There are two fundamental approaches that could be conceived to counteract the effects of IBMIR. The first is based on systemic treatment of the recipient, to prevent coagulation and complement activation at the transplantation site; the second is based on manipulations of the transplanted tissue to minimize its intrinsic characteristics that trigger IBMIR. The advantage of the former is its quite immediate clinical applicability, the primary disadvantage being that a systemic treatment may have generalized side effects (namely bleeding). In a mirrorlike fashion, manipulation of the tissue prior to implant would have the advantage of its localized effect, but the potential disadvantages linked to the quite cumbersome technological approach needed to achieve the goal. Gene therapy approaches, as an example, have intrinsic limitations of safety and efficacy, and there is concern about the immunogenicity of viral-encoded products.

In current clinical trials, islets are infused in the patients’ portal system in a solution that contains heparin, and therefore we may claim that, even before the formal demonstration of IBMIR occurrence, our approach was intuitively aimed at the prevention of coagulation in the portal venous system. The effectiveness of heparin, on the other hand, especially in preventing complement activation is less than optimal, and there have been recent proposals that alternative, more efficient compounds should be considered, such as low molecular weight dextran sulfate and melagatran (7, 8).

The paper by Dwyer et al. published in this issue of Transplantation convincingly presents evidence on the effectiveness of CD39 expression on islets in the prevention of IBMIR. CD39 is an ectonucleotidase that degrades the platelet agonist adenosine triphosphate (ATP), therefore holding promise as an IBMIR antagonist. The authors show that transgenic mice that express CD39 on islets have normal glucose metabolism, and that their islets, when exposed to human blood, fail to induce coagulation in roughly half of the experiments performed, with an average coagulation time in all experiments that is twice that of the controls.

Now that the phenomenon is quite well described and convincingly shown to occur in the clinical setting, the fundamental question is: how do we prevent it? Prevention of IBMIR could clearly result in clinical transplantation success with lower islet masses, and could also lead to a blunted immune response, perhaps requiring less potent immunosuppressive regimens to be administered.

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pig donors has been accomplished with success, and it could be easily conceived that multiple transgenes could synergize in the prevention of IBMIR. Complement regulating proteins such as decay accelerating factor, for example, have been expressed in transgenic pigs (11) and would represent natural candidates to combine with CD39. Recent progress in the results of islet xenotransplantation in primates (12, 13) suggests that clinical trials might not be too far down the line, and successful prevention of IBMIR might represent a crucial step forward towards success.

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