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Chapter 7

Umbilical Cord Blood-Derived Therapies as a Treatment for Graft-Versus-Host Disease

Richard Duggleby, Steve Cox,
J Alejandro Madrigal and Aurore Saudemont

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Abstract

Umbilical cord blood (UCB) has been increasingly used as a source of haematopoietic stem cells (HSCs) for transplantation. UCB transplantation (UCBT) has some advantages such as less stringent human leucocyte antigen (HLA) matching and lower impact of graft-versus-host disease (GvHD). UCBT is also characterised by a high rate of infections, graft failure, delayed engraftment and slow recovery of the immune system. UCB contains HSC as well as immune cells that could be considered to develop new treatments for the main complications post-UCBT but also to treat other diseases. GvHD remains a major complication post-CBT and post-haematopoietic stem cell transplantation (HSCT). In view of their ability to induce tolerance and suppress the functions of effector T cells, regulatory T (Treg) cells have been proposed as an adoptive therapy to modulate GvHD post-HSCT. In addition, we showed that UCB contains soluble NKG2D ligands that can modulate the functions of NKG2D expressing cells, making UCB plasma a product of interest to modulate inflammation and in particular skin GvHD. Here, we aim to describe some of the therapies currently developed using UCB, focusing on Treg cells and UCB plasma for the treatment of GvHD.

Keywords: umbilical cord blood, plasma, regulatory T cells, graft versus host disease, immunotherapy

1. Introduction

Haematopoietic stem cell transplantation (HSCT) is currently used to treat many bone marrow and blood disorders as well as malignancies and has become either an established life-saving treatment or a life-sustaining option for many patients. However, even nowadays, HSCT has

a high treatment-related mortality, as only half of the patients that receive a transplant will survive the procedure. This high mortality is due to major complications such as relapse, graft failure, delayed immune reconstitution, opportunistic infections and graft-versus-host disease (GvHD).

After allogeneic HSCT, donor natural killer (NK) cells and T cells can attack the allogeneic tumour in a phenomenon described as graft versus leukaemia (GvL), which is the beneficial aspect of tissue disparity. However, allografts contain lymphocytes able to recognise and respond against host antigens and cause potentially life-threatening GvHD affecting internal organs and systems. In addition, GvHD can affect the skin and eyes and can be very painful and distressing for the patient, thus impacting on the patient quality of life especially in the case of chronic GvHD. Moreover, GvHD increases the risk of a variety of bacterial, viral and fungal infections [1].

Hal Broxmeyer proposed the use of umbilical cord blood (UCB) as a source of haematopoietic stem cells (HSCs) for transplantation in 1982. The first umbilical cord blood transplantation (CBT) was performed for the first time in 1988 to treat a patient with Fanconi's anaemia [2]. Since then, UCB has been increasingly used as a source of HSC extending the availability of allogeneic HSCT to patients who would not have a matched donor. UCB has some advantages over the use of other grafts such as faster availability, less stringent human leucocyte antigen (HLA) matching, decreased incidence and severity of GvHD. However, patients who receive a UCB transplant are at higher risk of graft failure, infection and delayed engraftment and immune reconstitution. In addition, the use of UCB is restricted by the number of cells it contains, in particular of HSC, and it does not offer the option of a donor lymphocyte infusion if needed.

However, UCB does not only contain HSC enabling transplant but also contains immune cells such as regulatory T (Treg) cells and numerous proteins involved in inducing tolerance during pregnancy to prevent foetal rejection. Therefore, UCB is a unique resource that could also be used in order to develop immunotherapeutic approaches to counteract complications post-HSCT including post-UCBT. This chapter focuses on the latest studies and immunotherapeutic approaches relating to the use of UCB to treat GvHD post-HSCT.

2. Umbilical cord blood-derived therapies to modulate GVHD

2.1. Use of umbilical cord blood plasma for immunotherapy

In human pregnancy, immunological tolerance of the unborn foetus by the maternal immune system is essential. Without such mechanisms, the foetus would be readily 'rejected' as genetic differences arising from paternal HLA would elicit an immune response in a similar manner to a haplo-identical (50% match) transplant. Since this concept was postulated by Sir Peter Medawar in the 1950s, researchers have attempted to identify these mechanisms, not only to better understand pregnancy and pregnancy complications but also to allow tolerance of transplanted tissues such as kidneys, hearts or BM in the context of HSCT.

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The immune system of the unborn foetus is immature yet capable of defence against certain pathogens and therefore mechanisms of tolerance towards the genetically disparate maternal host must also play a role in successful pregnancy. This concept is less well understood but advances are now being made following the use of UCB as a source of HSC for transplantation. The neonatal immune system is biased towards a Th2-type regulatory immune response rather than a pro-inflammatory Th1 response, affecting acquired and innate cellular responses. Evidence for this has been gained from experiments using UCB cells and also by the identification of immunosuppressive substances found in umbilical cord blood plasma (CBP). For example, TGF-β produced by Treg cells controls proliferation and differentiation of many different cell types, including limiting cytotoxicity of natural killer (NK) cells, and is one of the many immunosuppressive substances found in CBP.

Notably, we have recently identified a new mechanism of immunological tolerance reducing NK cell cytotoxicity that is mediated by proteins found in CBP, called natural killer group 2 member D (NKG2D) ligands (NKG2DL) [3]. NKG2D is an activating receptor on NK and NKT cells and a costimulatory receptor on CD8+ T cells. Unusually, two gene families known as the MHC class I-related chain A and B (MICA/B) and UL16-binding proteins (ULBP1-6) encode the ligands for NKG2D. Furthermore, allelic polymorphism of these genes, in particular MICA and MICB, creates a uniquely diverse range of NKG2D ligands (NKG2DL) that can vary between individuals. Upregulation of NKG2DL on cells and tissues occurs in situations of 'stress' such as viral infection or oncogenic transformation, leading to cytolysis by NK cells or other NKG2D-bearing cells.

However, NKG2DL appear to have dual opposite roles as soluble NKG2DL engagement with NKG2D causes downregulation of this receptor with concomitant suppression of NK cell activation and proliferative potential, decreased cytolytic activity (degranulation) and reduced interferon-gamma (IFN-γ) production. We found that compared with healthy adult plasma, CBP contains significantly more soluble MICA, MICB and ULBP1 ligands. CBP affected degranulation, cytotoxicity and cytokine production of NK cells. We confirmed these results by physical removal of NKG2DL, where function was partially restored. In addition, blocking of NKG2D prior to the K562 killing assay mostly prevented K562 lysis, showing that NKG2D interaction was the main mechanism involved.

The immunosuppressive capacity of CBP and its effects on NK cells and T cells may offer potentially powerful therapeutic applications for diseases that have previously been difficult to treat successfully. In the case of GvHD post-HSCT, the cytokines produced by alloreactive T cells may prime NK cells and other innate immune cells, amplifying potential GvHD tissue damages. Despite attempts to manipulate the immune system before, during and after transplantation, GvHD is still the prominent cause of morbidity and mortality following HSCT. Here, we propose the use of CBP to treat local GvHD, initially focussing on local topical application of CBP via creams and drops to alleviate dermatological or ocular problems, such as chronic skin or eye GvHD. The immunosuppression of NK cells and T effector cells at the skin surface or conjunctiva should prevent the damages caused by cytotoxicity of these cells and alleviate symptoms, without causing further systemic immunosuppression.

The same principles could also be applied for the treatment of other diseases of common 'autoimmune' dermatological disorders (reviewed in: [4]) such as eczema, which affects large numbers of people, especially children. Psoriasis is another candidate disease driven by autoimmune skin inflammation and cytokine release that could be amenable to CBP immunotherapy. Another, less common but nevertheless extremely distressing condition is alopecia areata (AA), also known as spot baldness, and affects the scalp. This was also thought to be an autoimmune disease mediated by T cells, but recent genomewide association data have emerged directly implicating NK cell cytotoxicity as well as CD8+ NKG2D+ T cells against the hair follicle. It was found that in normal hair follicles, expression of NKG2DL ULBP3 is turned off. However in patients with AA, the follicles often express ULBP3 and are therefore vulnerable to attack via T-cell costimulation and NK cell degranulation together with production of high levels of pro-inflammatory interferon gamma (IFNγ). In this situation, therapy with CBP containing soluble NKG2DL could neutralise activation of effector cells and prevent destruction of the hair follicles. Another area of interest for treatment using CBP is localised therapy to alleviate symptoms of rheumatoid arthritis (RA). RA is a chronic autoimmune disease characterised by joint inflammation, cartilage and bone, destruction and elevated levels of pro-inflammatory cytokines. The lymphocytes in synovial fluid of affected joints contain up to 25% NK cells during early disease, the majority of which are $CD56^{bright}$ NK cells with high capacity for cytokine secretion. Compared with peripheral $CD56^{bright}$ NK cells, synovial $CD56^{bright}$ NK cells are more abundant and produce more TNFα and IFNγ, implicating these cells with initiation and perpetuation of dysregulated pro-inflammatory cytokine production [4]. We found that $CD56^{bright}$ NK cells become hyporesponsive after treatment with CBP and produce significantly less IFNγ, which could alter the pro-inflammatory cytokine milieu and reduce inflammation and the damage caused by RA.

In conclusion, CBP has the potential to treat a wide range of diseases that are mediated, at least in part, by inappropriate NK cell activation and tissue destruction. The effect of soluble NKG2DLs as immunosuppressive agents to limit NK cell activation as well as CD8+ T-cell costimulation is very powerful but also reversible by removing the source. However, it is still unknown which type of NKG2DL is responsible or whether combinations of different ligands are beneficial. We identified soluble ULBP1 in almost all and soluble MICB in the majority of CBP samples, whereas soluble MICA was present in about one third. Although ULBP1 is not polymorphic, soluble MICA and MICB ligands have considerable allelic polymorphism and differing levels of expression. We are currently carrying out experiments to determine which ligands mediate the effects and whether allelic polymorphism in promoter and expressed domains also plays a role in order to optimise the selection of CBP for immunotherapy and maximise the chances of therapeutic success.

2.2. Use of umbilical cord blood regulatory T cells for immunotherapy

Treg cells represent 5–10% of CD4+ T cells in humans and in mice and are characterised as $CD4^{+}CD25^{high}CD127^{low}Foxp3^{high}$ [5]. Treg cells are key players in maintaining tolerance and immune homeostasis and have been shown to inhibit the functions of various immune cells such as CD4 and CD8 T cells [6, 7], B cells, and NK cells [8]. Treg cells can act directly by

inhibiting the functions of target cells by releasing suppressive cytokines such as interleukin (IL)-10, transforming growth factor β (TGF-β) or IL-35, depleting the environment of IL-2 [9–12] or indirectly by interacting with antigen-presenting cells (APCs) and regulating their functions [13].

Because of their ability to induce tolerance and suppress the functions of effector T cells, Treg cells have been proposed as a cell therapy to prevent or modulate GvHD post-HSCT as a supplement or replacement for conventional pharmacological immunosuppression. The feasibility and safety of this therapy in transplanted patients has been demonstrated in different phase I/II clinical trials using mainly PB Treg cells (see **Table 1**). Trzonkowski et al. [14] showed that expanded Treg cells could control GvHD allowing withdrawal of steroid treatment in transplanted patients. Di Ianni et al. [15] demonstrated that non expanded donor Treg cells were able to counteract the potential GvHD that would otherwise be induced by the infusion of a high number of effector T cells in haploidentical HSCT patients while positively impacting on immune reconstitution. In addition, in the same haploidentical HSCT setting, Martelli et al. [16] reported reduced relapse rates after infusion of non-expanded donor Treg cells. Edinger and Hermann [17] demonstrated the safety and feasibility of the administration of expanded Treg cells in patients that presented high risk of leukaemia relapse. Finally, a recent trial showed that the use of expanded Treg cells to modulate chronic GvHD led to reduced immunosuppression post-HSCT; however, tumours were detected in two patients [18]. Overall, although the use of Treg cells to modulate GvHD is very promising, it is clear that more studies are needed in order to really understand the potential impact of a Treg cell therapy on tumour and viral immunity post-HSCT.

Centre	Phase	Cell dose	Product	Effects	Ref
Gdansk	I	1×10^5 to 3×10^6/kg	Expanded Treg cells	Safe, reduced immunosuppression	[14]
Minnesota	I	$1–30 \times 10^5$/kg	Expanded UCB Treg cells	Safe, reduced acute GvHD, increased infection	[26, 33]
Minnesota	I	$3–100 \times 10^6$/kg	Expanded UCB Treg cells with engineered cell line	Safe, reduced GVHD and no increased relapse	[27]
Perugia	I	$2–4 \times 10^6$/kg	Fresh Treg cells	Safe, reduced leukaemia relapses, reduced incidence of GvHD	[15, 16]
Regensburg	I	5×10^6/kg	Fresh Treg cells	Safe	[17]
Dresden	I	$0.6–5 \times 10^6$/kg	Expanded Treg cells	Tumours in 2 patients, stable chronic GvHD	[18]

Table 1. List of clinical studies testing the use of Treg cells to treat or modulate GvHD.

In these trials, Treg cells were mainly isolated from PB sources; however, two trials were performed using expanded Treg cells isolated from UCB. In fact, UCB is an attractive source of Treg cells because of several features. The frequency of Treg cells is identical in PB and UCB [5]. In addition, UCB has the advantage of being readily available as UCB can be obtained from

accredited UCB banks, offering the possibility to develop an off-the-shelf therapy. Which degree of matching should be used will need further evaluation in clinical studies, especially as HLA matching is less stringent when considering UCB; trials using UCB Treg cells already suggested that it is possible to use a 4/6 match for UCB Treg cells when considering a third-party therapy. Furthermore, it is possible to purify Treg cells with high purity in one single step as opposite to a two-step process when isolating PB Treg cells [19]. CB Treg cells comprise almost entirely of a naïve T-cell phenotype $CD45RA^{+}$ in contrast to the adult PB Treg cells than have a central memory phenotype ($CD62L^{high}CCR7^{high}CD45RO^{+}$). As a consequence, UCB Treg cells have a higher capacity to maintain Foxp3 expression, and a better suppressive capacity and stability after expansion [20]. UCB Treg cells may have a survival advantage over PB Treg cells as they have been shown to be more resistant to apoptosis than PB Treg cells [21]. Finally, we and others have demonstrated Treg cells from UCB to be able to inhibit the function of effector cells [19, 22, 23], while other groups have reported UCB Treg cells to have low suppressive capacity [24, 25]. The required cell dose for clinical use is crucial and dictates the practicality of the cell source considered and post-isolation manipulation if required.

In any case, whatever the cell source considered, only very few cells can be isolated from UCB or PB; therefore, most groups have focused on developing strategy to expand UCB Treg cells to enable cell therapy [26–28]. The majority of expansion protocols seek to expand Treg cells and maintain their natural Treg (nTreg) cell phenotype. Multiple studies have reported expanding nTreg cells from both PB and UCB [14, 26]. Recently, conditions to expand Treg cells have become increasingly well defined and translated into GMP compliant protocols. The majority of groups (see **Table 1**) use anti-CD3 antibody attached to beads in combination with anti-CD28 for costimulation and supplemented with IL-2 ranging from 300 to 1000 IU/ml. When expanding from PB Treg cells, rapamycin is often added to the expansion cultures, sometimes in combination with retinoic acid both to prevent the outgrowth of effector T cells and to promote Treg cell expansion, especially in the case of multiple restimulations [29]. With UCB Treg cells, it is noticeable that rapamycin seems not so vital. Brunstein et al. used beads or an engineered cell line in order to expand UCB Treg cells [26, 27]. This recently published study used anti-CD3 antibody-loaded K562 cells modified to express the high-affinity Fc receptor CD64 and the costimulatory ligand CD86 [27]. Using this culture condition, expansion of up to 10,000 fold of UCB Treg cells was achieved.

Following expansion, Treg cells should as much as possible retain their nTreg cell phenotype ($CD3^{+}CD4^{+}CD127^{low}CD25^{+}FOXP3^{+}CD62L^{low}CCR7^{+}$). FOXP3+ expression would seem vital; however, FOXP3 is also expressed on activated effector T cells and so in itself does not distinguish between them. However, FOXP3 expression should be high and sustained. In addition, Helios expression has been associated with natural Tregs, and its presence in expanded cells is also an additional indication that the cells have retained an nTreg phenotype. Expanded cells should be able to suppress the function of effector T cells in vitro. In addition, stability of the FOXP3 expression should also be tested. The methylation state of the FOXP3 locus is indicative of recent chromosomal remodelling and thus distinguishes between FOXP3 expression being induced over constitutive expression in Treg cells [30]. The study of Treg cell

development in the thymus indicates that the FOXP3 locus becomes demethylated during development and indicates a stable commitment to the Treg cell lineage [31, 32].

Two phase I clinical trials using third-party UCB Treg cells have reported the feasibility and safety of infusing expanded UCB Treg cells in patients that received double UCBT (**Table 1**). Brunstein et al. [26] showed reduced acute GvHD in this cohort of patients with increased incidence of infection [33] and recently reported similar impact of expanded UCB Treg cells on acute GvHD in another trial [27]. However, in both clinical studies Treg cells could only persist for a maximum of 2 weeks in vivo. These results therefore also highlight that we need to understand better the characteristics of expanded cells if we want these cells to persist for longer in patients once infused.

We previously showed that Treg cells could be isolated from fresh UCB units using only the marker CD25 and that the isolated Treg cells were able to suppress effector T cells in vitro [19]. However, this method led to variable purity and yield when isolating Treg cells from cryopreserved UCB units. Therefore, within the T-Control consortium (http://www.t-control.info), we focused our efforts on developing a method to isolate Treg cells from fresh or cryopreserved UCB using the streptamer reversible technology. This method allows the purification of Treg cells with good recovery and purity and offers the potential to have an off-the-shelf Treg cell product as well as selecting UCB units for specific HLA types. In order to overcome the lack of persistence of Treg cells in patients, we are planning to use this method to purify Treg cells from cryopreserved UCB units as to obtain a minimally manipulated cell product that could be tested in transplanted patients to control GvHD. However, we are also exploring the possibility to expand streptamer isolated Treg cells from cryopreserved UCB units for immunotherapy.

More studies are needed to really gain a better understanding of the characteristics of third-party UCB Treg cells in order to optimise their use as immunotherapy. Further preclinical and clinical studies will help to identify the best conditions to activate and expand UCB Treg cells for use in patients to treat GvHD but also to optimise their use as for PB Treg cells for other conditions such as inhibiting graft failure after organ transplantation or to treat autoimmune diseases such as arthritis or diabetes alone or together as a combined therapy with other suppressive cells such as mesenchymal stem cells.

3. Conclusion

Immunotherapy has been a promising option in order to improve the outcome of HSCT. UCB-derived immunotherapies are very promising, and future studies will help us understanding their potential better. UCB Treg cells could become an immunotherapy of choice for treating GvHD. In addition, one should also consider the use of UCB plasma that already contains proteins with the capacity to modulate the immune response in particular inflammation to treat skin GvHD as well as autoimmune diseases.

Author details

Richard Duggleby, Steve Cox, J Alejandro Madrigal and Aurore Saudemont*

*Address all correspondence to: aurore.saudemont@anthonynolan.org

Anthony Nolan and University College London, London, UK

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