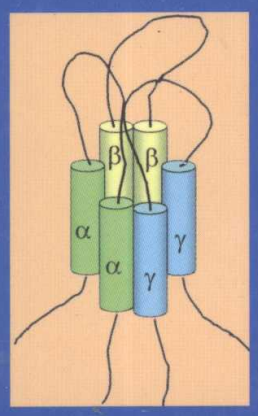
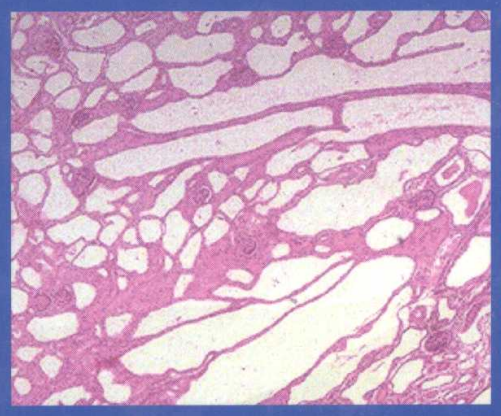
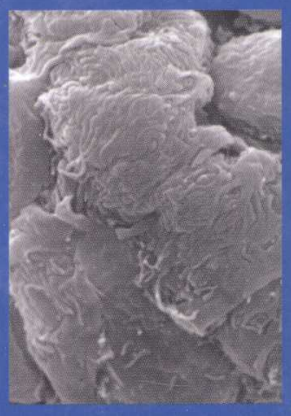
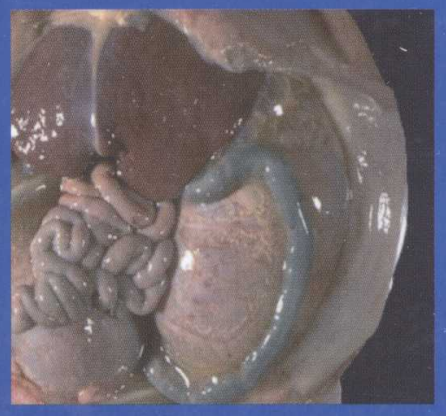
David B. Mount
Martin R. Pollak

Molecular and Genetic Basis of Renal Disease

A Companion to Brenner & Rector's The Kidney



Molecular and Genetic Basis of Renal Disease

A Companion to Brenner & Rector's The Kidney

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To my wife and children: Erika, Julia, and Nicholas
—DBM

To my parents: Helen and Barth Pollak
—MP

We also dedicate this textbook to our mentors:
Steve Herbert, Al George, Jr., Christine and Jon Seidman, and Barry Brenner
—DBM and MP

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Molecular and Genetic Basis of Renal Disease

Color Plates

Plate 1

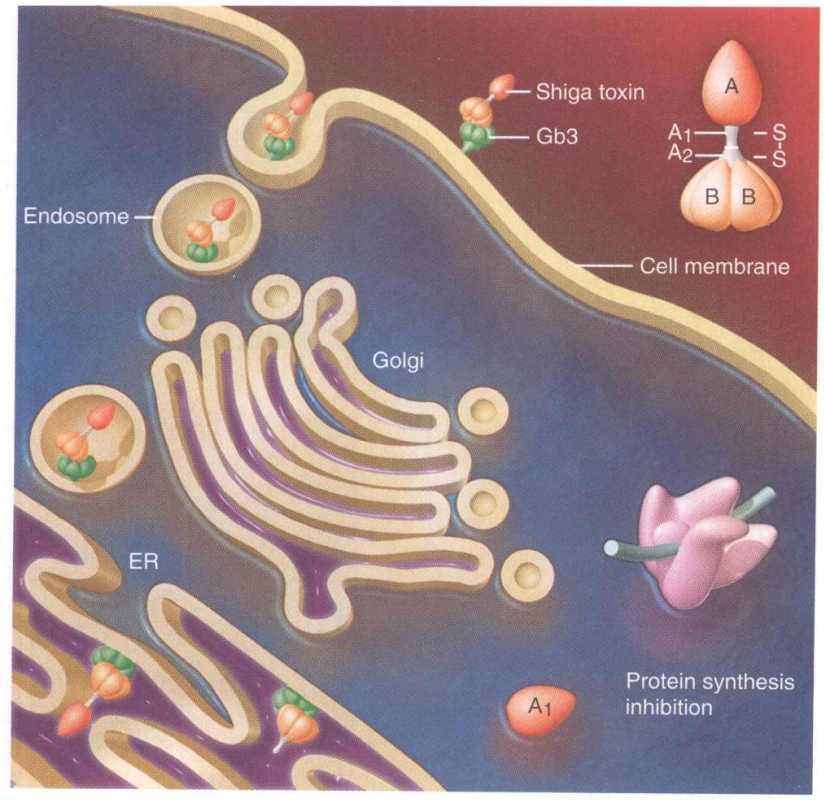

Figure 26-1 Classical paradigm of verotoxin-induced cellular toxicity in diarrhea-associated hemolytic-uremic syndrome. Verotoxins (VTs) are AB_5 exotoxins produced by pathogenic strains of enterohemorrhagic *Escherichia coli*, most prominently *E. coli* O157:H7. They are composed of five identical B subunits noncovalently bonded to a single A subunit in a donut-shaped pentameric ring. The A subunit consists of the enzymatically active A1 fragment and smaller A2 fragment. VT binds to susceptible cell surfaces, particularly endothelial cells, via a Gb_3 glycolipid receptor. This initial binding is followed by receptor-mediated endocytosis, retrograde transport of the toxin through the *trans*-Golgi apparatus and endoplasmic reticulum (ER). During its retrograde transport through the cell's acidic, intracellular compartments, VT is cleaved by furin to release the enzymatically active A1 fragment into the cytosol, where it potently inhibits protein synthesis by a direct and specific activity on ribosomes.

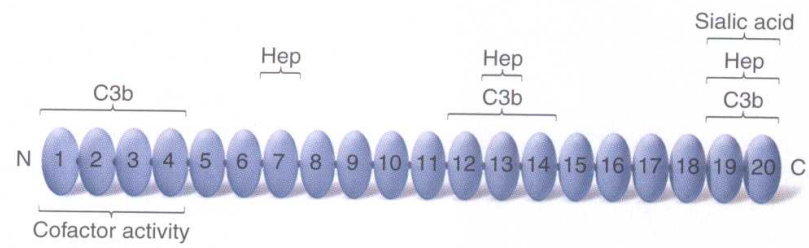

Figure 26-2 Modular organization and critical binding sites of human factor H. Factor H is a plasma-borne regulator of complement activation composed of 20 homologous subunits of approximately 60 amino acids termed short consensus repeats (SCRs) or complement control protein (CCP) modules. C3b, heparin (Hep), and sialic acid binding sites are depicted, as is the functional importance of SCR1-4 in conferring "co-factor activity" to the functional molecule. SCR19-20 represents a mutational "hot spot" in patients with atypical hemolyic-uremic syndrome, comprising over 70% of all disease mutations.

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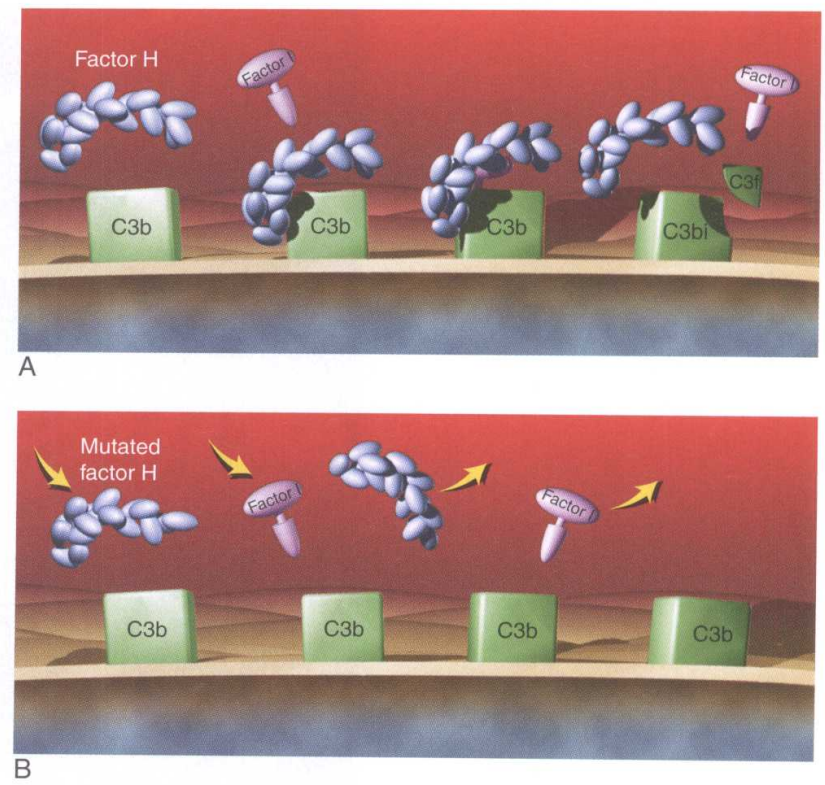
Plate 2

Figure 26-3 Mechanism of action of plasma-borne factor H in protection of endothelial cell surfaces against activation of the alternative pathway of complement in diarrhea-negative hemolytic-uremic syndrome (D-HUS). In the normal individual **(A)**, plasma-borne factor H binds C3b deposited on a damaged (or activated) endothelial cell surface. This interaction is critical in regulating the formation of C3bBb, the alternative pathway C3 convertase, and mitigating complement-mediated host cellular injury. Factor H accomplishes this important task by (1) diminishing factor B binding to C3b, thereby preventing the formation of C3bBb; (2) promoting the dissociation of C3bBb (so-called "decay-accelerating activity"); and (3) acting as a co-factor for factor I in the cleavage of membrane-bound C3b (so-called "co-factor activity"). In a patient with atypical HUS **(B)**, factor H is functionally deficient and cannot efficiently regulate the formation of C3bBb deposited on endothelial surfaces. Membrane-bound C3b is now left unchecked to generate C3bBb in an amplification loop that results in endothelial injury and pathologic thrombosis.



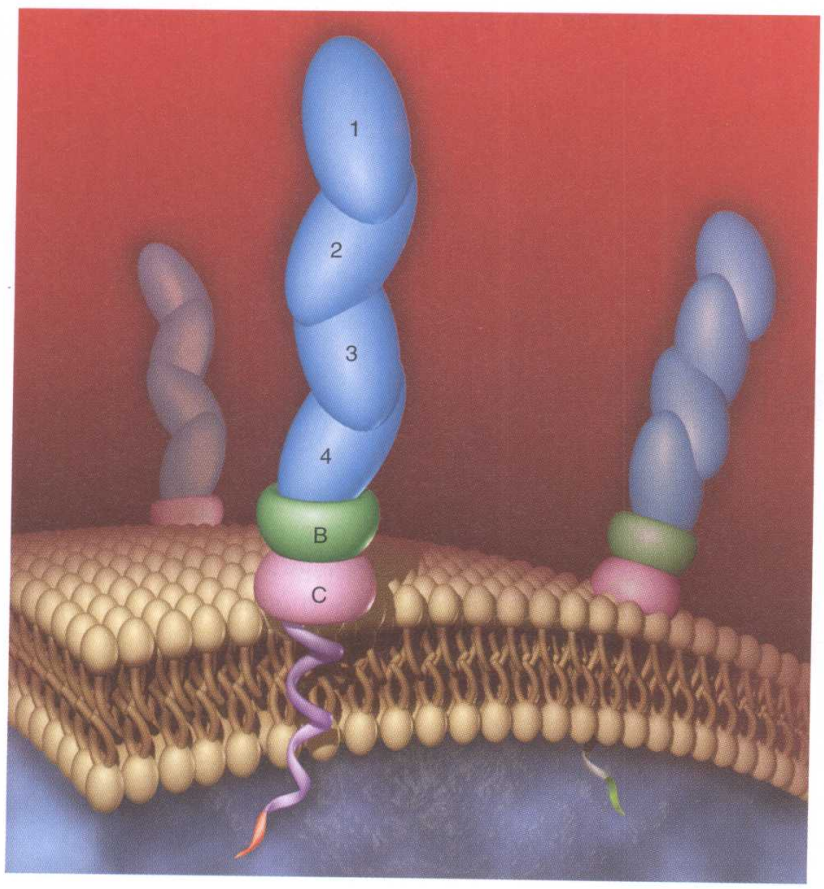


Figure 26-4 Structure of human membrane co-factor protein (MCP, CD46). MCP is a membrane-bound regulator of complement activation that may exist as multiple isoforms in a single cell type. All isoforms share four extracellular, N-terminal SCR domains, akin to those of factor H and other regulators of complement activation. These SCRs are followed by a domain rich in serine, threonine, and proline (STP region), a 12–amino acid juxtamembranous region of unknown sequence homology, transmembrane domain, cytoplasmic anchor, and cytoplasmic tail. The four major isoforms of MCP do not contain the A exon, and all utilize the C exon, while the B exon is alternatively spliced to generate BC- and C-containing STP regions. To date, all disease mutations in atypical hemolytic-uremic syndrome target the shared SCR4 domain.

Plate 3

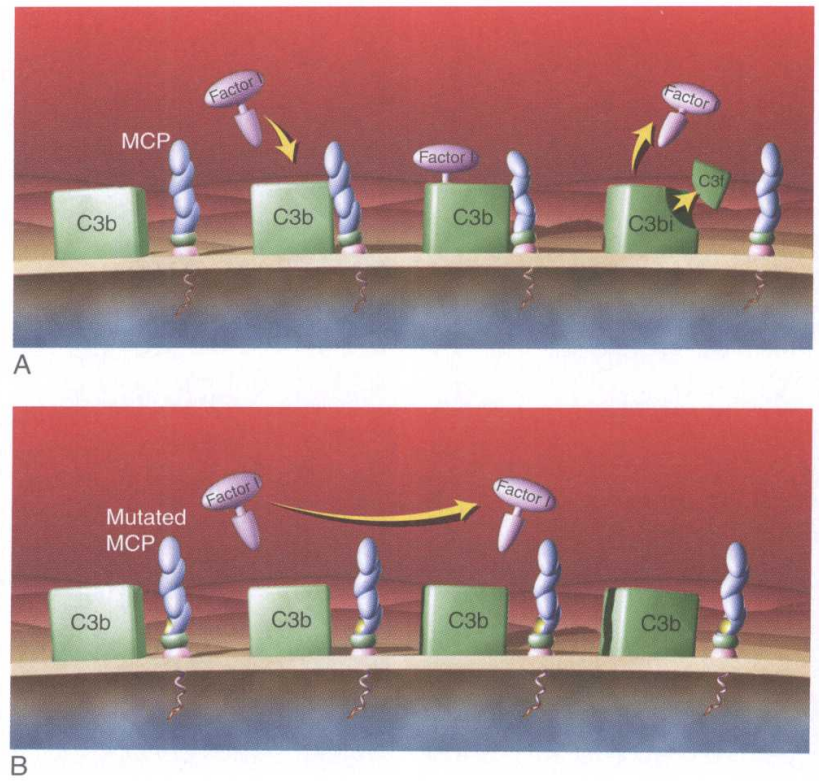


Figure 26-5 Mechanism of action of cell surface human membrane co-factor protein (MCP) in protection of endothelial cells against activation of the alternative pathway of complement in diarrhea-negative hemolytic-uremic syndrome (D-HUS). In the normal individual **(A)**, cell surface MCP binds C3b deposited on a damaged (or activated) endothelial cell surface. This interaction is critical in regulating the formation of C3bBb, the alternative pathway C3 convertase, and mitigating complement-mediated host cellular injury. MCP accomplishes this important task by acting as a co-factor for factor I in the cleavage of membrane-bound C3b, so-called "co-factor activity." In a patient with atypical HUS **(B)**, MCP is functionally deficient and cannot efficiently regulate the formation of C3bBb deposited on endothelial surfaces. All known mutations of the *MCP* gene target the SCR4 domain. As illustrated, the mutant MCP protein is most representative of a T822C transition previously described in two families (see text). Membrane-bound C3b is now left unchecked to generate C3bBb in an amplification loop that results in endothelial injury and pathologic thrombosis.

Figure 26-6 Structure of ADAMTS13 (a disintegrin-like and metalloprotease with thombospondin type I motifs). ADAMTS13 is the plasma-borne von Willebrand factor-protease. It is composed of a series of protein motifs including (from the N-terminus) a signal peptide, propeptide, reprolysin-like metalloprotease domain, disintegrin-like domain, thrombospondin repeat (TSR), cysteine-rich domain, ADAMTS spacer domain, seven additional TSRs, and two CUB (complement components C1r/C1s, urinary epidermal growth factor and bone morphogenic protein-1) domains. Acquired or inherited deficiencies of ADAMTS13 activity are causally linked with thrombotic thrombocytopenic purpura.

Plate 4

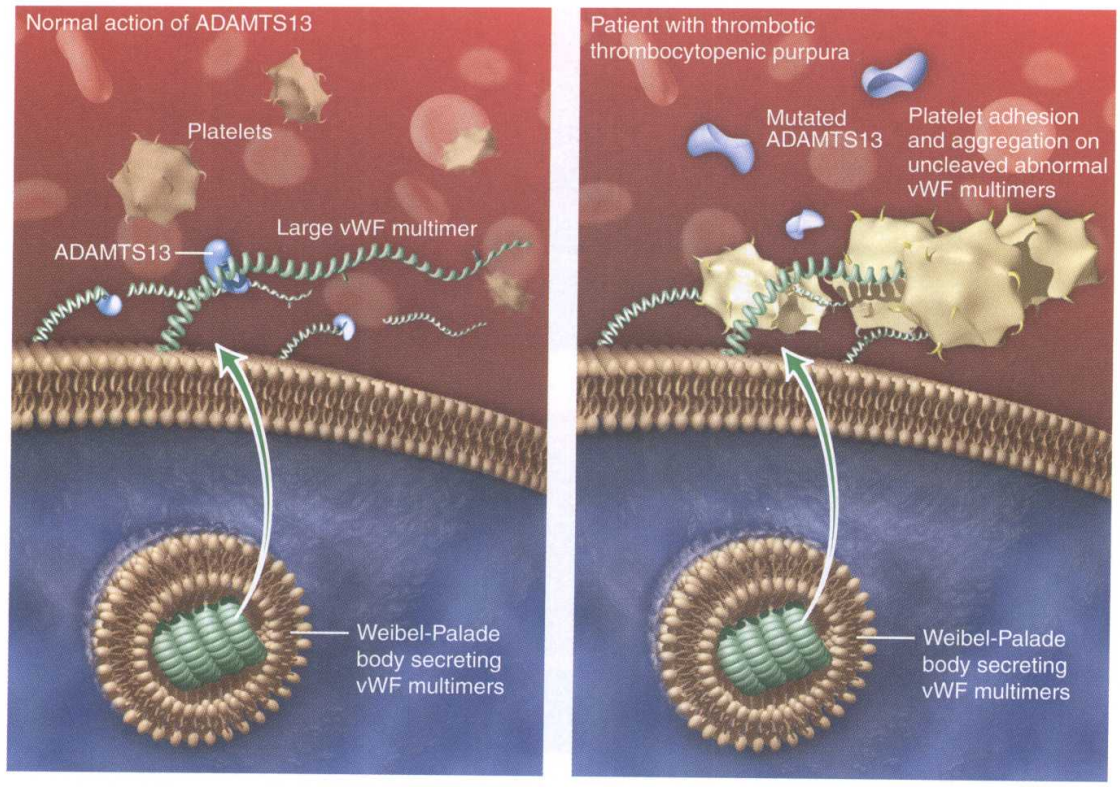


Figure 26-7 Mechanism of action of ADAMTS13 in normal individuals and patients with thrombotic thrombocytopenic purpura (TTP). Secretagogues stimulate endothelial cells to secrete "unusually large" von Willebrand factor (vWF) multimers from their intracellular storage sites, the Weibel-Palade bodies. Attached to the cell surface (and any exposed subendothelial matrix), these vWF multimers uncoil under the influence of high fluid shear stress, exposing sites for attachment of circulating platelets (via an interaction with platelet gp1bα receptors) and cleavage by ADAMTS13. In the normal individual **(A)**, ADAMTS13 successfully competes for target sites on uncoiled, surface-bound vWF multimers and cleaves them to produce characteristic vWF degradation products. In a patient with TTP **(B)**, ADAMTS13 activity is severely deficient and cannot effectively compete with circulating platelets for exposed binding sites. This results in platelet aggregation and pathologic thrombosis.

Plate 5

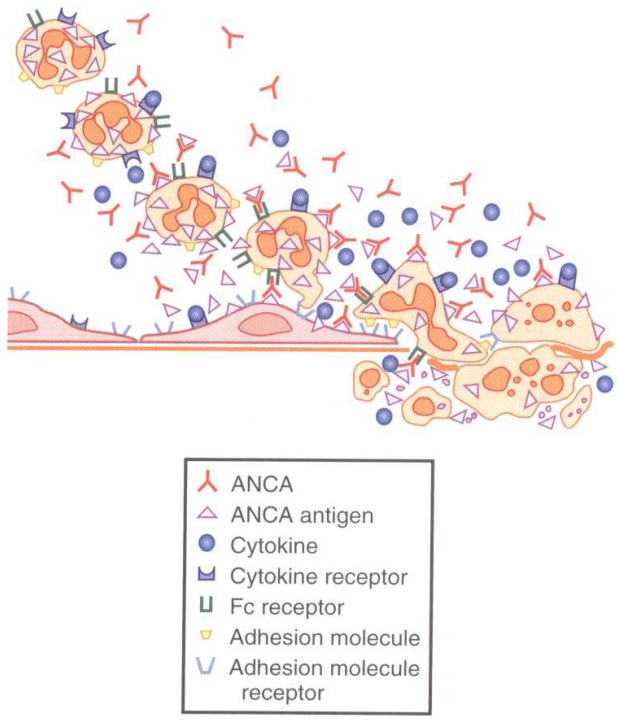


Figure 28-1 Schematic of ANCAs and their interaction with neutrophils causing neutrophil degranulation and tissue injury. (From Jennette JC, Falk RJ: Pathogenesis of the vascular and glomerular damage in ANCA-positive vasculitis. Nephrol Dial Transplant 13[Suppl 1]:19, 1998.)

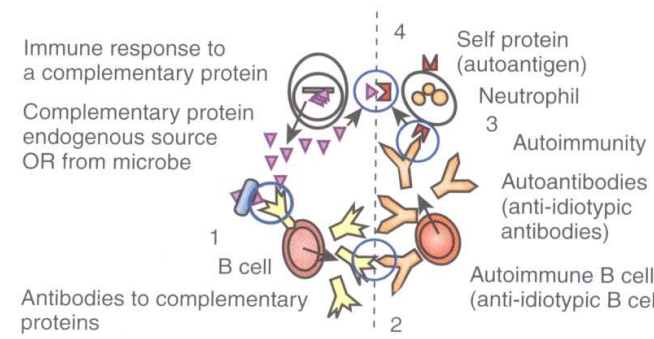


Figure 28-3 Schematic of the theory of autoantigen complementarity. The theory proposes that the immunogen that begins the sequence of events leading to the production of autoantibodies is not the autoantigen or its mimic, but rather its complementary peptide or its mimic. Step 1: The complementary proteins may be introduced by invading microbes or they may be produced by the individual through translation of antisense RNA. An antibody is produced in response to the complementary protein. Step 2: A second antibody is elicited against the first antibody, referred to as an anti-idiotypic response. Step 3: The resultant anti-idiotypic antibodies react with the autoantigen, whose amino acid sequence is complementary to the sequence of the initiating antigen. Step 4: Complementary proteins have a natural affinity because the hydropathy of one is the opposite of the other.

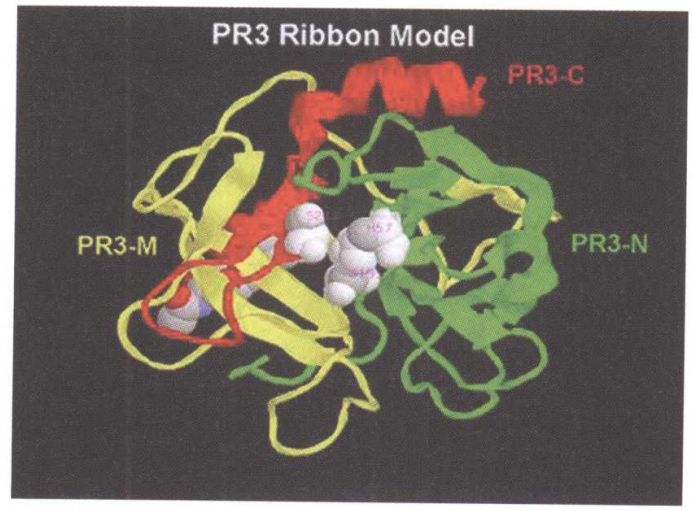


Figure 28-6 Ribbon model of proteinase 3 molecule. The 100–amino acid apoptosis domain appears as the darkest strand.

Contents

SECTION 1

The Tools of Molecular Nephrology

Chapter 1

The Impact of Molecular Genetics on Nephrology

Martin R. Pollak and David B. Mount

It is difficult to overstate the impact of the ongoing revolutions in genetics and genomics on biomedical science. In the three decades since the publication of the first edition of Brenner & Rector's *The Kidney,* the scientific and technologic tools available to biologists have transformed renal science. We now know the molecular basis of a large number of inherited kidney diseases and are seeing steady progress in dissecting the genetics of common and complex renal phenotypes. This, in turn, is just now beginning to influence the treatment of patients with kidney disease.

Our rapidly advancing understanding of the pathobiology of polycystic kidney disease (PKD) is among the best examples. When, just over 20 years ago, Reeders et al mapped the *PKD1* locus to chromosome 16, this sort of genome-wide linkage analysis in extended pedigrees was a laborious task based on Southern blot analysis of restriction fragment length polymorphisms.[1] With the subsequent cloning of the autosomal dominant PKD genes *PKD1* and *PKD2*, and the autosomal recessive PKD gene *PKHD1*, investigations into PKD biology have accelerated at a remarkable pace.[2–4] Genetically faithful animal models of human PKD are now being used to examine new approaches to therapy. The role of cilia in mediating cyst formation is becoming increasingly clear. Genetic screens in zebrafish support the notion of ciliary defects as a unifying theme in cystic disease (moving from "Fish to Philosopher" has clearly become an important biologic tool!).[5,6]

Advances in expression cloning methodologies have led to the identification of a many of the transport proteins that are critical components of the renal tubule. Related human genetic studies and genetic manipulations in the mouse have allowed for the integration of these many molecular components into a much deeper understanding of integrated tubule physiology in health and in disease states.

In some cases, molecular advances have led to novel and highly specific treatments. Work on Fabry disease has progressed from an understanding of the genetic basis of this lysosomal storage disease to the development of effective therapy with recombinant α-galactosidase.[7–9] Of course, the best clinical example of how molecular cloning and protein expression has transformed clinical practice in nephrology is recombinant erythropoietin, administered to most end-stage renal disease patients. In this case, molecular cloning has led to a clear improvement in the quality of life for many patients. The ability to clone genes for production of recombinant proteins and expression in cells and animals has also made an enormous indirect impact on biomedical studies. It is rare now to see a research publication that does not in some way utilize reagents developed through molecular genetic technologies.

Understanding even extremely rare forms of inherited diseases can lead to a much deeper understanding of the pathophysiology of common disease. The cloning of the nephrin gene by molecular genetic analysis of families with congenital nephrotic syndrome helped spark an explosion in our understanding of glomerular biology.[10] Our understanding of the acquired forms of thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome has advanced through a better understanding of inherited mutations in *ADAMTS13* and complement factor H.[11,12] Although this has not yet had a significant direct impact on therapy, these molecular advances allow investigations of novel treatment approaches to be much more focused on the underlying pathobiology.

Knowledge of the genetic basis of inherited disease has direct impact on diagnosis. Although genetic testing has yet to become commonplace in the practice of nephrology, molecular genetic analyses can be expected to become increasingly commonplace in guiding the diagnosis of a variety of disorders, from glomerular and cystic disease to electrolyte abnormalities and hypertension. Such testing will lead to more refined diagnoses and, in turn, better therapeutic decisions.

Although we are unable to predict the details, certainly advances in biomedical research will continue to transform the study and understanding of the kidney. We are just now beginning to see the impact of such advances on patient care. The most common forms of kidney disease are clearly

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