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Identification of tolerant recipients following liver transplantation

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ABSTRACT

The need to administer livelong immunosuppressive medication (IS) to transplant recipients to prevent graft rejection often results in severe side effects like infections, malignancies, renal failure and cardiovascular complications. This constitutes one of the major drawbacks of clinical organ transplantation. Therefore, a means to establish medication-independent graft acceptance (tolerance) would be a major breakthrough in the field. Transplantation tolerance can be readily generated in experimental animal models, but so far most efforts to purposely induce this phenomenon in the clinic have failed. Liver transplantation is a unique clinical setting in that up to 20% of recipients can spontaneously withdraw IS without rejecting their grafts and are considered as operationally tolerant. This clinical observation is probably the most extreme manifestation of the well-documented intrinsic tolerogenic properties of the liver. The high rate of spontaneous operational tolerance following liver transplantation and the relative resistance of liver allografts to the effects of cytopathic alloimmune responses make liver transplantation the most suitable clinical transplantation model to test IS withdrawal strategies and tolerance promoting therapies. Liver transplantation constitutes therefore a unique setting to learn the mechanisms underlying allograft tolerance in humans.

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1. Introduction

The liver possesses unique immunoregulatory functions, which most likely evolved from the need to tolerate harmless food-derived antigens [1]. Thus, antigen presentation inside the liver, particularly when antigens are delivered through the portal venous system, often results in immune silencing and apoptosis. In clinical liver transplantation the immunologically privileged status of the liver is noticeable in the lack of long-term deleterious effects of early acute rejection episodes, in the fact that these episodes are occasionally spontaneously resolved without the need of additional IS, and in the extremely low incidence of chronic rejection. Furthermore, in some liver recipients graft function can be maintained, apparently indefinitely, in the absence of any IS [2–10]. This phenomenon, termed "operational" tolerance is considered a proof of principle that immunological tolerance can be attained in humans. Operational tolerance is more prevalent in liver than in any other transplantation setting [3]. Due to these favorable immunological factors, in clinical liver transplantation the morbidity and mortality attributable to side effects of lifelong IS are currently higher than the risk posed by rejection [11]. Thus, the risk to benefit ratio associated with the achievement of graft acceptance in the absence of IS is particularly favorable in liver transplantation. Substantial efforts are currently being put into the development of therapeutic protocols capable of intentionally inducing transplantation tolerance in the clinic. Some recently tested strategies appear to be partially successful, at least in kidney transplantation, but they require aggressive conditioning regimens that substantially limit their clinical applicability [12,13]. In liver transplantation, a complementary and probably more accessible goal to advance towards successful IS avoidance is the search for biomarkers capable of identifying spontaneous operational tolerance in the clinic. Such biomarkers could constitute the basis for a treatment-stopping rule to guide clinicians undertaking IS minimization and/or withdrawal strategies. While various trials have assessed the feasibility of intentionally withdrawing IS from stable liver transplant recipients [3], none of them has been able yet to provide an accurate diagnostic tool to identify tolerant subjects among liver recipients under maintenance IS.

2. Definition of allograft tolerance in clinical transplantation

From an immunological point of view tolerance is defined as a state of immune non-reactivity towards a specific set of antigens that is indefinitely maintained in the absence of ongoing IS. In experimental models tolerance is induced through therapies aiming at either the deletion of alloreactive cytopathic T cells and/or the generation of regulatory T cells. In these models tolerance is formally proved by the demonstration that tolerant recipients accept same-donor second grafts without further IS and rapidly reject third-party grafts. In addition, in tolerized experimental animals T cells display donor-specific hyporesponsiveness and, in models of peripheral

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allograft tolerance, can adoptively transfer tolerance when injected into naïve hosts. Since these formal demonstrations of tolerance are unsuitable for clinical application, the term "operational" tolerance was chosen to designate the clinical situation in which a graft maintains stable function without features of acute or chronic rejection and without the need of chronic IS. Several intentional IS weaning trials in liver transplantation have been published in the literature employing operational tolerance as their clinical endpoint [3]. These studies have been extremely valuable to determine the feasibility of withdrawing IS from liver recipients. However, none of them has unambiguously identified the mechanisms responsible for the maintenance of the tolerant state. Furthermore, protocol biopsies have not been universally conducted and hence the possibility that operationally tolerant liver recipient might be developing silent low-grade graft damage has not been excluded yet [14].

3. Challenges of biomarker discovery in transplantation research

Biomarkers are conventionally defined as objective and measurable indicators of either physiological processes, pathological conditions or pharmacological responses. [15]. Biomarker discovery has been enormously boosted by the availability of high-throughput technologies to interrogate the genome, epigenome, transcriptome and proteome. Furthermore, in immunology the measurement of biologically active molecules (e.g. cytokines or chemokines) or cell surface membrane receptors has also been intensively exploited in the search for clinically useful biomarkers. In clinical transplantation, given the lack of a contrasted hypothesis to explain the phenomenon of spontaneous operational tolerance, the search for tolerance-related biomarkers has been mainly conducted in an exploratory manner. The two strategies that have been more successful in this quest have been multiparameter flow cytometry and microarray gene expression profiling conducted on peripheral blood samples.

With the appropriate fluorescent monoclonal antibody panels, multiparameter flow cytometry is capable of analyzing with great detail the number and surface phenotype of peripheral blood antigen-presenting cells and lymphocyte subsets employing minimal amounts of whole blood. This technique is capable therefore of generating an "immunological" profile of study subjects out of peripheral blood samples, and is a very powerful tool to discover new biomarkers. Despite constant improvements in flow cytometry equipment and data analysis software, however, the widespread clinical application of this technology continues to be hampered by issues of reproducibility across different laboratories. In contrast, the analysis of the transcriptome employing either microarrays or real-time PCR is currently more robust and more amenable to automation and standardization, and has resulted in the development of an already commercially-available non-invasive diagnostic test of heart allograft rejection (*Allomap Test*; http://www.xdx.com/allomap).

Transcriptomic analyses are commonly initiated by the non-targeted measurement of thousands of gene transcripts in the same biological sample employing microarrays. These types of data-driven experiments offer enormous opportunities for the identification of novel biomarkers and for the formulation of a new hypothesis, but they are also challenging in terms of data analysis, given the disproportion between the high number of genes measured and the limited number of samples available for microarray testing [16]. In transplantation, microarrays have been mainly employed to address two questions: i) determining which genes are differentially expressed among recipients representative of different medical conditions, such as tolerance *versus* rejection ("class comparison" studies); and ii) trying to predict to which medical condition a recipient would be assigned on the basis of its expression profile ("class prediction" studies). These types of studies containing high-dimensional datasets cannot be analyzed employing conventional comparative statistics, and more stringent standards of statistical significance have to be applied in order to account for the problem of multiple testing. Moreover, in "class prediction" studies it is usually feasible to generate a mathematical algorithm based on gene expression data capable of accurately classifying a sample into predefined categories even when data are completely random. To address this problem a predictive gene model has to be always validated on a set of data completely independent from the data employed for its development. Furthermore, due to issues of experimental "noise" (intra-platform variability), which often arise when hybridizations are made in different laboratories or in the same laboratory but on different batches, the validation of microarray expression results employing more robust transcriptional platforms such as real-time PCR is highly recommended. Despite the methodological limitations of gene expression profiling, the application of this technology to clinical transplantation in the characterization of operationally tolerant recipients has been broad and relatively successful, and is the one most likely to result in the identification of clinically useful biomarkers of tolerance in the near future [17–22]. While peripheral blood might not be the optimal tissue source to dissect the mechanisms responsible for allograft tolerance, the use of non-invasive blood monitoring has enormous and obvious clinical advantages, and is currently the strategy most widely pursued in the search for biomarkers. This trend could however change given the current availability of high-throughput gene expression platforms designed to interrogate RNA extracted from paraffin embedded biopsies [23,24].

4. Immunophenotypic analysis of peripheral blood cell populations in operationally tolerant liver recipients

Five articles have reported on the immunophenotypic characterization of peripheral blood mononuclear cells (PBMC) from operationally tolerant liver recipients. In these studies, operationally tolerant recipients (stable graft function off IS for various periods of time) have been compared with recipients under maintenance IS considered to be non-tolerant (although not in all cases a formal demonstration of the absence of tolerance by a prior attempt at IS withdrawal was conducted). Mazariegos et al. [25] quantified the relative frequency of monocytoid (mDC) and plasmacytoid (pDC) peripheral blood dendritic cell precursors in samples from 6 operationally tolerant recipients (0.8–7.9 years after complete IS cessation), 23 recipients undergoing prospective drug weaning (but still on minimal IS at the time of blood collection) and 11 recipients on conventional maintenance IS (in whom drug weaning had failed or had never been attempted). Both in tolerant recipients and in those receiving minimal IS the pDC/mDC ratio was significantly increased as compared with recipients on maintenance IS or with healthy individuals. Li et al. [26] assessed the frequency of B cells, NK cells and several T cell subsets in PBMCs from 12 tolerant (2–6 years after complete IS cessation) and 19 potentially non-tolerant (receiving maintenance IS) pediatric living donor liver transplant recipients. Tolerant recipients exhibited: i) increased numbers of B cells and presumably regulatory $CD4^+CD25^+$ T cells; ii) decreased numbers of NK cells; and iii) an alteration in tolerant recipients only of the normal distribution of the two major peripheral blood γδ T cell subsets (namely δ1 and δ2) with an expansion of δ1 T cells and an increase in δ1/δ2 T cell ratio. Martinez-Llordella et al. [19] analyzed PBMCs from 16 tolerant liver recipients (1–6 years after complete IS cessation), 16 non-tolerant recipients (recipients in whom a previous attempt at IS withdrawal had failed and were receiving low dose maintenance IS at the time of analysis) and 10 age-matched healthy individuals. Results were consistent with those of Li et al. [26] in that $CD4^+CD25^+$, δ1 T cells and δ1/δ2 T cell ratio were increased in tolerant recipients as compared with both non-tolerant recipients and healthy individuals. Conversely, no differences were found in B and NK cells between the 3 groups of

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