Species differences of endothelial extracellular nucleotide metabolism and its implications for xenotransplantation

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Abstract:
There is a severe shortage of human organs available for transplantation and xenotransplantation – use of animal organs has long been suggested to overcome this problem. Recent advances in understanding rejection in xenotransplantation and development of genetically engineered pigs that reduced hyperacute rejection were fundamental steps forward but other unresolved mechanisms remain an obstacle. Endothelium is a major target for all rejection mechanisms in xenotransplantation. This is caused not only by location of these cells at the first line of contact but also because endothelium is a very variable cell type across different species. This variability affects not only its immune characteristics but also physiology and metabolism. Nucleotide metabolism is particularly variable in endothelial cells of different species. We attributed particular importance to one such difference – much lower activity of ecto-5’-nucleotidase (E5’N) in pig endothelial cells as compared to human. To study its significance our group developed pig endothelial cell line stably expressing human E5’N. This allowed us to determine that E5’N controls the rate of adenosine formation from extracellular nucleotides even with ATP as the substrate. Expression of human E5’N in pig cells attenuated several mechanisms involved in xenotransplant rejection such as cytotoxicity induced by human NK cells, human platelet aggregation or human platelet adherence to endothelium. We conclude that species differences of endothelial nucleotide metabolism could contribute to rejection following xenotransplantation. These studies suggests that expression of human ecto-5’-nucleotidase in pigs genetically engineered for xenotransplantation could help to prolong graft survival.

Key words:
Xenotransplantation, adenosine ATP, endothelium, hyperacute rejection