Proteinuria Seen Through the Prism of Podocyte Biology : Podocytes in Uncommon and Common Glomerular Disorders

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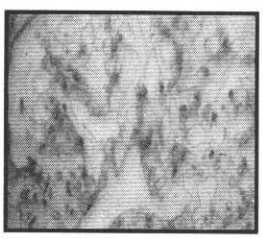
Question:

Why don't nephrologists think about podocytes when they think about proteinuric diseases?

Answer:

Because we can't see them on light microscopy
(only pathologists can see them!)



But podocytes actually represent the majority of the cell-associated glomerular volume

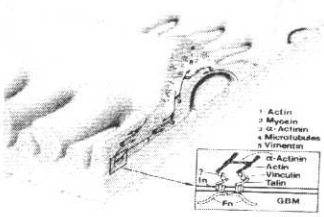
Fractional

podocyte volume	mesangial volume
36 ± 1 %	21 ± 3 %

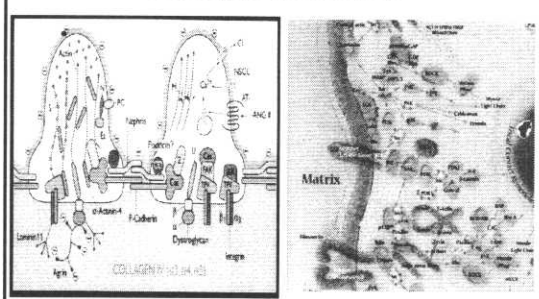
(remaining volume is endothelium, parietal epithelial cells, GBM, capillary lumen, and urinary space)

(Lee et al, KI:53:1398, 1998)

Podocytes are Interdigitating Cells Extending Processes that Cover the GBM

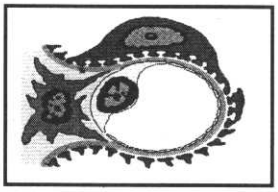


Podocyte Structural Components and Signal Transducers



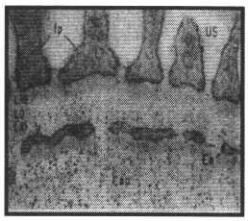
Endlich et al, Contr Neph 10:331, 2001)

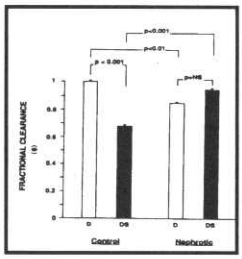
What is the seat of glomerular permselectivity?



Classical teaching: The GBM is the charge- and size-selective barrier to filtration

The GBM as a charge-selective barrier





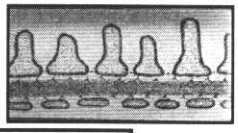
Abrogating the negative charge of the capillary wall facilitates the passage of negatively charged molecules which are otherwise retained in the circulation.
(Kanwar/Farqhsur)

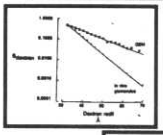
Dextran sulfate clearance
(Guasch et al, JCI 92:2274, 1993)

But the membranes of the endothelium and the podocyte are also negatively charged and probably contribute to charge selectivity.

In vitro, glomerular cells restricted passage of charged molecules more than GBM alone.

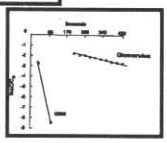
Thus, a cellular role for glomerular charge selectivity





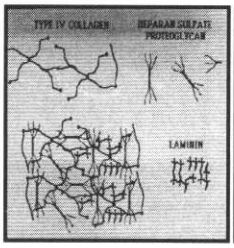
Dextran seiving; Glomeruli are more tight than GBM alone

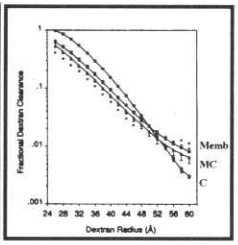
Daniels et al, JCI 92:929, 1993)



Fluorescent marker; Glomeruli are more tight than GBM alone

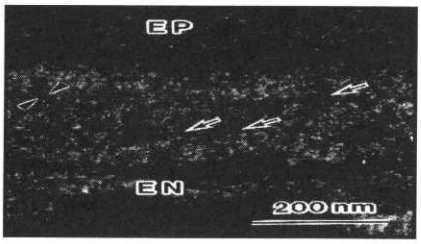
Size-selectivity is also mostly attributed to GBM properties in Nephrotic Conditions





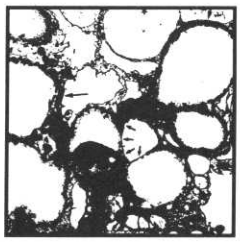
(Guasch et al, JCI 92:2274, 1993)

GBM pores purportedly regulating size-selectivity have been identified by EM in Nephrotic States (minimal change)



Ota et al, JASN 4:1965, 1994)

But podocyte detachment/denudement from the GBM has been incriminated as contributing to proteinuria in some glomerular disorders, potentially contributing to a size-selective defect



(Kriz et al, Kidney Int 45:S64, 1994)

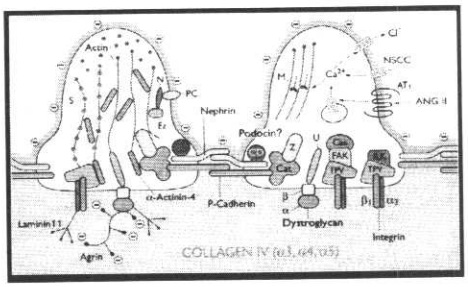
The data strongly suggest that glomerular cells, and particularly podocytes, may be important contributors to the maintenance of glomerular permselectivity

Ways in which podocytes may abrogate glomerular permselectivity:

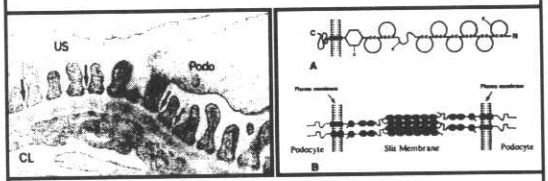
- Changes in nephrin
- Changes in other tight junction proteins
- Changes in the podocyte contribution to GBM ECM
- Changes in podocyte-GBM attachment via integrins and focal adhesions
- Changes in cytoskeletal structure resulting in effacement or GBM denudement
- Apoptosis/detachment
- Angiotensin II-dependent mechanisms
- Changes in signal transduction pathways which mediate these processes

Major new evidence that podocytes may contribute substantially to the maintenance of glomerular permselectivity:

Nephrin

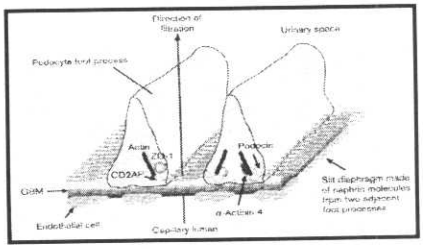


Nephrin
A Podocyte Slit Membrane Protein



(Kawachi et al, Am J Phys, 1997) (Ruotsalainen et al, PNAS, 1999)

Nephrin is like Glomerular Wrapping Paper



Trygvasson and Wartiovaara, Contr Neph 10:543, 2001)

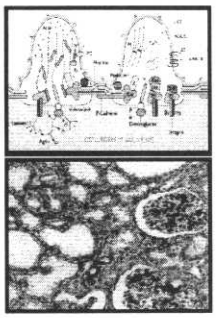
Infusion of an antibody to nephrin in rats induces proteinuria, but it takes between 2 and 24 hours to develop

(Blantz et al. JASN 4:1957, 1994))

Finnish Congenital Nephrotic Syndrome

- Disorder encountered predominantly in Finland, but seen elsewhere as well
- Prenatal onset of severe proteinuria
- ESRD evolves rapidly after birth
- Autosomal recessive disorder due to mutations in a gene (NPHS1) located on chromosome 19q13.1
- Gene encodes for nephrin, a 1241 amino acid, 180,000 M_r podocyte protein with intracellular, transmembrane, and extracellular domains

Finnish Nephrotic Syndrome



- LM is non-specific
- Foot process effacement
- Absent slit membrane
- Foot processes *do* interdigitate
- Interdigitating foot processes connect via junctional structures of normal width comprised (probably) of P-cadherin and ZO-1

Questions raised by the association of nephrin mutations with proteinuria

- Is nephrin the ultimate size-selective barrier to ultrafiltration?
  - PAN and $HgCl_2$ nephrosis is associated with nephrin dislocation from the slit membrane and ↓mRNA (Luimula et al. KI 58:1461, 2000)
  - Proteinuria occurs in anti-GBM, anti-Thy 1, and Heymann nephritis without change in nephrin
- Does nephrin predispose to proteinuria by inducing secondary changes in the ECM of the GBM due to podocyte dysfunction?
  - Nephrin neutralization with mAB 5-1-6 induces rapid proteinuria, albeit without inducing structural change in the slit membrane; but nephrin might orchestrate ECM order
- Are there alternative/additional mechanisms for podocyte-induced proteinuria?

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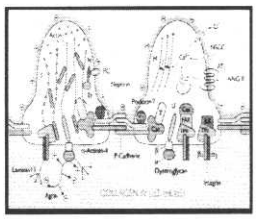
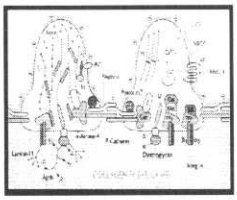
Other Podocyte Junctional Proteins: ZO-1, p-cadherin, alpha-catenin, and CD2-AP



- Epithelial cells are joined by tight junctions (zonula occludens)
- Podocytes are joined by modified tight junctions
- ZO-1, p-cadherin, alpha-catenin, and CD2-AP are members of the modified tight junction proteins connecting podocytes to each other and bridging the slit membrane with the cytoskeleton

Pathology Associated with Dysfunction of Junctional Proteins



- CD2-associated protein
  - genetically deficient mice have congenital nephrotic syndrome and die of CRF ~6wks of age
  - in these mice, there is effacement, but slit diaphragm and interdigitation of foot processes is preserved

(Shih et al. Science 286:312, 1999)

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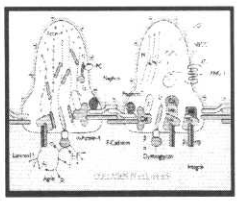
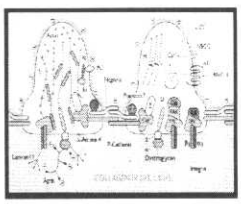
Integrins and Dystroglycans Bind Podocytes to the GBM



- Integrin $alpha_3beta_1$
  - binds foot process to laminin 11 and to collagen IV alpha 3,4, and 5 chains
  - Vinculin, paxillin, and talin are cytoplasmic proteins linking integrins with the actin cytoskeleton and forming the focal adhesion complex
  - Mouse alpha 3 integrin KOs lack foot processes and die in days; cultured podocytes are highly adherent and have abnormal cytoskeleton
    - Dvlpmt 122:3537, 1996; JASN 11:381A, 2000
- Dystroglycan complex
  - consists of utrophin (a transmembranous beta dystroglycan) and alpha-dystroglycan (an agrin and laminin alpha5 receptor)
  - expression is decreased in minimal change but not FSGS
    - (Regele et al. JASN 11:403, 2000)

Integrins and Dystroglycans Bind Podocytes to the GBM: Functional Implications



Inside-out function
eg, coordinates GBM ECM networks (laminin)

Outside-in function
influences cytoskeletal structure/signal transduction/cell cycle events

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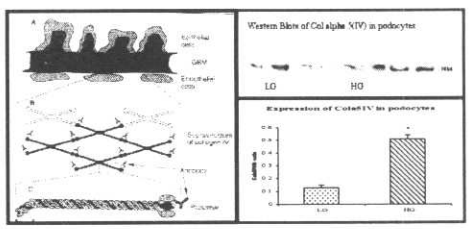
Podocytes Synthesize the Subepithelial GBM: Do Injured Podocytes Make Abnormal or Abnormal Amounts of GBM?



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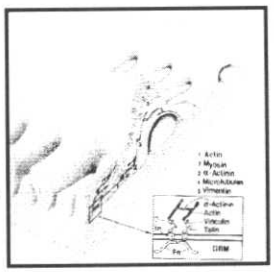
What is Foot Process Effacement?

Retraction of adjacent podocytes, characterized by:

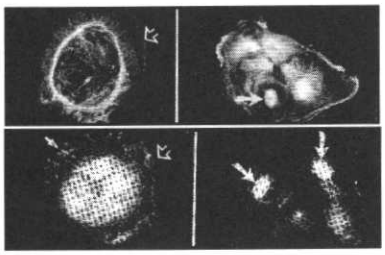
- Simplification of interdigitation pattern
- Cytoskeletal changes
- Shortened slit membranes



Foot process effacement has variably been viewed as the cause of proteinuria and/or the result of proteinuria

The new genetic KO mouse models linking effacement to specific junctional protein and cytoskeletal disruption which lead to proteinuria argue for the argument that effacement causes proteinuria

Complement Activation Disrupts Podocyte Actin Cytoskeleton and Focal Contacts



Left-normal actin cytoskeleton

Right-complement injured actin cytoskeleton

Left-normal talin focal contacts

Right-complement injured talin focal contacts

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Podocytes Detach and are Excreted in Urine in Glomerular Diseases

- Podocytes are excreted in urine:
  - In diabetes
    - NDT 15:1379-83, 2000
    - Diabetes Care 23:1168-71, 2000
  - In SLE DPGN
    - Nephron 87:192, 2001
    - Am J Med Sci 320:112, 2000
  - In IgA nephropathy
    - Am J Neph 20:373, 2000
  - In FSGS
    - Am J Neph 20:175, 2000

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Effects of Angiotensin II on Podocytes

- Podocytes have functioning A II receptors
  - (Nitschke et al, KI 57:41, 2000; Gloy et al, JCI 99:2272, 1997)
- In Heymann nephritis, ACEi maintain the filtration slit frequency
  - (Remuzzi et al, Lab Invest 79:1501, 1999)
- ACEi prevent ZO-1 redistribution and proteinuria in aging rats (Macconi et al, JASN 11:477, 2000)

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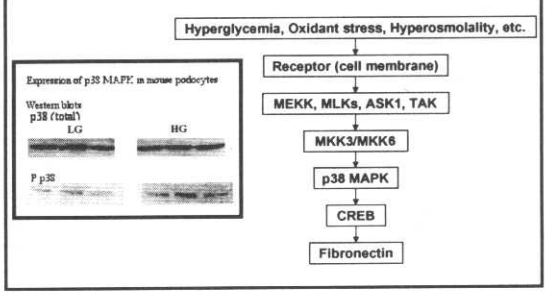
Glucose Activates Signal Transduction via the P38 Pathway in Podocytes



Protein Phosphorylation Patterns are Crude Indicators of Signal Transduction Activity

- Chemical toxins such as protamine sulfate, aminonucleoside of puromycin, and complement induce changes in podocyte shape in vitro and induce proteinuria in vivo. In vitro, podocyte exposure induces:
  - Increased cytoplasmic phosphorylation
    - (Reiser et al, KI 57:2035, 2000)
  - Decreased phosphorylation at podocyte focal contacts (talin, vinculin, paxillin complex)
    - Topham et al, KI 55:1763, 1999)

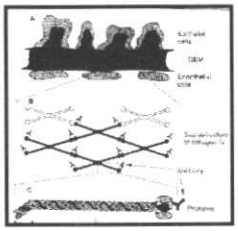
Multiple mechanisms may be operative in mediating the podocyte contribution to the maintenance of glomerular permselectivity. Primary or secondary disturbances in structural and/or functional podocyte proteins contribute to podocyte pathology and abrogation of glomerular permselectivity

How Podocytes Are Involved in Glomerular Disease

- Primary
  - Genetic disorders in which aberrant podocyte constituents, products, or signaling induce dysfunction
- Secondary
  - Disorders in which podocytes are injured, inducing aberrant podocyte constituents, products, shape, and function
    - Injury may be secondary to immune events or metabolic stressors

Alport Syndrome: A Primary Podocyte Disorder

- Prevalence ~1:5000
- X-linked
  - ~85% affected families
  - collagen α5(IV) mutation
- Autosomal dominant (Chr 2)
  - ~1% affected families
  - col α3(IV) splice mutation
    - col α3 and α4 share a promotor
- Mutation in α3, α4, or α5 suppresses the other 2 chains and cause collagen α1 and α2 overexpression

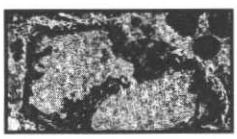


Alport Syndrome: A Primary Podocyte Disorder

- Renal manifestations
  - hematuria, proteinuria, progressive renal insufficiency
  - Extrarenal (variably expressed)
    - hearing loss, ocular defects, granulocyte inclusions, esophageal and/or genital leiomyomatosis, thrombocytopathia

Thin Basement Membrane Syndrome: A Primary Podocyte Disorder

- Due to a mutation in the collagen α4(IV) chain
- No associated retinal, ocular, or hearing abnormalities
- May coexist with Alport syndrome
- Most patients have microscopic hematuria (~85%), but heavy proteinuria may occur in a minority



•Overall a good prognosis (J Clin Path 43:32-8, 1990; AJKD 23:605-18, 1994)

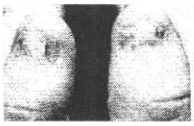
•There have been occasional reports of families with a progressive renal insufficiency (KI 51:1596-01, 1997)

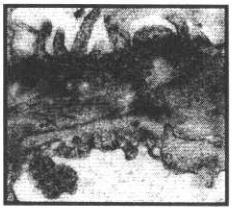
Nail-Patella Syndrome: A Primary Podocyte Disorder

- Incidence ~1/50,000
- Mutations of LMX1B gene on chr 9q34 (Dreyer et al, Nat Genet, 1998)
  - Gene encodes a transcription factor
  - Different mutations may cause either abnormal protein or DNA binding of the transcription factor, depending on the mutation locus
- Extrarenal disease
  - dysplastic nails
  - hypoplastic patellas
  - iliac horns
    - other bony abnormalities (scoliosis, straight clavicles, rib/scapula abnormalities, spina bifida occulta, arched palate)
  - elbow abnormalities
- Renal disease occurs in ~30-50%
  - proteinuria/ hematuria
  - impaired concentration & acidification
  - ~15% progress to ESRD

(Dreyer et al, Nat Genet 19:46, 1998)

Some Characteristic Features of the Nail-Patella Syndrome





- Dysplastic, hypoplastic, displaced patellae
- Iliac horns
- Elbow abnormalities causing impairment of full arm extension

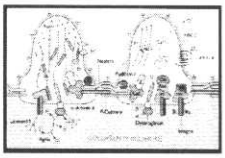
Monogenic Focal and Segmental Glomerulosclerosis:

Primary Podocyte Disorders

Autosomal Recessive FSGS (NPHS2)

(Genetics)

- Caused by mutation in NPHS2 (or SRN1) on chr 1q25-31 (Fuchshuber et al, Hum Molec Genet 4:2155, 1995)
- Gene encodes for podocin, a 383 aa, 42,000 M_r membrane protein, unique to the podocyte in the kidney
- Some homology to MEC-2 in C elegans, which links ion channels to cytoskeleton
- Missense, frameshift, and nonsense mutations have all been reported in individual families



Autosomal Recessive FSGS (NPHS2)

(Clinical aspects)

- Steroid-resistant childhood proteinuria usually presenting between the ages of 3 mos and 5 yrs, but occasionally later
- Progresses to ESRD
- Has been found in some individuals with apparent idiopathic FSGS
- Does not recur in renal allografts
- Standard microscopic analyses (LM, IF, EM) are indistinguishable from idiopathic FSGS.
- Some patients show only foot process effacement.

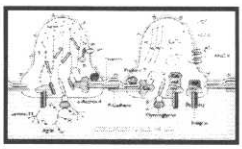
Autosomal Dominant FSGS (ACTN4)

(Genetics)

- Caused by mutations in ACTN4 on chr 19q13 (Kaplan et al, Nat Genet 24:251, 2000; Mathis et al, KI 53:282, 1998)) or 11q (1 family)(Winn et al, Genomics 58:113, 1999)
- 19q13 gene encodes for α-actinin-4, which cross-links and bundles actin filaments & interacts with cytoskeletal, cell-surface, and signalling molecules
- Penetrance is < 100%; thus disease expression dependent on additional factors

The mutant protein shows increased affinity for actin filaments in vitro (Kaplan et al, Nat Genet 24:251, 2000)

Important in maintaining cell shape, adhesion, and movement



Autosomal Dominant FSGS (ACTN4)

(Clinical aspects)

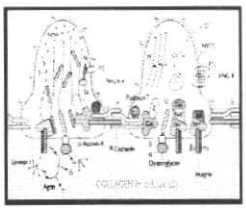
- Adult-onset proteinuria (starts non-nephrotic) with slow progression to ESRD
- Penetrance is *not* 100%. There are some individuals with the gene but without even microalbuminuria!
- Does not recur in renal allografts
- Light microscopy is indistinguishable from idiopathic FSGS

Wilms' Tumor Gene (WT1) Mutations: Primary Podocyte Disorders

- Wilms' tumor
- Denys-Drash syndrome
  - mutations in exon 9 WT1
  - Triad of
    - progressive glomerulopathy
    - Wilm's tumor
    - pseudohermaphroditism
- Frasier syndrome
  - mutations in WT1 intron 9 splice donor site
  - FSGS
  - pseudohermaphroditism
  - gonadoblastoma
  - reported in 2 XX females

- These mutations change the ratio of WT1 +KTS:-KTS isoforms
  - (refers to the presence or absence of lys-ser-thr)
- +KTS WT1 may be involved in RNA splicing
- -KTS WT1 may be involved in transcription regulation (Larsson et al, Cell 81:391, 1995)

FSGS due to an Abnormal Integrin: A Primary Podocyte Disorder



- Major podocyte integrin is $\alpha_3 \beta_1$; there may be minor amounts of β_4
- Congenital nephrotic syndrome secondary to FSGS also reported in an infant with homozygous mutation in β_4 integrin
  - child also had pyloric atresia and epidermolysis bullosa

(Kambham et al, AJKD 36:190, 2000)

Experimental FSGS: Primary Podocyte Disorders

- CD2-AP knockouts
  - interacts with nephrin cytoplasmic domain (Shih et al, Science 286:312, 1999)
- Insertional inactivation of Mpv17
  - may regulate MMP-2 expression; involved in metabolism of ROS (Weiher et al, Cell 62:425, 1990; Reuter et al, Mol Biol Cell 9:1675, 1998; Zwacka et al, EMBO J 13:5129, 1994)
- Rho GDI-α knockouts
  - regulates G-protein activity (Togawa et al, Oncogene 18:5373, 1999)
- TGF-β1 or GH overexpression (Kopp et al, Lab Invest 74:991, 1996; Wang et al, KI Supp 39:S90, 1993)

A Classification of Primary Podocyte Disorders by Type of Dysfunction

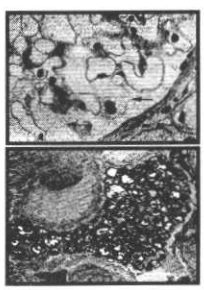
- Abnormal Products/Constituents
  - Alport syndrome
  - Thin basement membrane
  - Congenital Finnish nephrotic syndrome (NPHS1)
  - Autosomal dominant FSGS (NPHS2, podocin)
  - Autosomal recessive FSGS (α-actinin-4)
  - FSGS β_4 integrin
- Abnormal Signaling
- Abnormal transcription
  - Nail-Patella syndrome
  - WT1 mutations

How Podocytes Are Involved in Glomerular Disease

- Primary
  - Genetic disorders in which aberrant podocyte constituents or products induce dysfunction
- Secondary
  - Disorders in which podocytes are injured, inducing aberrant podocyte constituents, products, shape, and function
    - Injury may be secondary to immune events or chemical/metabolic stressors

Fabry Disease

- X-linked inborn error of metabolism resulting from deficiency of α-galactosidase A
- Globotriaosylceramide accumulates in epithelial and vascular endothelial lysosomes
- Syndrome predominantly affects males, and includes progressive renal insufficiency, CAD, CVA, acral paresthesias, angiokeratoma, corneal and lenticular opacities, and hypohidrosis
- A recombinant enzyme is reported to diminish endothelial deposits and plasma levels of ceramide



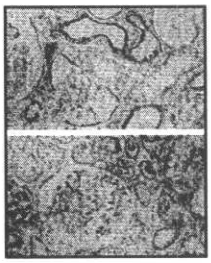
Eng et al, NEJM 345:9, 2001)

특별 강연

HIV Nephropathy

Podocytes and Tubular Epithelial Cells Harbor HIV

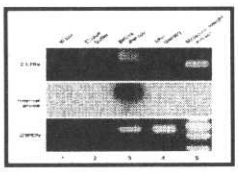
- Pathogenesis of HIV nephropathy may be due to direct infection of podocytes and tubular cells
- HIV (gag, full-length viral RNA) can be detected in renal epithelial cells during acute HIV infection (A) and during treatment with HAART (B)



(Winston et al. NEJM:26:1979, 2001)

•In situ hybridization for HIV-1 RNA before (upper) and after (lower) HAART therapy

HAART Improved Podocyte Markers and Renal Histology in HIV Nephropathy



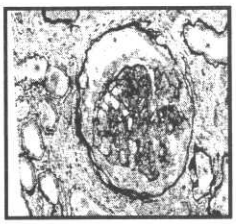
•Circular DNA indicative of recent cellular infection was seen before but not after HAART Rx

(Winston et al, NEJM:26:1979, 2001)

- HAART
  - diminished new HIV infection of renal cells (no circular DNA)
  - restored synaptopodin expression
  - suppressed the expression of proliferation marker Ki-67
  - improved acute glomerular capillary collapse, podocyte hyperplasia and effacement, tubular microcysts, and tubulointerstitial infiltrates
- The authors argue that the small amount of viral protein generated by residual transcripts may be insufficient to sustain nephropathy

Collapsing Focal and Segmental Glomerulosclerosis

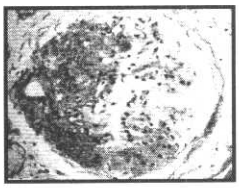
- Represents regression from the terminally differentiated state in which podocytes re-enter the cell cycle and multiply
- Infection with parvovirus B19 has been shown in podocytes, parietal and tubular epithelial cells by in situ hybridization, and have been implicated as a cause for podocyte growth dysregulation
  - (Mougdil et al , KI 59:2126, 2001)



Idiopathic Focal and Segmental Sclerosis

Some Podocyte Changes in FSGS

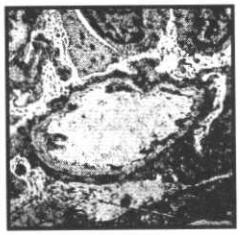
- Frequent loss of urinary podocytes which is reversible with drug-induced remission
  - (Nakamura et al, Am J Neph 20:175, 2000)
- Diminished staining for synaptopodin, particularly in segments of sclerosis
  - (Srivastava et al, KI 59:118, 2001)
- Dystroglycan staining is preserved (distinct from findings in minimal change!)
  - Regele et al, JASN 11:403, 2000))



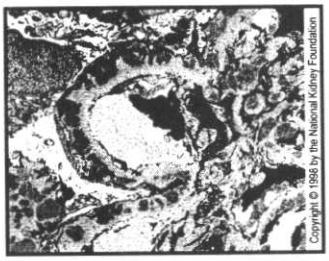
•As in minimal change, a circulating permeability factor has been implicated (at least in ~1/3 cases
- (Savin et al, NEJM 334:878, 1996)

Minimal Change

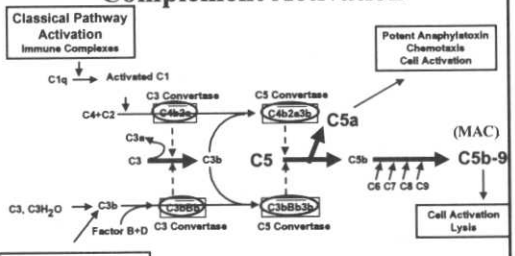
- Vascular permeability factors have long been implicated its pathogenesis
  - (Yoshizawa et al, Nephron 51:370, 1989; Tomizawa et al, Nephron 4:157, 1985)
- Characterized by diminished dystroglycan staining which is reversible by steroid-induced remission
  - (Raats et al, Am J Pathol 156:1749, 2000; Regele et al, JASN 11:403, 2000)
- Urinary podocyte loss was not observed in any of 12 children with minimal change
  - (Nakamura et al, Am J Neph 20:175, 2000)



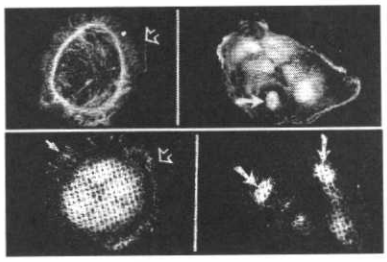
Membranous Nephropathy: An Immune Complex Disease



Complement Activation



Complement Activation Disrupts Podocyte Actin Cytoskeleton and Focal Contacts



Left-normal actin cytoskeleton

Right-complement injured actin cytoskeleton

Left-normal talin focal contacts

Right-complement injured talin focal contacts

Membranous Nephropathy: A Disorder of (Secondary) Podocyte Injury

IMMUNE COMPLEX DEPOSITION

In situ immune complexes — Circulating immune complexes

COMPLEMENT ACTIVATION & MAC INSERTION

GLOMERULAR V. EPITHELIAL CELL INJURY

- Altered cellular metabolism-↑ROS, lipid peroxidation
- Altered growth factor/cytokine secretion
- Altered cell-matrix and cell-cell interactions
- Altered cytoskeleton

PROTEINURIA

Diabetic Nephropathy

Pathogenesis of DN

Glucose/AGE
Uptake, Metabolism, Signal Transduction

Hyperlipidemia

Systemic/Intraglomerular ↑ BP

Growth factors, Cytokines and their receptors

Integrins, Selectins, Cytoskeleton

Oxidative metabolic pathways

Diffuse or Nodular Mesangial Extracellular Matrix Expansion

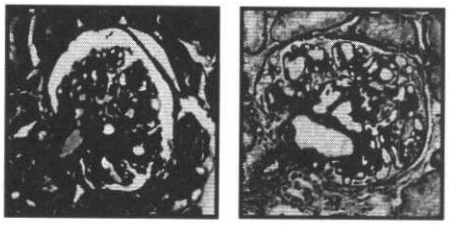
A relationship between declining creatinine clearance and expansion of the mesangium has been demonstrated in patients with Type 1 diabetes mellitus

(Mauer et al, JCI, 1984)

However, within the diagnostic categories of normoalbuminuria, microalbuminuria, and overt proteinuria, there is substantial overlap in the degree of mesangial expansion

Chavers et al: NEJM 320:966, 1989
Fioretto et al: Diabetes 43:1358, 1994
Adler et al, KI, in press 2001

There is substantial overlap in the degree of mesangial expansion in patients classified predominantly by albuminuria



Worst normoalbuminuric Best overtly proteinuric

Evidence for Podocyte Injury in DN

- Podocyte effacement occurs and is ameliorated by ACEi
  - *Diabetologia* 38:1197-1204, 1995
  - *J Am.Soc Nephrol.* 11:648A, 2000
- Podocyte number is diminished and correlates with albuminuria
  - *J Clin Invest.* 99:342-48, 1997
  - *J Am.Soc Nephrol.* 11:113A, 2000
  - Diabetologia 42:1341-44, 1999
- Podocytes are excreted in urine
  - NDT 15:1379-83, 2000
  - Diabetes Care 23:1168-71, 2000

A Speculative Revisionist Version of the Pathogenesis of Diabetic Nephropathy

Mesangial Expansion
encroaches/occludes capillary lumen
(slow progression)

+

Podocyte Injury
apoptosis/detachment from GBM/signal transduction change/cytoskeletal change
(proteinuria and accelerated progression)
leading to

Tubulointerstitial Fibrosis/Atrophy
(final common pathway for progressive renal insufficiency)

Many genetic disorders characterized by proteinuria are actually primary podocyte diseases.

More are likely to be discovered.

Most common glomerular disorders characterized by proteinuria involve secondary podocyte injury which probably contributes in a significant way to progression of renal disease.