

INSIDE LAB INVEST

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The Yin and Yang of pretransplant kidney perfusion

A fundamental distinction between living related kidney transplantation and cadaveric kidney transplantation is that preharvest kidney perfusion is outstanding in the living donor, but may be highly suspect in the cadaveric donor. It is thus noteworthy that the incidence of post-transplant acute renal failure — 25% — in recipients of cadaveric kidneys has remained essentially unchanged in the past 20 years. There is a good correlation between the frequency of apoptosis in renal tubular epithelial cells in biopsies obtained at the time of cadaveric kidney harvest, and the incidence of acute renal failure in the first 2 weeks after transplantation. Key members of the inflammation cascade and mitochondrial apoptotic pathway have been noted to be strongly differentially regulated in cadaveric kidneys, but previously published molecular studies are based on deductive, rather than inductive, investigation. In this issue **Hauser *et al*** (p. 353) have now performed genome-wide profiling using an impressive set of source materials: 12 donor kidney wedge biopsies each of living donor kidneys with good primary allograft function, cadaveric donor kidneys with good function, and cadaveric donor kidneys with biopsy-proven acute renal failure in the recipient. Genomic microarray findings were validated by real-time PCR. In total, 132 genes were identified that significantly separated living donor from cadaveric donor kidneys; 48 genes classified the donor kidneys according to their post-transplant course. The main functional roles of these 48 genes were cell communication, apoptosis, and inflammation. In particular, members of the complement cascade were activated in cadaveric, but not in living donor kidneys. These findings

provide strong impetus for identifying patients at risk for postischemic acute renal failure following cadaveric kidney transplantation.

New insights on mechanisms of formalin fixation and antigen retrieval

The introduction of antigen retrieval (AR) techniques during the early 1990s was a significant advance in tissue antigen detection by immunohistochemistry. Most methods involve brief exposure of formalin-fixed, paraffin-embedded tissue sections to high temperatures before incubation with primary antibody. However, the exact conditions required for optimal antigen reactivity vary considerably and must be determined by trial and error. Indeed, the basic mechanisms of AR are still incompletely understood. In this issue, two papers by **Rait *et al*** (p. 292) examine the effects of formaldehyde 'fixation' on bovine pancreatic ribonuclease A (RNase). The investigators show that formaldehyde treatment results in rapid intra- and intermolecular crosslinks that increase thermostability and in effect, 'lock in' the secondary structure of the protein. This finding helps to explain why proteins in formalin-fixed tissue sections can withstand the high temperatures used in AR techniques. Remarkably, heating formaldehyde-fixed RNase A at 65°C resulted in reversal of protein crosslinks and partial restoration of enzymatic activity. In a second article, the investigators show that intramolecular modifications by formaldehyde (crosslinks and formaldehyde adducts) inhibit antibody binding more significantly than intermolecular crosslinking of protein molecules. Reversal of crosslinking was correlated with restoration of immunoreactivity. This work could lead to improved standardization of immunohistochemical methods and may facilitate proteomic studies that require the extraction and characterization of proteins from existing archival, formalin-fixed tissues.