Fighting chronic rejection of transplanted organs

In many diseases the only available cure is organ transplantation. However, if the transplanted organ does not derive from an identical twin (which is genetically identical to the recipient) it becomes rejected by the immune system of the recipient. This type of rejection, which, if not medicamentally prevented, occurs few days after transplantation, is called the acute or fast rejection. Fortunately, nowadays transplantologists use excellent immunosuppressive drugs, which block the immune response (designed to fight genetically different entities such as alien organs or bugs) of the recipient and allow survival of the transplanted organ. Unfortunately, however, few months or years after transplantation every transplanted organ deteriorates and stops functioning. This process of transplant deterioration over time is called “chronic rejection”. One of the hallmarks of chronic rejection is the occlusion or clogging up of the organ vessels, which leads to the lack of blood flow, organ starvation and its death. At present there is no cure for chronic rejection. The affected transplant recipients’ need another transplantation and have to be put back on the transplantation waiting list, which is extremely long because of the shortage of organ donors. Thus, the chronic rejection of transplanted organs is highly detrimental and unresolved problem in transplantation.

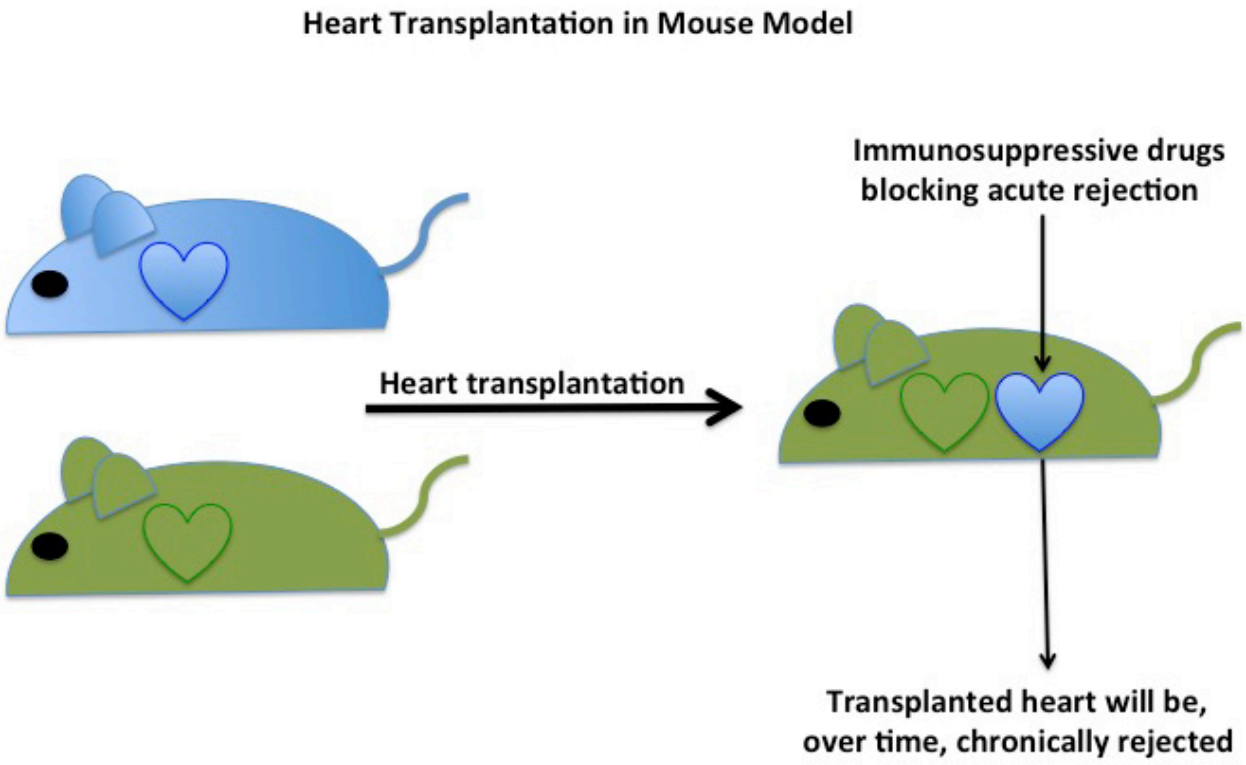

Fig. 1. In mouse model of heart transplantation the heart from one type of mouse is transplanted to the belly of genetically different mouse. Transplanted mouse receives immunosuppressive drugs, which block acute (fast) rejection but can not block chronic rejection of transplanted heart.

Although the molecules and cells involved in development of chronic rejection are not fully understood one of the possible culprits are the macrophages - the motile immune cells, which migrate from the blood to the transplanted organ, accumulate around blood vessels and promote their clogging. Motility and migration of macrophages depend on the system of actin filaments, which form the internal skeleton of the cell- called “the actin cytoskeleton.” The actin cytoskeleton organization and function, thus the macrophage migration, are regulated by several enzymes collectively called “the RhoA pathway”.

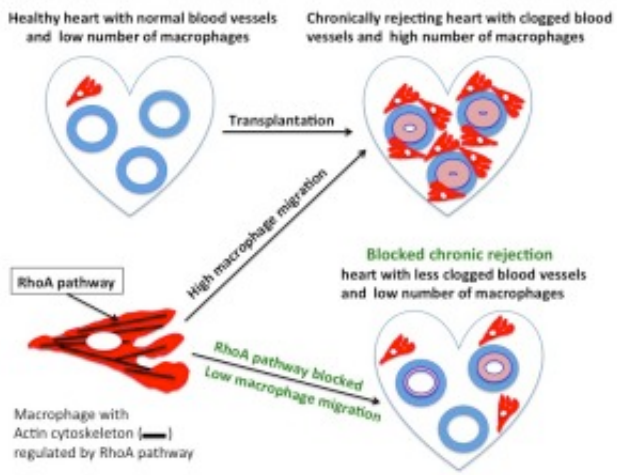

Fig. 2. Normal healthy heart has non-occluded blood vessels and low number of macrophages. After transplantation, macrophages migrate into the transplanted heart, accumulate around blood vessels and promote their clogging. Migration of macrophages depends on actin cytoskeleton, which is regulated by RhoA pathway enzymes. The tampering with RhoA pathway blocks macrophage migration into the transplanted heart and inhibits chronic rejection.

To better understand the role of macrophages in chronic rejection we used heart transplantation in mouse model system, in which a heart from one mouse is transplanted to the belly of another (genetically different mouse). The transplanted heart is connected to the major abdominal artery and vein of the recipient. Thus, the recipient mouse has two hearts: own healthy heart and transplanted one, which over time will be chronically rejected (Fig. 1.). We also generated mice in which RhoA molecule had been removed from macrophages. In several studies from our laboratory we looked at the effect of tampering with RhoA pathway on macrophages and chronic rejection of transplanted hearts.

Our studies showed that the tampering with RhoA pathway affected macrophage actin cytoskeleton, prevented them from entering transplanted heart, and inhibited chronic rejection (Fig.

2.). Moreover, our study showed that the regulation of macrophage cytoskeleton depends not only on RhoA pathway enzymes but also on another enzyme called “the Caspase-3.” These novel findings will shed a light on our understanding how macrophages cause chronic rejection, help in development of novel therapies to fight chronic rejection of transplanted organs and prolongs effectiveness of transplantations.

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Mouse macrophage polarity and ROCK1 activity depend on RhoA and non-apoptotic Caspase 3.
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