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Transplantation tolerance: the big picture. Where do we stand, where should we go?

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Summary

A major goal in organ transplantation has been to safely exploit the natural processes of immune tolerance in order to minimize the dose and duration of drug immunosuppression. In this commentary, I argue that we can learn from how tumours avoid rejection, to evolve a three-stage tolerance-inducing strategy for transplanted tissues.

Keywords: anergy, suppression, tolerance, transplantation, tumour immunology

Research in transplantation immunology has a long tradition for generating fundamental discoveries. Many of these have underpinned new developments in other areas of immunological research. One long-standing goal has been to tolerize transplant recipients to their grafts, therefore doing away with the need for long-term immunosuppressive therapy. Despite many worthy efforts, it has proven difficult to establish simple tolerance-inducing protocols for use in standard clinical settings. It may be that aiming at complete tolerance is simply too great a challenge, whereas exploitation of some tolerance mechanisms may be more realistic, with the intention of reducing the duration and amount of drug immunosuppression.

I rarely have an opportunity to crystal ball what the future might be, but I value this opportunity to speculate.

Much of the research aimed at harnessing tolerance mechanisms has focused upon disabling lymphocytes. Little attention has been paid to understanding what the transplanted tissue can contribute, other than its antigens. However, recent advances in tumour immunology offer clues as to what such tissue-derived contributions might be.

One of the newly accepted hallmarks of cancer is that cancers can evade immune destruction [1]. This is not simply about the immune system being tolerant of 'self'. Cancers accrue mutant neoantigens throughout their development, and these are potentially immunogenic, as recent successes from checkpoint inhibition trials have demonstrated [2].

By their very nature, tumours start small and then evolve. At any one point in time, throughout their evolution they probably present a much smaller 'antigen' load than allogeneic tissue transplants. Unlike kidney or heart transplants, they do not offer an immediately vulnerable vasculature, nor the same upfront intensity of danger signals [3], to incite innate and adaptive immunity. Whereas transplants play easily into the activation/licensing of dendritic cells (DC), tumours have limited and intermittent powers in that respect. In fact, the tumour and the local microenvironment it cultivates, may be more likely to 'decommission' DC, such that they can rarely alert to 'danger'. Consequently, the immune system is likely to ignore many DC-presented antigens, and even become tolerant of others [4].

The ability of tumours to cultivate or sculpt their microenvironment [5] should ring bells with transplant immunologists who have long accepted that some non-cancerous tissues can do the same thing. These special cases have long been referred to as 'immunologically privileged sites' [6], exemplified by allogeneic pregnancies, anterior chamber-associated immune deviation and kidney and liver transplants in certain strains/species. It has also been established that certain therapeutic strategies can endow transplanted tissues with an acquired form of immunological privilege where, in some cases, tissue-resident regulatory T cells prevent tissue-infiltrating effector T cells from rejecting [7]. This has been demonstrated following the use of co-receptor blockade with a combination of non-lytic anti-

CD4 and anti-CD8 antibodies in achieving tolerance to highly immunogenic skin grafts in mice. Tolerated grafts, when retransplanted onto lymphocyte-deficient recipients, were accepted by the host. If, however, their regulatory T cells (T_{reg}) were ablated at the time of retransplantation, then the grafts were rejected by their resident effector T cells.

What, then, might a developing cancer and a tolerated graft have in common? For me, the most obvious explanation relates to limited antigen dose and diversity during the tolerance window. For evolving cancers, the limited neoantigen diversity and dose, in the context of unlicensed or decommissioned DC, would probably favour induction of tolerance processes. In the case of antibody-mediated co-receptor blockade, the adaptive immune system is blindfolded sufficiently long enough for the graft to heal, and for its emissions of danger signals to cease. Thereafter, as therapeutic antibody levels gradually decay, the staggered exposure of T cells to small amounts of graft antigens might favour tolerance processes over immunogenic ones.

If one thinks of the three Es (elimination, equilibrium, escape) of immune editing as applied to the stages of cancer development [8], one can then ask how such checkpoints might look in the context of tolerization to transplants. Briefly, the therapy blindfolds the immune system and so prevents elimination of the graft. The staggered exposure to graft antigens as therapy is withdrawn gradually engages the immune system, but gives tolerogenic processes the upper hand over immunogenic ones. This establishes an equilibrium between the immune system and the graft, manifesting (as in cancer) in an operational tolerance. In so far as transplanted tissues cannot change the inherited repertoire of antigens they express, any escape (from rejection), unlike in cancer, will not be from modifying the antigens presented, but from tipping the balance of the equilibrium to a more stable form of tolerance, with a greater emphasis on clonal inactivation, for example. In other words, any long-term graft escape would involve a transition from a potentially unstable equilibrium dependent upon the combination of immunosuppressive drugs working in concert with host-derived immunoregulation towards a more stable state, dependent upon an increased degree of lymphocyte clonal deletion.

Looking to the future, I would like to propose the application of three sequential phases of immunosuppressive therapy based on how cancers escape from immune eradication.

The underlying guidelines are predicated on buying time to allow a gradual transition from immediate control of graft rejection, to the enabling of host immunoregulatory mechanisms, the empowering of the healed graft to play its part in fighting back and finally, the generation of expendable lines of donor cells to be used in the third phase of management- the overall goal being to ultimately maximize the extent of clonal inactivation/depletion of alloreactive lymphocytes. Importantly, the components for all three phases would need to be co-ordinated in order to guarantee adequate host immunity to control infection and to maintain adequate immunosurveillance.

The first phase aims to prevent immediate graft elimination (rejection) and near-absolute control of danger signals. The second requires the establishment and maintenance of an equilibrium, whereby drugs and immunoregulatory mechanisms act together to ensure graft survival and function for long enough to enable transition to the third stage. The third stage aims at fine-tuning the tolerance processes to enable a more substantive clonal inactivation/deletion. If successful, then the final equilibrium will be sufficiently stable, against all possible insults, to ensure that the graft escapes rejection permanently. It may well be that the different stages will require the use of different immunosuppressive drugs/strategies to achieve their goals.

Three phases of immunosuppression

For Phase 1, I envisage robust approaches to prevent immediate graft elimination. These should be based on the following:

(1) Identifying and neutralizing innate danger mechanisms associated with a given grafted organ (e.g. complement, innate cells).
(2) Identifying short-term drug cocktails to perfuse the tissue before transplantation, with attention to modifying the endothelium to be less receptive to leucocyte adhesion and complement damage and to initiation of processes within the graft geared to creating the desired privileged microenvironment. Looking a long way ahead, however, one can anticipate that stem cell research will provide us with a source of naturally privileged third-party organs, tailored genetically to offer substantive resistance to rejection. These might be transplantable at a much earlier stage than is currently practised, and allowed to reach tissue maturity in their host. The reduced level of danger signals might compensate for incomplete donor–host major histocompatibility complex (MHC) matching, so setting limits for the numbers of donor sources required.
(3) Given the enormous number of immunocompetent lymphocytes that would need to be 'contained' to achieve the required equilibrium, a good starting-point would be to immediately reduce that initial number substantially. This would only have value if the rebound homeostatic expansion could be controlled adequately. As homeostatic expansion of T cells requires T cell receptor (TCR)-mediated 'self-recognition', its blockade would simultaneously provide a blindfold to adaptive immunity.

Preliminary lymphocyte depletion may provide a useful window for infusion of purified regulatory T cells and exploitation of the drivers of homeostatic expansion in favour of regulation.

Once graft healing and remodelling of the tissue microenvironment has begun, immunosuppressive protocols might be adjusted, in Phase 2, to permit the tissue to exert all necessary fightback (privilege) mechanisms to achieve the interim equilibrium. Any maintenance immunosuppressive drugs given at this stage would be selected on the basis of encouraging immunoregulatory mechanisms.

Finally, given major advances in stem cell research, I envisage that for each organ donor it should be possible to isolate/tailor induced pluripotent stem (IPS) cell lines carrying all donor MHC classes I and II alloantigens, and most minor histocompatibility antigens, and to use these as expendable (i.e. not needed for graft function) cells for infusion in Phase 3, the escape phase, to supplement graft-derived antigens to overwhelm immune mechanisms and achieve substantive clonal deletion of host alloreactive T cells. Ideal expendable sources of donor antigen would be cells endowed with veto properties, as exemplified in haemopoietic stem cell transplantation [9].

If immunosuppressive drugs are needed in this phase, then they should be agents that, given short term, would not interfere with the clonal purging.

This scheme implies that we need to examine currently available drugs and seek new ones, geared to provide optimal performances for each phase. Their application and withdrawal/tapering would need constant monitoring criteria, possibly based on sensitive biomarkers for low-level immune signalling.

What is new about this? The main theme here is to accept that one does not have to achieve all therapeutic manipulations in an early window, and that there may be advantages to progress in stages, as do tumours.

Disclosure

There are no disclosures.

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