phil activation. 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. Mice deficient in IL-17A had high anti-MPO titers, akin to humans who have autoantibodies but who are asymptomatic. Further explanation will be required to define precisely the role of IL-17A and IL-17A-producing cells in human ANCA disease.

DISCLOSURES
None.

REFERENCES
9. Nogueria E, Hamour S, Sawant D, Henderson S, Mansfield N, Chavele KM, Pusey CD, Salama AD: Serum IL-17 and IL-23 levels and autoantibodies but who are asymptomatic. Further explanation will be required to define precisely the role of IL-17A and IL-17A–producing cells in human ANCA disease.

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

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

*Instituto de Investigación Sanitaria-Fundación Jimenez Díaz 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 Itigo Al- varez de Toledo, Madrid, Spain

Since the seminal observation that high glucose induces renal cell apoptosis in culture and in vivo, investigators have sought to identify the molecular mechanisms of renal cell apoptosis in diabetic nephropathy. In this issue of JASN, Brezniceanu et al. 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 Caspase-12 and Diabetic Nephropathy: From Mice to Men?

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

*Instituto de Investigación Sanitaria-Fundación Jimenez Díaz 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 Itigo Alvarez de Toledo, Madrid, Spain

Since the seminal observation that high glucose induces renal cell apoptosis in culture and in vivo, investigators have sought to identify the molecular mechanisms of renal cell apoptosis in diabetic nephropathy. In this issue of JASN, Brezniceanu et al. 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 acetaminophen-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 become evident that murine caspase-12 is an inhibitor of inflammation that dampens antibacterial responses by inhibiting caspase-1 and the NOD2/RIP2 pathways. In mice, deletion of the gene encoding caspase-12 confers resistance to peritonitis and septic shock by enhancing bacterial clearance.

A common human single-nucleotide polymorphism (SNP) of caspase-12 results in a premature stop codon yielding a truncated protein that contains only the N-terminal CARD prodomain (caspase-12S). Thus, caspase-12S lacks the large and small subunits of the active mature enzyme, present in the full-length variant molecule. Truncated caspase-12 is inactive and lacks catalytic and anti-inflammatory activity. The caspase-12S variant is now present in 98% of humans. Only in certain sub-Saharan African populations (28% of individuals) is the full-length caspase-12 polymorphism present. The driving force for the positive selection of caspase-12S is thought to be increased resistance to sepsis, which seems more important in higher density European and Asian populations than in the original African population.

With this background, Brezniceanu et al. observed increased expression of caspase-12 co-localization to apoptotic proximal tubular cells in murine diabetic nephropathy. Unexpected, because human HK-2 cells carry the caspase-12–inactivating SNP, the authors also observed the expression and activity of a full-length protein, which was upregulated by high glucose and, as previously reported in rat tubular cells, by albumin. Moreover, small interfering RNA targeting of human caspase-12 protected cells from albumin-induced tubular cell apoptosis. These are provocative observations that add to the controversy surrounding the role of caspase-12 in cell death and in humans.

There was a discrepancy between caspase-12 activity and caspase-3 activity/apoptosis that depends on the nature of the stimulus and suggests that caspase-12 enzymatic activity is not the sole determinant of apoptosis. In this regard, additional mechanisms for the proapoptotic action of caspase-12, besides the proteolytic activity displayed by other caspases, should be explored. The recent 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 REnDinREN/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

1. Ortiz A, Ziyadeh FN, Neilson EG: Expression of apoptosis-regula-
tory genes in renal proximal tubular epithelial cells exposed to high
ambient glucose and in diabetic kidneys. J Invest Med 45: 50–56,
1997.

2. Brezniceanu ML, Lau CJ, Godin N, Chenier I, Duclos A, Ethier J, Fili-
pe JG, Ingelfinger JR, Zhang SL, Chan JSD: Reactive oxygen species
promote caspase-12 expression and tubular apoptosis in diabetic

A, Armelloni S, Santamaria B, Berthier CC, Kretzler M, Egidio J, Ortiz

4. Sanchez-Nino MD, Sanz AB, Lorz C, Ginerke A, Rastaldi MP, Nair V,
Egidio J, Ruiz-Ortega M, Kretzler M, Ortiz A: BASP1 promotes
621, 2010.

5. Lindenmeyer MT, Rastaldi MP, Ikehata M, Neusser MA, Kretzler M,
Cohen CD, Schlondorf D: Proteinuria and hyperglycemia induce en-

6. Cybulsky AV: Endoplasmic reticulum stress in proteinuric kidney dis-

7. Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yankner BA, Yuan J:
Caspase-12 mediates endoplasmic reticulum-specific apoptosis and

8. Lorz C, Justo P, Sanz A, Subira D, Egidio J, Ortiz A: Paracetamol-

9. Scott AM, Saleh M: The inflammatory caspases: guardians against

10. Roy S, Sharom JR, Houde C, Loisel TP, Vaillancourt JP, Shao W,
Saleh M, Nicholson DW: Confinement of caspase-12 proteolytic
activity to autoprocessing. Proc Natl Acad Sci U S A 105: 4133–
4138, 2008.

N, Ulevitch RJ, Green DR, Nicholson DW: Enhanced bacterial clear-
ance and sepsis resistance in caspase-12-deficient mice. Nature 440:

12. LeBlanc PM, Yeretsian G, Rutherford N, Doron K, Nadiri A, Zhu L,
Green DR, Gruenheid S, Saleh M: Caspase-12 modulates NOD sig-
naling and regulates antimicrobial peptide production and mucosal

13. Saleh M, Vaillancourt JP, Graham RK, Huyck M, Srinivasula SM,
Alnemri ES, Steinberg MH, Nolan V, Baldwin CT, Horvath MS, Buchman
TG, Zehnbauer BA, Hayden MR, Farrer LA, Roy S, Nicholson DW:
Differential modulation of endotoxin responsiveness by human

Stalker J, Huckle E, Burton J, Leonard S, Rogers J, Tyler-Smith C:
Spread of an inactive form of caspase-12 in humans is due to recent

15. Ohse T, Inagi R, Tanaka T, Otta T, Miyata T, Kojima I, Ingelfinger JR,
Ogawa S, Fujita T, Nangaku M: Albumin induces endoplasmic reticu-
lum stress and apoptosis in renal proximal tubular cells. Kidney Int 70:

M, Bödolah-Abram T, Bebok Z, Shushi L, Kerem B, Kerem E: Gen-
tamicin-induced correction of CFTR function in patients with cystic
fibrosis and CFTR stop mutations. N Engl J Med 349: 1433–1441,
2003.

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 Uni-
versity School of Medicine, Nashville, Tennessee

doi: 10.1681/ASN.2010040415

Renal transplantation is the treatment of choice for most pa-
tients with ESRD because transplantation dramatically im-
proves both the length and the quality of life for dialysis pa-
tients. 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 as
die while waiting for a deceased donor transplant than actually
receive one.

The burgeoning use of kidneys from extended-criteria don-
or (ECDs) and donation after cardiac death (DCD) has pos-
tively affected the shortage of kidneys. ECD kidneys now ac-
count 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 or-
gans available to procure.1 The survival benefits of ECD kid-
neyes 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 re-
main ing on dialy sis.2

DCD kidneys have excellent short- (1 year) and long-term
(10 to 15 years) survival with outcomes similar to SCD kid-
neyes.3 In a 1997 editorial in Clinical Transplantation, Teresa
et al.4 predicted that full use of DCD kidneys could resolve the
shortfall of the kidney supply. Although DCD kidneys now ac-
count 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 trans-
plant 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-

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

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

Copyright © 2010 by the American Society of Nephrology