transplantation
india

POST TRANSPLANT ISCHEMIA REPERFUSION INJURY, INNATE IMMUNITY AND ALLOGRAFT REJECTION

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The concept and knowledge of transplant immunology by and large, has evolved from a variety of theoretical considerations, analysis of experimental data and clinical events. Somehow or the other, ischemia reperfusion injury as a biological event, has not been granted its proper place in the hierarchy of immunological events which lead to allograft dysfunction. Transplant biologists are trying to answer one of the key questions: Does perfusion injury make the allograft more immunogenic?

The classical concept of an adaptive immune response was based on Burnet's theory of "self vs non-self". In 1994, Poly Matzinger theorized a concept deviating from this classical dogma and named it as `Danger hypothesis'. The principal theme of this concept was that tissue injury as an event activates anti-allograft immune response to protect from danger of extinction, rather than immune attack on MHC-non-self incoming allograft. Walter Land has further expanded this theme and has proposed that ischemia reperfusion injury is associated with generation of reactive oxygen species. Macrophages, monocytes and neutrophils are activated along with endothelial damage and migrate in to the interstitium through the swollen endothelial lining. The tissue damage leads to the activation of anti-T cell mechanisms, activation of free oxygen radicals and up-regulation of MHC expression. Direct and indirect pathways of allo-rejection process are augmented as an end result of these interactions. Mohammed Sayegh has used autologous ischemic kidney model in rats blocking CD28-B7/2 with CTLA-4 Ig and has observed up-regulation of B7 co-stimulation. This is the experimental evidence that rejection process could be activated in the absence of MHC disparity.

Innate immune system has been evolved to protect the host against an invading pathogen as an immediate first line of defense whereas the adaptive immune system operates through antigen presenting cells via T/ B cells to protect against attack by viral, bacterial and cancer cells. Literature has accumulated evidence suggesting that activation of adaptive immune responses requires a specific direction from the innate immune system. The dendritic cells provide a link between the adaptive and innate immune systems by activating the innate immune signaling receptors known as toll-like receptors (TLRs). The mammalian TLR system comprises of a family of germ-line encoded trans-membrane receptors that recognize conserved viral, bacterial, protozoal and fungal molecular structures called pathogen-associated molecular patterns (PAMPs).

Tissue injury is known to release danger signaling stress proteins (heat shock proteins-HSPs) in the host. They act as putative ligands for TLRs or can get independently released in to circulation in the event of severe form of injury and by their interaction, innate immune system gets activated.

In our experience of 650 renal transplantations with tolerance induction protocol which is a deletion chimeric model using high dose hematopoietic stem cell transplantation; we have observed absence of classical tubulo-interstitial rejection. However we have observed C4d negative mild vascular rejection (type IIA). We believe that this rejection/ like phenomenon is a result of ischemia reperfusion injury in its severe form, leading to the cascade of activation of HSP- TLR interaction eventually leading to donor vascular endothelialitis. This immune event is the beginning of allo-arteriosclerosis which has been classified as chronic vascular rejection. Munich trial using superoxide dismutase has been addressed to prove this hypothesis in clinic effectively.