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Biological individuality and the new frontiers of immunological tolerance in hematopoietic stem cell transplantation

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Hematopoietic stem cell donors: rethinking traditional choices

From the time of the first successful experiences of allogeneic bone marrow transplantation,[1,2] and during the long previous history of failure,[3] it became clear that HLA-identity/compatibility between donor and recipient was an essential condition for the success of the transplant. Such compatibility is constantly found in homozygous twins (who also have identical minor histocompatibility antigens) and statistically in 25% of siblings. This HLA-compatibility was a necessary condition for the desired creation of a "biological chimera"; but transplant tolerance had to be promoted by lowering the recipient's immune response to prevent rejection, at least unless the patient was not seriously immunocompromised as, for example, in some cases of severe combined immunodeficiency. In particular, the use of total body irradiation since 1959, of cyclophosphamide since 1972, and of the combined use of both of these since 1974 are recognized as historical landmarks. Even after an HLA-compatible transplant, it was

necessary to prevent or limit graft-*versus*-host disease. The first drug to be used for this purpose was methotrexate, a drug whose usefulness is still acknowledged even after prednisone and cyclosporine have entered into use.[3]

Burnet's biological law of "exclusive self tolerance"[4,5] (that is of what is our "own" and what is, therefore, antigenically "self"), although since re-evaluated,[6,7] fully justifies the need for HLA-compatibility between donor and recipient, and for protecting the chimera.

Progress has been made in achieving ever more refined HLA allelic typing (from serological to molecular) enabling the most precise definition of the recipient's and donor's profile while the use of suitable immunosuppressants (cyclosporine A since 1978 and tacrolimus since 1990) has become increasingly efficacious. Both these factors have not only made significant contributions to the successes of transplantation techniques and procedures, but have also demonstrated the possibility of extending "non-self" tolerance to wider HLA criteria than in even the recent past, and of reducing the seriousness and frequency of graft-*versus*-host disease (or rejection).[8] All things considered, the "transplant culture" has meant that man, in his awareness of his immunological individuality, may live and consider himself a "biological Ego".[9,10]

Exactly 20 years after the first two successful bone marrow transplants,[1,2] the usefulness of umbilical cord blood as a source of hematopoietic stem cells was demonstrated.[11] Umbilical cord blood transplantation was seen to have several advantages over bone marrow transplantation (Table 1).[12] At around the same time, techniques were also developed and optimized to collect hematopoietic stem cells from peripheral blood.[13] The extended tolerance in one (or two) HLA-mismatched umbilical cord blood transplants (Table 1) has been ascribed to a characteristic "naivety" of umbilical cord blood lymphocytes. Importance was also given to their possible reduction of immune activity due to a continuous contact/"trafficking" with the mother's lymphocytes. Moreover, in an antigenic context, the embryo-fetus has been considered from every point of view a haploidentical allotransplant, physiologically tolerated according to the "laws of nature".[14]

Recently, great importance has also been given to the confrontation of the fetal and neonatal immune system with non-inherited maternal antigens.[15] It had been demonstrated, at least *in vitro*, that conventional alloantigen reactive cytotoxic T lymphocytes specific for non-inherited maternal antigens are undetectable or present at a low frequency in the neonate, as compared to the frequency of the same cells directed towards non-inherited paternal antigens.[16] Indeed, recent studies suggest that exposure during fetal or perinatal life (e.g. breast-feeding) to non-inherited maternal antigens may have a strong lifelong immunomodulatory impact on the immune response of the hematopoietic stem cell donor towards the recipient, improving transplant outcome.[15]

There are now many different options available to find an HLA donor compatible with a candidate-recipient who does not have a consanguineous donor: the World Registry network has over 13 million HLA-typed volunteers and there is a network of cord blood banks supplying around 400,000 cryopreserved cord blood units. However, in spite of this, there are certain conditions in which a compatible donor cannot be found. These conditions often depend on ethnic group. In any case, the choice of a matched consanguineous donor is to be preferred but this choice is particularly suitable for patients affected by specific diseases, such as Fanconi anemia, severe aplastic anemia, or Hodgkin's disease.

As was first seen 23 years ago,[17] parents of fertile age with a single child who needs a hematopoietic stem cell transplantation can proceed to a new pregnancy in the hope (25% probability) that the newborn ("programmed donor") is HLA-compatible with the sick sibling. In the case in which the patient is affected by a genetically transmitted disease, due to the obvious risk that the same condition could be inherited by the programmed donor, the programmed birth of a donor sibling requires an "*in vitro* fertilization technique with pre-implantation diagnosis".[18] This technique allows HLA compatibility with the candidate-recipient sibling to be immediately identified while at

Table 1. Advantages and theoretical disadvantages associated with umbilical cord blood transplantation in comparison with bone marrow transplantation.

Advantages	Theoretical disadvantages
For the umbilical cord blood transplant recipient	
• Prompt availability (less time wasted between donor identification and hematopoietic stem cell transplantation) • No risk of donor refusal • Less time required to identify an unrelated HLA-compatible donor • Reduced risk of both acute and chronic graft-*versus*-host disease • Possibility of performing transplantation using a one (or two) antigen HLA-disparate donor • Low risk of viral contamination (e.g. cytomegalovirus, Epstein-Barr virus) with consequent low risk of transmission of infectious disease	• Increased risk of graft failure • Delayed platelet and neutrophil recovery • Absence of adoptive transfer of specific immunity towards infectious agents due to the immaturity of the fetal immune system and lack of previous exposure to antigens • Increased risk of transmission of inherited disorders
For the umbilical cord blood transplant donor	
• Ease and safety of collection, without the risk associated with general anesthesia (required for bone marrow harvesting) • Lower incidence of psychological problems related to the figure of the child-donor and to possible transplant failure	• Ethical problems associated with donation (i.e. increased propensity to conceive a child to save a child)

the same time selecting a healthy pre-embryo. Of course, strong ethical considerations should be made by parents who intend to give birth to a "programmed donor". They must love the newborn for him or herself, independently of his/her role as the life-saving donor of the sick sibling.[19]

The research into and the discovery of new immunosuppressive methodologies and therapies pervade the whole story of the progressive success in the outcome of hematopoietic stem cell transplantation over the last four decades. An important turning point in the last two decades was the increased interest of researchers towards the definition (and choice) of the graft "cell composition", which could be particularly advantageous for the recipient.[20]

Manipulation of an allogeneic hematopoietic stem cell graft across the natural genetic barriers of immunological tolerance

In the epidemiology of hematopoietic stem cell transplant needs there are, in fact, high percentages (up to 30-40% of Caucasians) of transplant candidates for whom no matched donor can be found. For these candidates, alternative biological solutions are, therefore, required. These aim to obtain a sufficiently advantageous cellular graft profile for the transplant to be successful.

The entity of the HLA-mismatch between recipient and donor can consist of the allelic difference at one locus or rather in having to select a consanguineous haploidentical (3 of 6 HLA-mismatched loci) donor.[20] In this latter case, unless particular strategies are adopted, creating a biological chimera runs a serious risk of engendering graft failure or graft-*versus*-host disease.

The story of this challenge began in 1983 when Reisner *et al.*[21] successfully transplanted hematopoietic stem cells from a related haploidentical donor into a patient with severe combined immunodeficiency. The strategy of modifying the cellular composition of that graft, obviously intended to avoid graft-*versus*-host disease, consisted in T-cell depletion (approximately 3 log). This biological chimera has now been followed up over more than 25 years and over that time hundreds of patients have been successfully treated with haploidentical T-cell-depleted hematopoietic stem cell transplants from family members. However, leaving aside patients with severe combined immunodeficiency, T-cell-depleted hematopoietic stem cell transplantation has a greater risk of rejection and neoplastic relapse. Furthermore, the transplant recipient is more exposed to a serious lowering of his anti-infective defenses due to the delay in reconstitution of adaptive immunity. Mainly for these reasons, from 1995 to 1999, there was a growing interest (and success) in the use of grafts of hematopoietic progenitor cells with a high percentage of $CD34^+$ stem cells, especially in leukemia patients. These "megadoses" were seen to be particularly

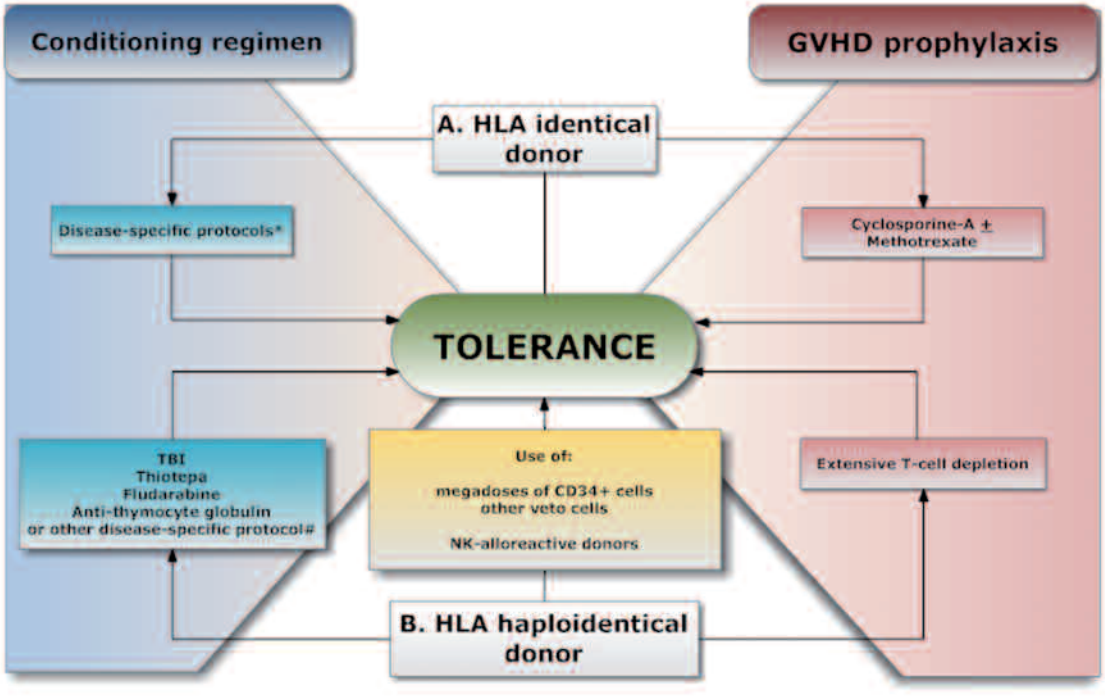

Figure 1. Strategic criteria for inducing tolerance of the hematopoietic stem cell graft both in the case of an HLA-identical donor (A) and of an HLA-haploidentical donor (B). ALL: acute lymphoblastic leukemia. AML: acute myeloid leukemia. MDS: myelodysplastic syndrome. TBI: total body irradiation. ATG: antithymocyte globulin. *ALL: TBI + thiotepa + cyclophosphamide ± ATG. AML or MDS: busulphan + cyclophosphamide + melphalan. Severe aplastic anemia: cyclophosphamide ± ATG. Fanconi anemia: low-dose cyclophosphamide + fludarabine ± ATG. Thalassemia: thiotepa + treosulfan + fludarabine ± ATG. #ALL: TBI + thiotepa + fludarabine + ATG. AML or MDS: busulfan + cyclophosphamide + melphalan + ATG; Fanconi anemia: TBI (200 cGYy) + low-dose cyclophosphamide + fludarabine + ATG.

efficacious in overcoming the HLA barrier and in preventing graft rejection.[20] On the basis of a retrospective analysis, it was then seen that in patients with either acute lymphoid or acute myeloid leukemia, transplantation from a haploidentical parent was more effective in terms of 5-year event-free survival if the donor was the mother and not the father.[22]

All this being said, and still with reference to leukemia patients, a highly immunosuppressive conditioning regimen is essential before haploidentical transplantation. A codified protocol for leukemia includes: total body irradiation, thiotepa, fludarabine and antithymocyte globulin (Figure 1). The extreme depletion of T lymphocytes from the graft is central to guaranteeing protection against graft-*versus*-host disease. This goal is obtained at the expense of the graft-*versus*-leukemia effect, a phenomenon known since the 1980s and one that, in the HLA-compatible setting, is mostly mediated by T-lymphocytes directed towards tumor-specific determinants or minor histocompatibility antigens. However, it has been demonstrated, at first mainly in adults with acute myeloid leukemia[23] and more recently in pediatric patients with acute lymphoid leukemia,[24] that natural killer (NK) cells exert a graft-*versus*-leukemia effect when an HLA-mismatched NK alloreactive relative is used as a donor. It can be seen that the donor-*versus*-recipient NK-cell alloreactivity constitutes a biological phenomenon that derives from a mismatch between donor NK clones (carrying specific inhibitory receptors for self HLA I molecules) and HLA class I ligands on recipient cells.[23]

To summarize, it is reasonable to conclude that the most favorable results may be obtained by the synergistic adoption of three different strategies: (i) a substantial depletion of T lymphocytes from the graft; (ii) use of hematopoietic stem cells that are not only T-cell-depleted but also enriched by "megadoses" of $CD34^+$ cells and, moreover, by other cell populations endowed with veto activity;[25] and (iii) the choice of an HLA-disparate NK alloreactive donor, preferably the mother.

The veto activity itself also modulates tolerance (Figure 1), enhancing the ability of the "non-self" to graft in the transplanted host. Regulatory T cells also require special consideration in this regard.[25,26]

Recently the use of *ex vivo* expanded mesenchymal stem cells has been proposed in the setting of hematopoietic stem cell transplantation either to treat patients who have developed steroid-resistant severe acute graft-*versus*-host disease[27] or to favor engraftment if co-transplanted with hematopoietic stem cells.[28]

Indeed, many biological features of mesenchymal stem cells (e.g. immunosuppressive function) have stimulated great interest. Mesenchymal stem cells have been shown to modulate the function of dendritic cells and T lymphocytes involved in the pathophysiology of graft-*versus*-host disease. Moreover, the interaction between mesenchymal stem cells and human lymphocytes has been shown to favor the differentiation of T-lymphocyte subsets displaying a regulatory suppressive phenotype.[29] Experimental areas of the application of regulatory T cells also foresee their possible clinical use in relation to conditions of allo- and auto-immunity.[26]

In conclusion, it can be said that the dogma of the need for complete HLA-compatibility between donor and recipient, which since 1968 had been considered a mandatory requirement for programming bone marrow transplantation, has lost part of its rigidity. One could also say that the successes achieved thanks to the use of haploidentical grafts have made it possible for nearly every candidate recipient to find a related donor. There is little doubt that the long-term success of transplants depends on choosing, case by case, the most suitable strategy. A good example of this is the leukemic patient. For these patients, the strategy must be "dosed" in a timely fashion to strengthen the graft-*versus*-leukemia effect while limiting the risk of graft-*versus*-host disease. In particular, the choice of an HLA-disparate NK alloreactive donor is now considered one of the best strategies to adopt.

On a practical level, both T-cell depletion and infusion of "megadoses" of hematopoietic stem cells with a high content of $CD34^+$ cells and of veto cells have demonstrated their efficiency in overcoming the natural major barriers of the defense of "self". Nevertheless, they have by no means limited, on a conceptual basis, the essential natural immunological need for these defenses. These will obviously remain indispensable for the integrity of biological individuality, of the "self", for as long as man walks on this earth.

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