AJKD
In Translation

The Renal Connexome and Possible Roles of Connexins in Kidney Diseases

Gabriele Sala, BPsySc, Salvatore Badalamenti, MD, PhD, and Claudio Ponticelli, MD, Hon FRCP

Connexins are membrane-spanning proteins that allow for the formation of cell-to-cell channels and cell-to–extracellular space hemichannels. Many connexin subtypes are expressed in kidney cells. Some mutations in connexin genes have been linked to various human pathologies, including cardiovascular, neurodegenerative, lung, and skin diseases, but the exact role of connexins in kidney disease remains unclear. Some hypotheses about a connection between genetic mutations, endoplasmic reticulum (ER) stress, and the unfolded protein response (UPR) in kidney pathology have been explored. The potential relationship of kidney disease to abnormal production of connexin proteins, mutations in their genes together with ER stress, or the UPR is still a matter of debate. In this scenario, it is tantalizing to speculate about a possible role of connexins in the setting of kidney pathologies that are thought to be caused by a deregulated podocyte protein expression, the so-called podocytopathies. In this article, we give examples of the roles of connexins in kidney (patho)physiology and propose avenues for further research concerning connexins, ER stress, and UPR in podocytopathies that may ultimately help refine drug treatment.
Am J Kidney Dis. 67(4):677-687.

INDEX WORDS: Connexins; gap junctions; endoplasmic reticulum (ER); ER stress; unfolded protein response (UPR); podocytes; nephrotic syndrome; kidney pathology; steroid-resistant; cytoskeleton; slit diaphragm; proteinuria; mutation; drug research; review.

BACKGROUND

Podocytes are highly specialized glomerular cells with a complex architecture. Their plasma membrane has foot projections that wrap around the glomerular basement membrane and interdigitate between foot projections of neighboring podocytes, forming slit diaphragms. The slit diaphragm is a specialized cell junction that allows for highly coordinated glomerular filtration. Proteins of the slit diaphragm recruit other cytoplasmic adaptor proteins for signal transduction cascades that fine-tune glomerular filtration.[1,2] Signals from the slit diaphragms are able to modulate the structure and function of the actin cytoskeleton of podocytes.[3] In recent years, molecular and genetic studies have shown that mutations in genes coding for proteins of the slit diaphragm, or any cell perturbation causing disorganization of the actin cytoskeleton, may lead to increased glomerular permeability, loss of filtration selectivity, and subsequent proteinuria.

CASE VIGNETTE

A 16-year-old girl presented with frequently relapsing nephrotic syndrome. Her clinical history was unremarkable until the age of 14 years, when she abruptly developed generalized edema. Idiopathic nephrotic syndrome was diagnosed and she was treated with prednisone, 1.5 mg/kg/d. Proteinuria resolved within 1 week. High-dose prednisone therapy was continued for 1 month and then slowly tapered. At a prednisone dosage of 0.5 mg/kg/d, nephrotic-range proteinuria recurred. Prednisone dosage was increased to 1.5 mg/kg/d, and complete remission was achieved. In a few months, 3 other relapses occurred after any reduction of corticosteroid dosage and remitted when prednisone dosage was increased. Because the girl developed cushingoid features, cyclosporine, 5 mg/kg/d, was introduced. However, frequent relapses of nephrotic-range proteinuria continued.

On presentation, the patient's blood pressure was 140/90 mm Hg and generalized edema was present. Laboratory test results included serum creatinine level of 0.9 mg/dL (corresponding to estimated glomerular filtration rate of 95 mL/min/1.73 m^2 using the CKD-EPI [Chronic Kidney Disease Epidemiology Consortium] equation), serum albumin level of 2.8 g/dL, serum cholesterol level of 270 mg/dL, and proteinuria with protein excretion of 8.5 g/d. A kidney biopsy showed that 20 of 22 glomeruli had mild mesangial proliferation. The other 2 glomeruli had areas of sclerosis close to the vascular pole. Immunofluorescence showed immunoglobulin M deposits in the area of sclerosis. Severe effacement of foot processes was noted on electron microscopy. A diagnosis of focal segmental glomerulosclerosis was made.

After remission was attained with high-dose prednisone therapy, the patient was infused with rituximab, 500 mg, every week for 4 weeks, and complete remission was maintained for 6 months. However, she then developed a further relapse of nephrotic-range proteinuria. A second course of rituximab was planned.

Although corticosteroids, cyclosporine, and rituximab have immunosuppressant features and represent a nonspecific treatment, they may also protect the function of the glomerular barrier. This

From the Nephrology and Dialysis Unit, Humanitas Clinical Research Center, Rozzano (Milano), Italy.

Received April 16, 2015. Accepted in revised form September 30, 2015. Originally published online November 21, 2015.

Address correspondence to Gabriele Sala, BPsySc, Humanitas Clinical Research Center (Nephrology and Dialysis Unit), Via Manzoni 56, 20089 Rozzano (Milano), Italy. E-mail: gabrielesala88@gmail.com

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2015.09.030

suggests that further treatments could target the molecular mechanisms regulating the structure and function of the podocyte cytoskeleton.[4-6]

PATHOGENESIS

Nephrotic syndrome is a kidney disorder characterized by massive proteinuria, hypoalbuminemia, hypercholesterolemia, and edema. Nephrotic syndrome may be the result of either primary glomerular diseases or systemic disorders. Although defects in the tubular degradation pathway may contribute to urine protein loss,[7] the current view is that nephrotic-range proteinuria mainly depends on podocyte function abnormalities at the level of the slit diaphragm. Whatever the cause, podocyte dysfunction may affect several adhesion/extracellular matrix components that are necessary to maintain the organization of the podocyte actin cytoskeleton.[8,9] Defects in the podocyte actin cytoskeleton may cause flattening and effacement of foot processes and disruption of slit diaphragms. In more severe cases such as focal segmental glomerulosclerosis, podocyte injury may eventually lead to podocyte hypertrophy and detachment from the glomerular basement membrane. Detached podocytes may make contact with parietal cells. After extensive podocyte loss, parietal cells may become activated and invade segments of the glomerular tuft by adhesion to denuded glomerular basement membrane. From this entry site, activated parietal cells may attempt to regenerate podocytes, but the excessive proliferative response may generate new lesions such as pseudocrescents and segmental sclerosis, eventually leading to glomerular collapse.[10,11]

RECENT ADVANCES

Structure and Function of Connexins

Connexins are a family of membrane-spanning proteins that have been classically referred to as the building blocks of gap junctions.[12] To date, more than 20 connexin isoforms have been detected in mammalian cells, with evidence supporting their evolutionary conservation.[13,14] Most cell populations express more than 1 connexin subtype at the same time, and their temporal expression is variable.[15] Connexins interact with a large number of other cytoplasmic and extracellular proteins. In particular, it has been shown that connexins have numerous associations with various cytoskeletal proteins, including microtubules, actin, α-spectrin, and tight junction proteins.[16]

Connexins form 2 main types of structures: connexons (also called hemichannels) and gap junctions (Fig 1). Connexons are structures composed of 6 connexins aligning with each other on the cell membrane, forming a central pore. They are large (10-15 Å) nonspecific channels with variable conductance that permit communication between the cell and the extracellular milieu. Each connexon can be composed of connexins of the same (homomeric) or different (heteromeric) types. Connexons respond to variations in a number of physiochemical parameters, including blood pH, serum calcium ion concentration,[17]

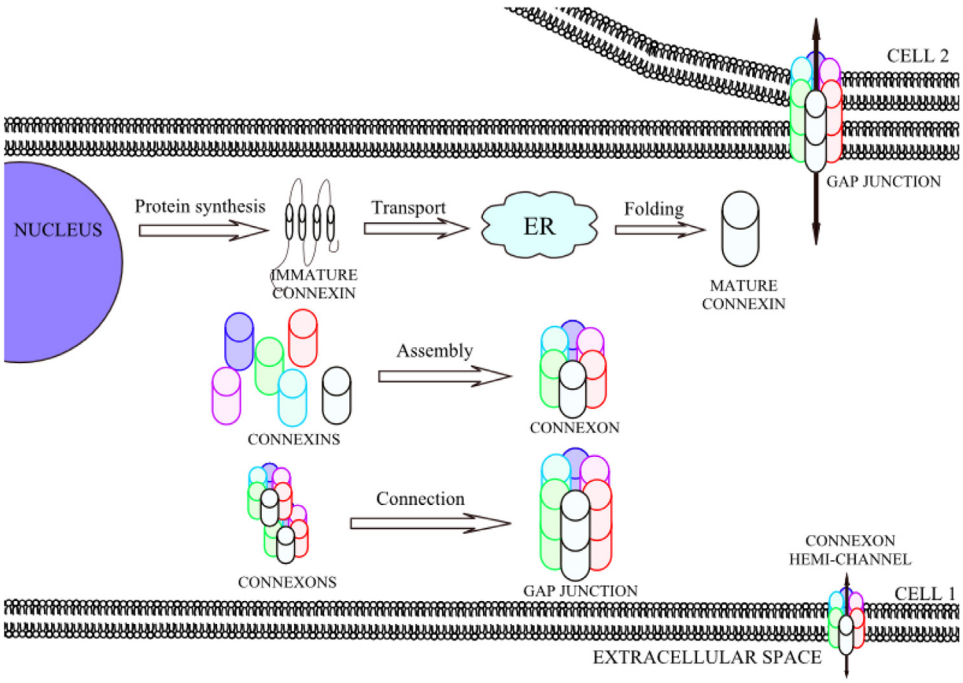

Figure 1. Overview of connexin synthesis and assembly into hemichannels and gap junctions. Abbreviation: ER, endoplasmic reticulum.