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Xenotransplantation: on the way to Clinical Application?

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INTRODUCTION

Heart transplantation is the accepted therapeutic option that improves the life expectancy and quality of life of patients with end-stage heart failure. One of its major limitations is donor shortage that leads to a high mortality rate in the waiting list. Public and Transplantation Societies policies and campaigns did not significantly improve this scenario. Several strategies to increase the heart donor pool have been proposed and results have been reported and discussed in consensus conferences.

These strategies include the use of "high-risk donors", or the so-called "marginal donors", *e.g.* elderly people or donors with a minor or correctable cardiopathy. Nevertheless, they also had no significant impact in the donor pool.

The use of animals' hearts or xenotransplantation is the only possibility of overcome this problem.

The first human cardiac transplantation was a xenotransplantation performed by Dr. James Hardy[1]. After, Bernard's first interhuman transplant, xenotransplantation was performed by Dr. Cooley (1968) [2,3], Dr. Ross (1968)[4], Dr. Barnard (two cases, 1977)[5], and Dr. Bailey (1984)[6], using hearts from sheep, pig, and baboon. Except for Dr. Bailey's case (20 days), the patients survived only hours. It was clear that hyperacute rejection was an outstanding barrier.

Some advantages of xenotransplantation are: 1 – unlimited availability of organs; 2 – planned operation; and 3 – repeated elective transplant. Potential disadvantages are: 1 – possibility of an animal infectious disease; 2 – great immunological differences; and 3 – physiological differences[7].

EXPERIMENTAL BACKGROUND

It was soon clear that the major problem of xenotransplantation was the immunological barrier, leading to acute humoral xenograft rejection or delayed rejection (acute vascular rejection).

The increased interest in this kind of transplantation led to the choice of the pig as donor, instead of a nonhuman primate. The reasons for this choice were: the number of piglets, the fact that the pigs' hearts are easier to manipulate and that their hearts are bigger than the nonhuman primates' hearts, and the less chance of zoonosis.

When we look at the evolution of the species, humans came from a separation of other mammals 75-80 million years ago. The monkeys of the New World separated from the branch of Old World monkeys and humans 30-40 million years ago. At this particular period, it was deleted the gene that produces the galactosyl-α-1,3 galactose, or simply GAL, a carbohydrate that is the most important antigen in the xenotransplantation. GAL is expressed in most of the cells of all mammals, including pigs, except for Old World monkeys and humans. Unfortunately, GAL is present, for instance, in intestinal bacteria, and humans have preformed antibodies (Ab) against GAL[8].

The first strategies to avoid hyperacute rejection were depletion of Ab by plasmapheresis and immunoadsorption and depletion or inhibition of complements, among many others. Nevertheless, Ab return with graft loss[9,10].

Initial genetically engineered pigs were animals that expressed one or more human complement regulatory proteins (CRP). This is of paramount importance because when the Ab antiGAL binds to the antigen, it triggers the complement cascade with coagulation of the vessels[11].

Later on, transgenic pigs' development, besides the manipulation to express human CRP, included the most important manipulation, which is deletion of the gene that express α-1,3galactosyl transferase, so these pigs do not have GAL in their cell surface. This kind of gene knockout (GETKO) pig was the major achievement in this field.

As thrombotic microangiopathy was still a problem through several mechanisms, including other xenotransplant non-GAL

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