phil activation.\textsuperscript{15} The data from Gan et al. suggest that Th17 cells could be another hit in the pathogenesis. In this model, ANCA disease did not progress in the absence of IL-17A.\textsuperscript{4} Mice deficient could be another hit in the pathogenesis. In this model, ANCA

**REFERENCES**


**DISCLOSURES**

None.

**Caspase-12 and Diabetic Nephropathy: From Mice to Men?**

Maria D. Sanchez-Niño,* Ana B. Sanz,† and Alberto Ortiz‡§

*Instituto de Investigación Sanitaria-Fundacion Jimenez Diaz and †Servicio de Nefrología, Fundación para la Investigación Biomédica del Hospital Universitario La Paz, Madrid, Spain; ‡Universidad Autónoma de Madrid, Madrid, Spain; and §Fundación Renal Iñigo Alvarez de Toledo, Madrid, Spain

Since the seminal observation that high glucose induces renal cell apoptosis in culture and in vivo,\textsuperscript{1} investigators have sought to identify the molecular mechanisms of renal cell apoptosis in diabetic nephropathy. In this issue of JASN, Brezniceanu et al.\textsuperscript{2} explore proapoptotic genes that are upregulated differentially by reactive oxygen species (ROS) in renal proximal tubular cells of diabetic (db/db) mice. Expression of caspase-12 and other endoplasmic reticulum (ER) stress genes, such as HSPA5/GRP78/BiP and CHOP, are increased in the proximal tubules of these mice compared with nondiabetic and diabetic catalase transgenic mice. Reduction of ROS generation also inhibits albumin-stimulated expression and activity of caspase-12 in a human proximal tubule cell line (HK-2). Furthermore, knockdown of caspase-12 with small interfering RNAs reduces albumin-induced apoptosis in HK-2 cells. The authors of this article conclude that albuminuria may induce ROS-mediated ER stress and subsequent tubular apoptosis in diabetic kidneys. The involvement of caspase-12 in this process, especially in human cells, stands out as the most original part of the article; however, no information is provided on human
diabetic nephropathy, and the key question is how relevant these data are to humans.

There is increasing evidence that renal cells, including tubular cells, are lost through apoptosis in experimental and human diabetic nephropathy. Recent efforts to identify novel changes in the human transcriptome have also added a host of participants to the process of renal cell apoptosis during diabetic nephropathy. These studies have uncovered evidence of the presence of ER stress in renal cells in human diabetic nephropathy. Stimuli that increase the demand on the ER to synthesize proteins or degrade improperly folded proteins cause this stress. Several components of the diabetic milieu, such as high glucose, free fatty acids, albumin, oxidative activity, and inflammation, induce ER stress in renal cells.

Cells respond to ER stress by an adaptive response that leads to upregulation of ER chaperone proteins HSPA5/GRP78/BiP and HYOU1/ORP150 and the prosurvival transcription factor XBP1, among others. These genes are upregulated in progressive human diabetic nephropathy. Despite this evidence of ER stress in human diabetic nephropathy, it is still unclear to what extent this stress contributes to cell loss. In this regard, expression of potentially lethal unfolded protein response genes, such as CHOP, is unchanged or repressed in human diabetic nephropathy.

Caspase-12, a member of the caspase family of intracellular cysteine proteases, was first identified in mice. Murine caspase-12 is processed during ER stress–induced apoptosis, and caspase-12−/− mice are protected from tubular injury induced by tunicamycin. Whereas degradation or proteolysis of caspase-12, as observed in acetyaminophen-exposed tubular cells, is a well-established hallmark of ER stress, its central role in ER stress–induced apoptosis has been questioned. Contrary to other caspases, caspase-12 proteolytic activity seems to be limited to autocleavage. Thus, caspase-12 may be incapable of efficiently processing cellular substrates and initiating apoptosis. The functional consequences of autocleavage are unknown, but it has been proposed to result in caspase-12 inactivation. Calpains may also process caspase-12. More recently, it has been shown that calpains can process caspase-12, as observed in acetaminophen-exposed tubular cells, in a well-established hallmark of ER stress, its central role in ER stress–induced apoptosis has been questioned. The observation that caspase-12 interferes with NF-κB activation and nuclear localization may provide clues for further study.

The SNP encoding full-length caspase-12 is more prevalent in individuals of African descent, and the risk for progression to ESRD from diabetic nephropathy and other proteinuric kidney diseases is higher in black as compared with white individuals. It may be interesting to study the influence of caspase-12 SNPs on the course of proteinuric kidney disease in these populations. A different question is also the relevance of the findings by Brezniceanu et al. for wider human populations that lack full-length caspase-12. It is plausible that the observed expression of full-length caspase-12 in HK-2 cells is the result of the presence of aminoglycosides in the cell culture media. Aminoglycosides promote translational reading through premature stop codons and have been tested in clinical trials of genetic disease caused by single-nucleotide mutations resulting in a premature stop codon.

In summary, although there is evidence of a role for caspase-12 and ER stress in albumin-induced tubular cell injury, there are significant differences between the in vivo human and experimental situations that preclude the direct extrapolation of animal model or cell culture results to the clinic at this point.

ACKNOWLEDGMENTS

This study was supported by grants FIS PS09/00447 and ISCIII-RETIC REDinREN/RD06/0016 and a grant from the Programa Intensificación Actividad Investigadora (ISCIII/Agencia Lain-Entralgo/CM) to A.O. and by a FIS postdoctoral fellowship to A.B.S.

DISCLOSURES

None.
REFERENCES


See related article, “Reactive Oxygen Species Promote Caspase-12 Expression and Tubular Apoptosis in Diabetic Nephropathy,” on pages 943–954.

Renal Donation after Cardiac Death

Nicholas Shah and Anthony Langone
Division of Nephrology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee


doi: 10.1681/ASN.2010040415

Renal transplantation is the treatment of choice for most patients with ESRD because transplantation dramatically improves both the length and the quality of life for dialysis patients. More than 80,000 patients in the United States are on the deceased-donor waiting list, with average wait times now exceeding 5 years. Yearly mortality on the deceased-donor list exceeds 6% per year and 10% per year in high-risk groups such as patients with diabetes. More patients are now thought to die while waiting for a deceased donor transplant than actually receive one.

The burgeoning use of kidneys from extended-criteria donors (ECDs) and donation after cardiac death (DCD) has positively affected the shortage of kidneys. ECD kidneys now account for 18% of all renal transplantations performed in the United States. Unfortunately, it seems this resource may have reached its ceiling for the maximum number of potential organs available to procure.1 The survival benefits of ECD kidneys have been validated in high-risk dialysis populations (age >40 years and history of diabetes, among others), in whom concerns regarding the ECD kidney, such as 70% decreased survival compared with standard-criteria donors (SCDs), are outweighed by the increased mortality and morbidity of remaining on dialysis.2

DCD kidneys have excellent short- (1 year) and long-term (10 to 15 years) survival with outcomes similar to DCD kidneys.3 In a 1997 editorial in Clinical Transplantation, Terasaki et al.,4 predicted that full use of DCD kidneys could resolve the shortfall of the kidney supply. Although DCD kidneys now account for 10% of all deceased donors in the United States, they remain underused still.

There is a reluctance to use DCD kidneys in general and by select transplant centers in particular because of an expected higher rate of delayed graft function (DGF) and primary graft nonfunction. DGF rates are reported, center “report cards” may affect contracts with commercial payers, and new transplant referrals to the transplant center can be adversely affected by an increase in DGF. In addition, DGF leads to extended hospital stays, resulting in increased costs that lower the prof-

Copyright © 2010 by the American Society of Nephrology

Correspondence: Dr. Anthony Langone, Division of Nephrology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN 37232. Phone: 615-370-4048; Fax: 615-343-6216; E-mail: anthony.langone@vanderbilt.edu

Published online ahead of print. Publication date available at www.jasn.org.