International Journal of Surgery 23 (2015) 296–300

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

Progress towards overcoming coagulopathy and hemostatic dysfunction associated with xenotransplantation

Peter J. Cowan [a, b, *], Simon C. Robson [c]

[a] Immunology Research Centre, St Vincent's Hospital Melbourne, Melbourne, Victoria, Australia
[b] Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia
[c] Transplant Institute and Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

HIGHLIGHTS

- Dysregulated coagulation is a major barrier to successful xenotransplantation.
- Microvascular thrombosis is frequently observed in rejected xenografts.
- Consumptive coagulopathy can develop in recipients.
- Likely causes include antibodies and cross-species molecular incompatibilities.
- Genetic modification of the donor pig may provide the solution to this problem.

ARTICLE INFO

Article history:
Received 3 July 2015
Received in revised form
16 July 2015
Accepted 17 July 2015
Available online 26 July 2015

Keywords:
Xenotransplantation
Coagulation
Inflammation
Coagulopathy
Thrombocytopenia

ABSTRACT

Dysregulation of coagulation and disordered hemostasis are frequent complications in the pig-to-nonhuman primate preclinical xenotransplantation model. The most extreme manifestations are the systemic development of a life-threatening consumptive coagulopathy, characterized by thrombocytopenia and bleeding, which is balanced at the opposite extreme by local complications of graft loss due to thrombotic microangiopathy. The contributing mechanisms include inflammation, vascular injury, heightened innate, humoral and cellular immune responses, and molecular incompatibilities affecting the regulation of coagulation.

There also appear to be organ-specific factors that have been linked to vascular heterogeneity. As examples, liver xenografts rapidly induce thrombocytopenia by sequestering human/primate platelets; renal xenografts cause a broader coagulopathy, linked in some cases to reactivation of porcine CMV, whereas cardiac xenografts often succumb to microvascular thrombosis without associated systemic coagulopathy but with local perturbations in fibrinolysis.

Overcoming coagulation dysfunction will require a combination of genetic and pharmacological strategies. Deletion of the xenoantigen αGal, transgenic expression of human complement regulatory proteins, and refinement of immunosuppression to blunt the antibody response have all had some impact, without providing a complete solution.

More recently, the addition of approaches specifically targeted at coagulation have produced promising results. As an example, heterotopic cardiac xenografts from donors expressing human thrombomodulin have survived for more than a year in immunosuppressed baboons, with no evidence of thrombotic microangiopathy or coagulopathy.

Contents

* Corresponding author. Immunology Research Centre, St Vincent's Hospital Melbourne, PO Box 2900, Fitzroy 3065, Victoria, Australia.
E-mail address: peter.cowan@svha.org.au (P.J. Cowan).

http://dx.doi.org/10.1016/j.ijsu.2015.07.682
1743-9191/

1. Factors underlying dysregulated coagulation in xenograft recipients

Coagulation is a tightly controlled physiological process designed to preserve the integrity of the vascular system [1]. Endothelial injury results in exposure of active tissue factor (TF) to the blood, triggering a molecular cascade that results in the formation of a fibrin-enmeshed platelet plug. Finely tuned regulatory systems, comprising cell surface and circulating components, cooperate to ensure that clotting is localized, proportionate to injury, and resolved at the appropriate time.

The key endothelial anticoagulant/antithrombotic proteins include thrombomodulin (TBM), tissue factor pathway inhibitor (TFPI), endothelial protein C receptor (EPCR) and CD39. Because coagulation and complement activation are interconnected, the complement regulatory proteins (CRPs) CD46, CD55 and CD59 also play a role.

Porcine xenografts face a series of challenges that tip the balance towards coagulation and inflammation (Fig. 1). First, human and nonhuman primate (NHP) sera contain significant levels of pre-existing anti-pig antibodies [2,3]. The target antigens are predominantly carbohydrate structures on glycoproteins and glycolipids, indicating that these 'natural' antibodies arose as a consequence of cross-species differences in glycosylation. While the key specificity is galactose-α1,3-galactose (αGal), antibodies to N-glycolylneuraminic acid (Neu5Gc) are also likely to be important in the pig-to-

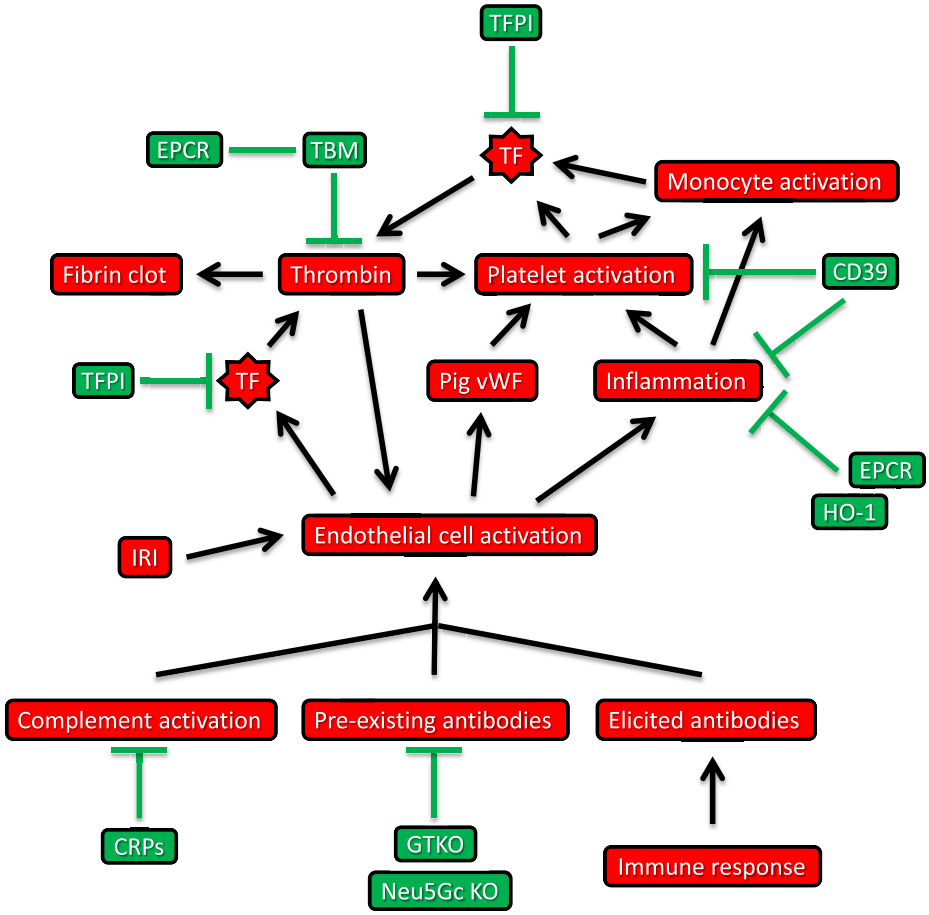

Fig. 1. Pathways to dysregulated coagulation and inflammation in solid organ xenotransplantation. Poor control of TF and thrombin by TFPI and TBM, respectively, will potentially drive a pro-inflammatory, procoagulant positive-feedback loop. Genetic strategies designed to disrupt this process are shown in green.