Alzheimer’s and Kidney Disease: Common Molecular Culprit?

By Cathy Yarbrough

The suspected molecular villain in Alzheimer’s disease (AD)—the amyloid precursor protein (APP)—may also play a role in kidney function, new research finds. While the findings do not suggest that APP “causes” kidney disease, they reveal that this protein may play important, although poorly understood, roles in renal function. Continued research on APP may help unravel kidney disease’s complex mechanisms and prompt researchers developing drugs targeted for the treatment of AD to also examine the compounds’ effects on patients’ kidneys.

“‘We’ve known about APP since the late 1980s, but we’ve not yet determined APP’s role in the brain, much less other body organs and tissues,’ said Lorenzo Refolo, PhD, a neuroscientist specializing in APP’s molecular and cell biology at the National Institute on Aging.

That said, APP is highly expressed throughout the kidney, said Daniel Biemesderfer, PhD, of Yale University School of Medicine. Biemesderfer’s lab has found that mice whose APP amyloid precursor-like protein-2 (APLP) genes were inactivated had a reduced glomerular filtration rate, lower urine osmolality, and poorly developed renin granules in the juxtaglomerular cells. “The distinct renal phenotype of the APP-/- mice suggests an important but not understood role in renal physiology,” Biemesderfer said.

Thomas Willnow, PhD, of the Max-Delbrueck-Center for Molecular Medicine in Berlin, traced the APP kidney connection to a unique protein—SorLA.

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Gene Variants that Protect Against Parasitic Disease Increase Kidney Disease Risk

By Tracy Hampton

Certain genetic variants found in more than 30 percent of African Americans may be considered a double-edged sword: a new study indicates that they protect against a parasitic infection but increase the risk of developing kidney disease (Genovese G, et al. Association of trypanolytic spoL1 variants with kidney disease in African-Americans. Science. doi: 10.1126/science.1193032 [published online ahead of print July 15, 2010]).

“The findings are very exciting,” said Thomas Hostetter, MD, chief of the division of nephrology at the Albert Einstein College of Medicine. “Large risks from single genes seem rare for common diseases.”

Studying how these genetic alterations contribute to kidney injury could help clinicians understand and potentially prevent kidney disease in individuals of recent African ancestry.

The good and the bad

The scenario may sound familiar—researchers have known for years that people with the hereditary blood disease sickle-cell anemia are protected against getting malaria. This is due to a muta-
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Kidney Disease

are long F-actin–rich cellular extensions, are long F-actin–rich cellular extensions, din, dendrin, actin, and actinin.” The kidney-brain connection is a “real hot spot” in research, said Sebastian Bachmann, PhD, professor and chairman of anatomy and cell biology at the Humboldt University in Berlin.

“Leading papers from world class scientists are currently focusing on this issue and find substantial material that proves it is worthwhile to concentrate on common mechanisms in kidney and brain,” Bachmann said. “This is well exemplified with APP and SorLA in both organs.”

Since its discovery, most research on APP has targeted the brain and has led to the “amyloid hypothesis,” which proposes that plaques in the production, accumulation, or disposal of β-amyloid, an APP microscopically fragment, somehow trigger Alzheimer’s, perhaps by clogging the cell-to-cell communication, thus activating immune cells that trigger inflammation and destroy neural cells.

Although APP’s normal function has not yet been defined, scientists have discovered that in its complete form, APP extends from the inside to the outside of brain cells by passing through a fatty membrane around the cell. When APP is activated to do its normal job, it is cut by other proteins into smaller sections that stay inside and outside cells. One of the sections, β-amyloid, is chemically “stickier” than other APP fragments and accumulates by stages into microscopically amyloid plaques that are considered a hallmark of brains affected by Alzheimer’s.

According to the Alzheimer’s Association, several experimental drugs targeting β-amyloid have reached human clinical trials, but more time and studies are required before these compounds’ effects on Alzheimer’s symptoms or on brain cells can be clearly determined.

The results of Willnow’s studies at the Max-Delbrueck-Center for Molecular Medicine indicate that low levels of SorLA are a primary cause of accelerated production of amyloid β-peptide, the principal component of senile plaques, and of senile plaque formation. Willnow’s lab has shown that SorLA regulates intracellular transport and processing of APP. Indeed, his lab also has found that high levels of SorLA expression reduce—and low levels of SorLA promote—senile plaque formation. Thus, altered SorLA activity may be an important risk factor for AD, according to Willnow.

Willnow hypothesizes that in the kidney, SorLA controls trafficking and activity of SPAK, an enzyme that regulates the cellular stress response and is part of a signaling pathway that regulates salt transport and blood pressure.

In kidney cells, SorLA also may influence the intracellular trafficking of shutting compartments that contain the protein aquaporin2 (AQP2), regarded as “the plumbing system for cells.” AQP2s are located in the apical cell membranes of the kidney’s collecting duct and in intracellular vesicles located throughout the cell.

AQP2 is mainly localized in the cell’s Golgi apparatus, where it interacts with target proteins such as APP. Willnow has demonstrated that the Golgi’s premature release of APP due to low SorLA activity subjects APP to accelerated proteolytic cleavage into amyloid peptides. These results may explain how AD pathology is affected by the activity of the sorting receptor SorLA in the brain.

Willnow’s lab has not yet investigated APP in the kidney. “Our main interest is the functional characterization of SorLA in the kidney,” he said. “Of course, we will also explore whether the activity of the receptor in the kidney may include control of APP processing in renal cell types and what the physiological relevance of APP and its processing products may have in the kidney.”

Findings from the Biemesderfer lab indicate the presence of what appears to be previously unknown signaling pathways in the kidney that involve APP and APLP.

Biemesderfer and his colleagues became interested in APP after discovering that the proximal tubule scavenger receptor megalin is subjected to regulated intramembrane proteolysis (RIP). Suspecting that RIP’s relationship with megalin may represent part of a signaling pathway linking events at the brush border with regulation of target gene expression, the lab conducted research that led to the identification of ADAM10 as a proximal tubule protease. The ADAM10 findings suggested that the proximal tubule has receptor proteins that are subjected to RIP.

“From some old literature we noticed that there are large amounts of APP and APLP2 mRNA in kidney,” said Biemesderfer. Based on this information, his lab initiated the studies that found high levels of APP and APLP2 in adult mouse kidney and in several proximal tubule cell lines. The lab then identified where renal APP is expressed along the nephron. They localized APP at the cellular and subcellular levels in mouse kidney and described the renal phenotype of APP−/− mice, whose APP and APLP1 genes have been inactivated.

“Our data suggest that these proteins are involved in signaling pathways in proximal tubule that may regulate gene expression,” Biemesderfer said.

In other work, Rong Cong, PhD, and colleagues in Biemesderfer’s lab reported that the protease ADAM10 and APLP2 are expressed in cultured proximal tubule cells. They also reported that ADAM10 activity has a pronounced effect on expression of specific proteins of the renal brush border. Biemesderfer’s lab continues to investigate APP in the kidney. “Our goal is to understand how APP and APLP2 function in kidney and especially in the proximal tubule,” he said. “Based on gene knockout studies in brain, it is thought that APP and APLP2 serve redundant functions. Therefore, our next study will use mouse genetics to knock out both genes in proximal tubule. We predict a phenotype that will give us important clues as to the function of these proteins in this part of the nephron.”

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 ASN Launches Facebook Group

Facebook is not just for college kids anymore. It is the fifth most popular website in the world and reaches over 500 million users on a monthly basis. With projections of phenomenal growth in the future, Facebook and other social media sites represent a shift in how people discover, read, and share news, information, and content.

ASN serves an important community of people interested in improving kidney health. The society extends in support of this community by using Face book to convey information of interest to members and, most importantly, receive feedback from members.

ASN’s Facebook page is a forum for participants to stay informed about advocacy and public policy, educational opportunities, breaking news, plans for ASN Renal Week, current research, grant funding and ASN services. We hope this venue helps members connect with each other, facilitates discussion, and sharing of information, and provides key feedback to the society so that ASN may continue to improve services to members.

ASN members and medical students can join the ASN Facebook group through a link on the ASN website homepage (www.asn-online.org) or by searching for the group on Facebook. (Please note that there is a difference between the ASN fan page and the ASN group. The Society is not affiliated with the fan page.)