial progenitors and mesenchymal stem cells are also present. These cells have a potential use in the rapidly expanding fields of regenerative medicine, tissue engineering and gene therapy.

Cord blood stem cells in current use

Cord blood stem cell technology has many advantages over embryonic and other adult stem cells for several reasons, including the following: (i) cord blood represents a potentially unlimited source of stem cells that can in theory be collected at every birth; (ii) cord blood is relatively simple to process and store using tried and tested technology and, once frozen in liquid nitrogen, is biologically stable; (iii) the collection of cord blood is a non-invasive procedure with no danger to either mother or baby. If cord blood is not collected, it is discarded as biological waste; and (iv) cord

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blood carries a lower risk of infection, low incidence of graft-versus-host disease and a human leukocyte antigen (HLA) mismatch tolerance of up to 50%. It contains immature, naïve T lymphocytes (Hollands, 2009).

These advantages have all been utilized in the use of cord blood in haemopoietic stem cell transplantation to treat a wide range of malignant and non-malignant blood disorders. Nevertheless, other therapeutic uses of cord blood, especially in regenerative medicine, are yet to be fully explored and used clinically.

Cord blood haemopoietic stem cell transplantation has been carried out more than 8000 times to date, mainly in children and young or small adults. These transplants have been in the treatment of leukaemia and haemoglobinopathy covering approximately 45 different blood disorders. It is interesting to note that none of these cord blood transplants have resulted in tumour formation in the recipient, which is a serious and ongoing concern in embryonic stem cell technology and a reality in fetal stem cell transplantation (Amariglio et al., 2009). An average cord blood unit contains approximately $3-4 \times 10^8$ nucleated cells, which is enough for a 30—40 kg recipient patient to ensure safe engraftment (Hollands, 2009). Therefore, the use of cord blood in transplantation into adults is limited due to the relatively low nucleated cell and CD34+ content of a single cord blood unit. This may result in slower engraftment kinetics with increased risk of transplant related mortality when compared with bone marrow (Laughlin et al., 2004; Rocha et al., 2004). In an attempt to fully exploit allogeneic cord blood stem cell transplantation in adults, ongoing research is investigating methods of increasing the nucleated cell/CD34+ count in a single cord blood unit by ex-vivo expansion technologies (Ehring et al., 2003; Lewis et al., 2001; McNiece et al., 2000). Research using cell encapsulation technology and 'zero gravity' bioreactors (KB Seres and P Hollands, unpublished data) has shown an initial expansion of CD34+ in the region of two- to five-fold which, if developed to good manufacturing practice standards, would significantly increase the clinical utility of cord blood units. Other technology using copper chelating technologies are equally promising and are undergoing clinical trial (Peled et al., 2004). There are also good clinical outcomes following the use of two or more cord blood units for transplantation into one recipient patient (Barker et al., 2005). Both expansion technology and multiple unit transplants will increase the number of nucleated cells/CD34+ available for transplant and consequently enhance engraftment kinetics in adult patients. Results in expansion technology focusing on CD34+ myeloid progenitor cells alone have been disappointing and it is now thought that, to efficiently increase engraftment kinetics, enrichment of the other cellular components of the cord blood may also be needed. These cells are thought to facilitate maturation of cord blood stem cells and the creation of a suitable microenvironment for engraftment (Barker et al., 2003).

Cord blood in regenerative medicine

In addition to the haemopoietic transplantation of cord blood, there is considerable interest in the use of cord blood stem cells in regenerative medicine (Park et al., 2008). Cord blood is a readily available alternative source of non-controversial stem cells for transplantation (Ishikawa et al., 2004; Kakinuma et al., 2007; Sanberg et al., 2005; Yoshida et al., 2005). Current research suggests that, apart from haemopoietic stem cells, cord blood also contains different populations of stem and progenitor cells, most notably mesenchymal stem cells and endothelial progenitor cells.

The mesenchymal stem cells in cord blood have a supportive role in haemopoiesis (Zhao et al., 2004) and can differentiate into a variety of tissue lineages with a wider plasticity than previously thought (Gang et al., 2004; Niemeyer et al., 2004). The differentiation of neurons from cord blood was recently described (McGuckin et al., 2008) and the differentiation of endocrine cells (Gao et al., 2008) and bone/connective tissue has also been described (Yu et al., 2008). There is, of course, still a lot of work to do to take these basic observations to the clinic but the promise of cord blood stem cells in regenerative medicine technology is still immense and grows almost daily.

One potential clinical application of cord blood mesenchymal cells is based on their properties to enhance haemopoietic stem cell engraftment. Ex-vivo expansion of cord blood CD34+ cells has been carried out in cultures containing cord blood mesenchymal cells. The cord blood mesenchymal cells appear to secrete a variety of growth factors that directly act on haemopoietic stem cells (Liu and Hwang, 2005; Lu et al., 2006; Ye et al., 1994). Following these observations clinical studies were carried out which showed that co-transplantation of cord blood mesenchymal cells with haemopoietic stem cells increases engraftment kinetics and reduces graft-versus-host disease (Le Blanc et al., 2003a). Such an approach may possibly be used to overcome the current restrictions on the use of cord blood-derived haemopoietic stem cells in adults.

It is also interesting to note that cord blood mesenchymal cells have immunoregulatory properties and can suppress T cell proliferation and T cell-mediated allogeneic responses (Le Blanc et al., 2003b) while mediating T regulatory cells (Aggarwal and Pittenger, 2005; Krampera et al., 2006). Lee et al. (2002) demonstrated the immunomodulatory properties of mesenchymal stem cells used for the treatment of severe steroid resistant graft-versus-host disease in patients with acute myeloid leukaemia. Although this immunomodulatory function of mesenchymal stem cells has attracted lots of attention in transplantation tolerance and autoimmune disease therapies (Zhao et al., 2004), recent studies have shown that mesenchymal stem cells also suppress other T cell functions, which may result in tumour formation (Djouad et al., 2003). There is further research required in this area but the promise for the future is potentially enormous.

There are many studies demonstrating the potential clinical use of cord blood mesenchymal stem cells in the rapidly growing field of regenerative medicine. These include cartilage production for the treatment of articular cartilage damage such as rheumatoid arthritis, osteoarthritis and trauma (Fuchs et al., 2005; Noel et al., 2004), hepatogenesis for cell therapy and transplantation to treat liver diseases (Hong et al., 2005; Lee et al., 2004), osteogenesis for bone formation (Hutson et al., 2005) and neovascularization for the treatment of ischaemic conditions such as in Buerger's disease and myocardial infarction (Kim et al., 2006). In addition, current research in cord-blood-derived stem cell technology has focused on neuronal repair in brain

diseases, especially in traumatic injury, neurodegenerative disease and stroke. Cord blood has been proposed as a possible source of stem cells in the treatment of stroke (Hess and Borlongan, 2008) and the systemic delivery of cord blood to stroke patients is a possible route to therapy (Yu et al., 2009). It has recently been suggested that cord blood cells may also provide neurotrophic effects, which could mediate cell survival and angiogenesis and have an anti-inflammatory role in stroke (Park et al., 2009). The practical and regulatory issues of such proposed treatments still remain to be resolved (Borlongan, 2009). This evidence suggests that cell replacement therapy is a feasible approach for the future treatment of some central nervous system pathologies. Clinical trials, in patients with Parkinson's disease, have shown that cell replacement therapy improved the symptomatic effects of the disease (Freed et al., 2001). The progress to design a functional cell replacement therapy for the treatment of neurodegenerative diseases is hampered, however, by the limited availability and objections to the use of embryonic stem cells for research and clinical purposes. Cord blood is readily available and easily forms neuronal cells and, as such, should be the source of choice for such work.

Cord blood is also a rich source of endothelial progenitor cells, which have similar properties to embryonic angioblasts (Shin et al., 2005). Such cells could be used in regenerative medicine to repair and regenerate vascular endothelium, especially in ischaemic diseases (Schmidt et al., 2004). Poor neovascularization is normally induced by ischaemic and hypoxic signals; however, this natural protective mechanism decreases with age and in diseases such as diabetes (Loomans et al., 2004). In this context, a variety of studies have found that transplanted endothelial progenitor cells have beneficial effects in the neovascularization of ischaemic tissues (Dimmeler et al., 2005). Cord-blood-derived endothelial progenitor cell technology and transplantation is still very much in the research laboratory but nevertheless there are numerous publications from a variety of workers suggesting the feasibility of this approach. For example, in hind-limb ischaemia, it has been found that injection of cord-blood-derived endothelial progenitor cells improved neovascularization in ischaemic areas (Finney et al., 2006; Murohara, 2001; Nagano et al., 2007). In a separate study it has been shown that in diabetic patients endothelial progenitor cell neovascularization is impaired, suggesting that ex-vivo expanded cord-blood-derived endothelial progenitor cells could be potentially used as a novel approach to treat diabetic neuropathy (Naruse et al., 2005).

Cord blood transfusion

Most of the attention in previous years has focused on cord blood as a source of stem and progenitor cells. Nevertheless, it has been proposed that cord blood transfusion may have several beneficial affects, especially in the treatment of ischaemic tissue injury, for instance in stroke, myocardial infarction, traumatic brain injury and some neurodegenerative diseases. These ideas are based on the following facts: (i) cord blood red cells contain fetal haemoglobin, which has a much higher affinity for oxygen than adult haemoglobin and could be used to improve oxygenation of injured tissues. It may also be beneficial in certain haemoglobinopathies, e.g. sickle cell disease (Chaudhuri et al., 2007); (ii) cord blood contains more 'primitive' stem cell populations, which can give rise to multiple cell lineages (Chaudhuri et al., 2007). Furthermore, lymphocyte populations of cord blood are composed of immunologically naïve cells (no class II HLA) that are not recognized by the host immune system and allow a higher (approx. 50%) HLA mismatch with lower incidence of graft-versus-host disease (Szabolcs et al., 2003); and (iii) cord blood contains anti-inflammatory/reparative cytokines, e.g. interleukin-1 receptor antagonist which has been shown to decrease inflammation in ischaemic tissues after stroke and consequently inflammatory tissue damage (Fukuda et al., 2002; Vendrame et al., 2005).

Cord blood has been effectively used as a transfusion in many diseases including leprosy (Bhattacharya, 2006a) and HIV-associated anaemia (Bhattacharya, 2006b) and has even been found to be beneficial to terminal cancer patients (Bhattacharya, 2006c). The logistics of cord blood transfusion are nevertheless complicated and for such a procedure to become routine practice would require a whole new infrastructure similar to that of the UK Blood Transfusion Service. Proponents of the technology would argue that this would be money well spent as the benefits of cord blood as a transfusion product are clear to see.

These properties of cord blood could also be utilized in bioengineering applications, for instance to construct a biocompatible interface to improve implant tolerance and survival, especially for artificial orthopaedic implants (Laurencin et al., 1999; Vats et al., 2002).

Conclusion

It is evident that cord blood stem cell technology has not yet been fully exploited in a wide range of therapeutic applications, especially in the field of regenerative medicine. Whilst most of stem cell research and resources are focused on embryonic stem cells, the progress of embryonic stem cells to the clinic is hampered by the scientific, ethical, religious and political issues surrounding them. In addition embryonic stem cells have extremely limited availability when compared with cord blood. Cord blood, which is still considered as a biological waste product in most countries, could be used as an alternative non-controversial source of stem cells with unlimited availability and a wide range of unexploited therapeutic benefits.

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