Molecular Mechanisms Underlying the Functional Adaptation of Adult-Sized Kidneys Transplanted into the Pediatric Recipients

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Recent development in the field of high throughput methods including genomics and proteomics has facilitated robust and comprehensive analysis of genes and proteins. This development stimulated efforts in identification effective and clinically applicable gene and protein biomarkers in the field of solid organ transplantation including kidney transplantation. Some achievements have been made through transcriptomics in terms of mRNA expression profiling and identification of potential biomarkers using clinical samples such as biopsied tissue, peripheral blood and urine. In the last decade, microarray technology has revolutionized biological research by allowing the screening of tens of thousands of genes simultaneously. Microarrays have been useful in identifying potential biomarkers for chronic rejection in peripheral blood mononuclear cells, novel pathways for induction of tolerance, and genes involved in protecting the graft from the host immune system.

In case of size discrepancy with donor and recipient size, posttansplantation renal function is influenced by the difference in size. When pediatric donor kidneys are transplanted into the adult recipients, a rapid adaptation to the size of the recipient is seen. In contrast, an attenuation of the GFR is observed when adult donor kidneys are transplanted into small pediatric recipients, both in humans as in an animal model. The discrepancy between the vasculature size of pediatric renal allograft recipients and the adult-sized kidney grafts leads to renal hypoperfusion, decrease in absolute GFR and finally decrease in renal volume, referred to as functional adaptation of these kidneys to the recipients' size. However, it was reported recently that this functional adaptation was not completely reversible in the smallest recipients and was associated with irreversible histological damage, but the underlying mechanisms remain unknown.

We hypothesized that the adaptation of adult-sized kidney into the pediatric recipient is not only a passive physiologic consequence of low renal blood flow and GFR, but is associated with gene expression alteration likely involved in the regulation of renal vascular resistance and auto-regulation and renal growth factors, which could add to the irreversible injury observed in the smallest recipients. Our aim of the study is to unveil the molecular mechanisms underlying the functional adaptation of adult-sized kidneys transplanted into pediatric recipients. We selected 21 pediatric and adolescent recipients of an adult-sized kidney who did not have delayed graft function or rejection episodes. Whole-genome expression profiles of renal allograft biopsies obtained at 3 months were assessed using Affymetrix oligonucleotide microarrays and correlated with absolute glomerular filtration rate (aGFR).

Despite the pristine condition of the kidneys at implantation, renal allograft function at 3 months after transplantation was highly variable, with aGFR ranging from 31.2 to 106 mL/min. In total, 724 unique genes correlated significantly with aGFR (q-value <5%). Canonical pathway analysis identified overrepresentation

of relevant pathways involved in regulation of tubular salt reabsorption as well as enzymatic pathways for organ development and hypertrophy. The single gene that correlated best with aGFR was stanniocalcin-1 (STC1). STC1 expression also correlated with the recipient's size at the time of transplantation as well as the chronic allograft damage index at 6 months.

Functional adaptation of adult-sized grafts to the pediatric recipient is associated with molecular adaptation for normal volume homeostasis of the recipient. Our finding also suggests that STC1 plays an important role on functional adaption in pediatric kidney transplantation.