A new study by Galeano and colleagues in this issue of the JCI reports the first glucomerol disease caused by a genetic defect in sialic acid biosynthesis (see the related article beginning on page 1585). Mice that harbor mutations in the Gne/Mnk gene produce lower amounts of sialic acid, suffer from hematuria, proteinuria, and structural defects in the glomerulus and die within days after birth. Remarkably, the lesion can be reversed through dietary addition of N-acetylmansnosaminic acid, a sialic acid precursor, raising the intriguing possibility that this approach might have therapeutic benefit in patients with glucomerol disease.

Nonstandard abbreviations used: Gne, uridine diphospho-N-acetylmannosamine 2-epimerase; HIBM, hereditary inclusion body myopathy; ManNac, N-acetylmannosaminic; Mnk, ManNac kinase; PC, podocafoxin; SD, slit diaphragm.

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In this issue of the JCI, Galeano, Huizing, and colleagues (1) describe kidney defects in knockin mice that harbor the M712T muta-
**Figure 1**

The biochemical pathway of sialic acid formation. CMP, cytidine monophosphate; ManNAc-6-P, ManNAc-6-phosphate; NeuAc-9-P, N-acetylneuraminic acid–9-phosphate; sialyl-OGS, sialylated oligosaccharides; PEP, phosphoenolpyruvate; UDP-GlcNAc, uridine diphospho-N-acetylgalactosamine. Adapted from Galeano et al. (1). CTP, cytidine triphosphate.

growth retardation and major structural abnormalities in the kidneys. The urinary space and renal tubules in these mice are packed with red blood cells and protein without any obvious inflammation, suggesting a major defect in formation and function of the glomerular filtration barrier. Accordingly, electron micrographs show segmental splitting of the glomerular basement membrane and fusion or absence of foot processes (Figure 2). Formation of the foot processes requires slit diaphragm (SD) proteins that are found in specialized intercellular junctions between foot processes. Phosphorylation of the SD protein nephrin (NPHS1) results in recruitment of Nck (non-catalytic region of tyrosine kinase) SH2-containing adaptor proteins and actin cytoskeletal reorganization (18–21). Although Galeano et al. (1) show that the SD proteins NPHS1 and podocin (NPHS2) are expressed in glomeruli from Gne mutants at wild-type levels, their subcellular localization and/or phosphorylation status were not examined.

Sialylation of PC is reduced in glomeruli from Gne<sup>M712T/M712T</sup> mutant mice (1). Because PC is known to associate with actin cytoskeletal proteins in the podocytes, and loss of this interaction disrupts glomerular barrier function, hyposialylation might explain the renal defect in the Gne<sup>M712T/M712T</sup> mutants. However, there are significant differences in phenotypes between PC KO mice and the Gne<sup>M712T/M712T</sup> mutants. PC KO mice also die in the perinatal period with renal defects that include failure of SD formation, fusion of foot processes, and a complete lack of filtration with no urine in the bladder (21). However, no splitting of the glomerular basement membrane or leakage of red blood cells into the renal tubules was observed. In addition, PC KO mice exhibit extrarenal defects such as hernias and omphaloceles (protrusions of the intestine and omentum through a hernia in the abdominal wall near the navel) due to the broad expression of PC during fetal life. By contrast, no other defects were observed in the Gne<sup>M712T/M712T</sup> mutants in any other organs including muscle, heart, and...
or lungs. Furthermore, Gne KO mice rescued by a Gne transgene harboring another common mutation (V572L, which is found in patients of Japanese origin with HIBM) survived but develop muscle defects and fibrosis of the diaphragm and heart. Interestingly, some of these mice died suddenly, although the cause was unclear. Although the authors stated that other internal organs had no defects, analysis of renal function was not described in detail (22).

Why are the glomerular defects apparently more profound in GneMT12T/M712T mutants than in PC KO mice or other animal models of sialylation defects? Several possible explanations exist. While PC is expressed by the podocyte, the endothelium and glomerular basement membranes also make significant contributions to the glomerular filtration barrier, and it is reasonable to assume that proteins in these compartments may also require sialic acid for normal functioning. In keeping with this hypothesis, PC is also expressed by endothelial cells and splitting of the glomerular basement membrane (with hematuria) seen in the GneMT12T/M712T mutants is reminiscent of the lesion seen in Alport syndrome, a disease caused by mutations in the collagen type IV α5 (COL4α5), COL4α4, and COL4α3 genes; the proteins encoded by these genes are major constituents of the glomerular basement membrane (23).

Toward a novel treatment for glomerular diseases

Strikingly, Galeano et al. (1) show that supplementation of the pregnant mouse’s diet with ManNAc, a precursor to sialic acid that readily crosses cell membranes, prolongs survival of the GneMT12T/M712T mice. This treatment was associated with an almost 10-fold enhancement of GNE enzyme activity in the kidney. Furthermore, sialylation of PC was also significantly increased in the kidneys of treated mutants, and there was marked improvement in ultrastructure of the filtration barrier.

Admittedly, there are striking differences between the human and mouse phenotypes caused by the identical GNE/Gne mutant alleles. Further understanding of the nature of this species difference could provide important insights into the regulation of protein sialylation in the kidney and its contribution to filtration barrier function. There is abundant evidence that human glomerular proteins are sialylated and that alterations in sialylation patterns can be associated with disease, although sialylation defects of individual proteins have not been reported. Thus, based on the dramatic effects of dietary ManNAc supplementation in this very aggressive model of glomerular pathology along with the simplicity and tolerability of this intervention, it seems plausible that this pathway might be useful as a more general therapeutic approach for glomerular diseases of many causes. This approach is especially attractive, as current therapies are nonspecific, associated with significant adverse side effects, and are often ineffective.

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2. Hinderlich, S., et al. 1997. A bifunctional enzyme catalyzes the first two steps in N-acetylneuraminic acid biosynthesis of rat liver. Purification and char-
A beneficial role for IL-1β in Alzheimer disease?

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While the term neuroinflammation often conjures up images of cellular damage, mounting evidence suggests that certain proinflammatory molecules, such as the cytokine IL-1β, may have beneficial and protective effects. In a report in this issue of the JCI, Shaftel and coworkers have generated an elegant mouse model in which local hippocampal overexpression of IL-1β in an Alzheimer disease (AD) transgenic mouse model resulted not in the expected exacerbation of the amyloid β plaque deposition common to AD, but instead in plaque amelioration (see the related article beginning on page 1595). Thus, manipulation of the immune system may be a potential therapeutic approach to protect against AD, although further studies are needed to understand all of the downstream effects of this manipulation.

The role of neuroinflammation in Alzheimer disease (AD) remains somewhat of a mystery. Although inflammatory proteins such as cytokines, chemokines, complement, and acute phase proteins are elevated in AD brain, the status of each as a “good guy” or a “bad guy” is still unclear (1). On one hand, inflammation may be a secondary response to progressive neurodegeneration in the brain. In this instance, immune cells in the brain, such as microglia and astrocytes, may become activated and secrete inflammatory molecules that may then further accelerate pathogenesis (2). On the other hand, recent evidence points to a potentially beneficial and protective role of inflammation in the brain (3). In this case, inflammation appears to induce microglial phagocytosis of amyloid β (Aβ) protein, reducing its deposition into plaques. Aβ protein is proteolytically cleaved from its large precursor, amyloid precursor protein (APP), and secreted; in AD, Aβ accumulates extracellularly into plaques, a hallmark pathological feature of the disease (4).

In a study reported in this issue of the JCI, Shaftel and coworkers present provocative new findings in support of the latter scenario (5). The authors overexpressed the proinflammatory cytokine IL-1β (IL-1β) in a region- and time-dependent fashion in transgenic mice overexpressing human mutant APP and presenilin 1 (APP/PS1 mice), a mouse model designed to partially mimic AD pathology in which extracellular Aβ plaques accumulate in the brain with aging. Excisional activation transgene (XAT) technology was used to first generate IL-1βXAT transgenic mice (5). Upon injection of feline immunodeficiency virus–Cre (FIV-Cre) to locally activate the IL-1β transgene in brain, these mice were shown to have elevated levels of IL-1β and glial fibrillary acid protein (GFAP), indicative of astrocytic activation, as well as of ionized calcium-binding adaptor molecule 1 (Iba-1) and MHC class II, indicative of microglial activation. Expression of the transgene was still apparent 1 year after injection. These mice were then crossbred with APP/PS1 mice, and the resulting mice expressing the APP/PS1 and IL-1βXAT transgenes (APP/PS1+IL-1βXAT)