

Physiopathologie des glomérulonéphrites extracapillaires

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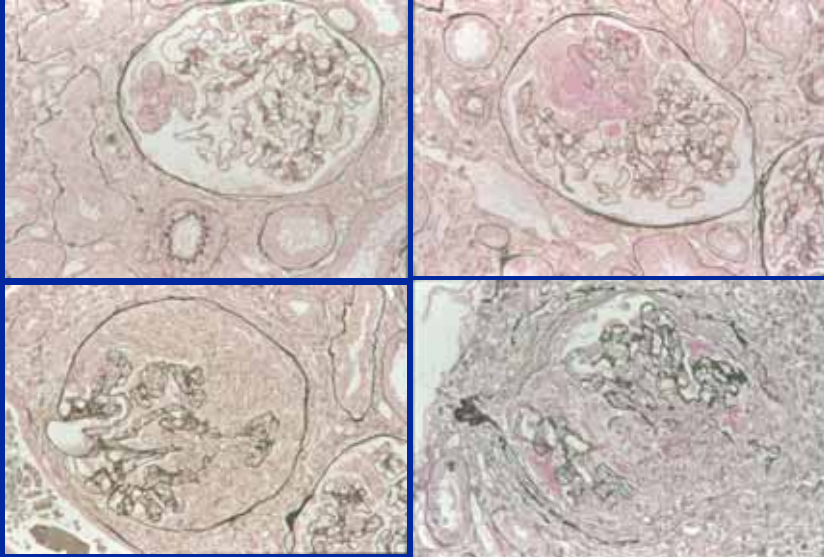
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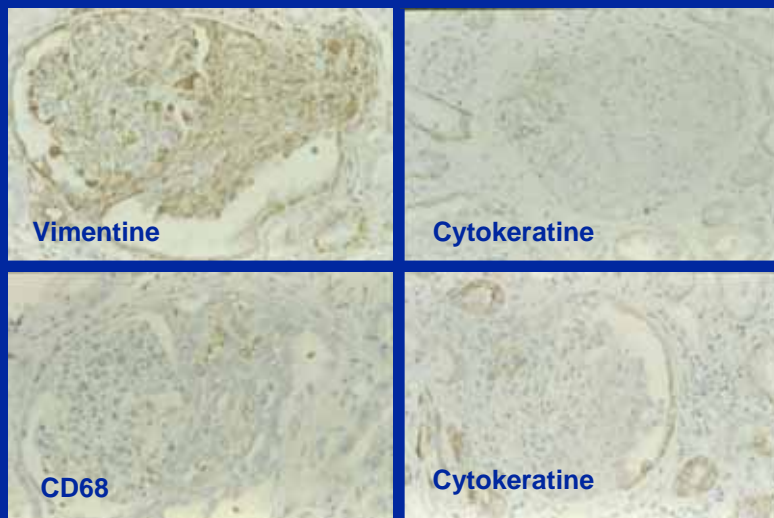
Glomérulonéphrite extracapillaire Principales caractéristiques

- prolifération extracapillaire
- insuffisance rénale rapidement progressive: GNRP
- mauvais pronostic en l'absence de traitement
- urgence thérapeutique+++:
immunosuppression agressive
- récupération possible de l'insuffisance rénale
- risque de complications léthales

Progression of crescent formation



Cellular composition of glomerular crescents



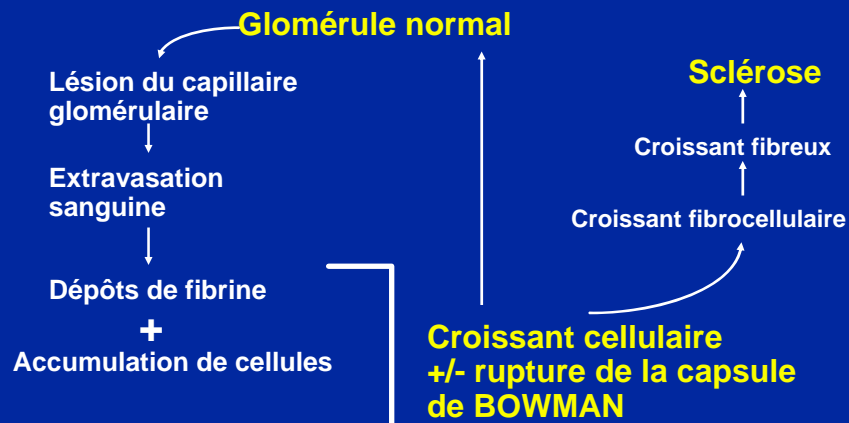
Physiopathologie des croissants (1)

- **Composants cellulaires**
 - Cellules épithéliales glomérulaires
 - » pariétales
 - » viscérales
 - monocytes-macrophages
 - lymphocytes T
 - fibroblastes

Physiopathologie des croissants (2)

- **Composition de la matrice extracellulaire**
 - fibrine
 - fibronectine, laminine
 - thrombospondine
 - ostéopontine
 - collagènes interstitiels (I, III)

Physiopathologie des croissants



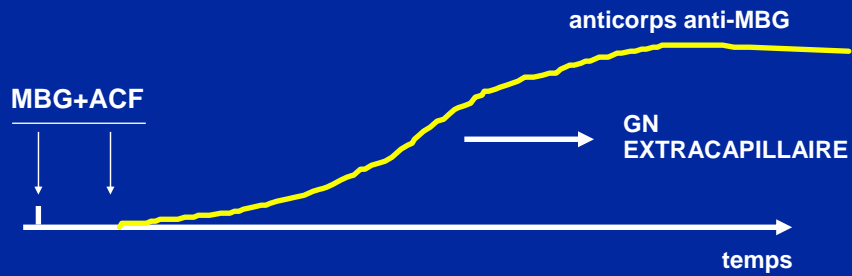
Mechanisms of Injury of the Glomerular Capillary Wall

- **Deposition of anti-GBM antibody :**
 - epitopes= $\alpha 3(\text{IV})$ NC1 domains
 - role of the genetic background and of T cells
 - experimental model: active or passive immunization
- **Deposition of immune complexes :**
 - from the circulation
 - formed in situ
- **Other mechanisms:** ANCA-mediated injury, T cell-mediated injury,...

Physiopathologie des croissants

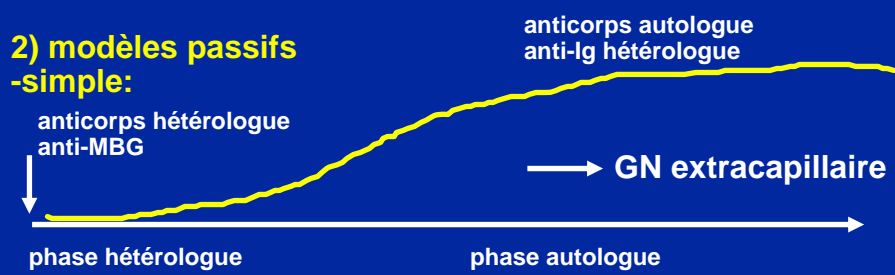
Modèle expérimental: GN par anticorps anti-MBG

1) modèle actif

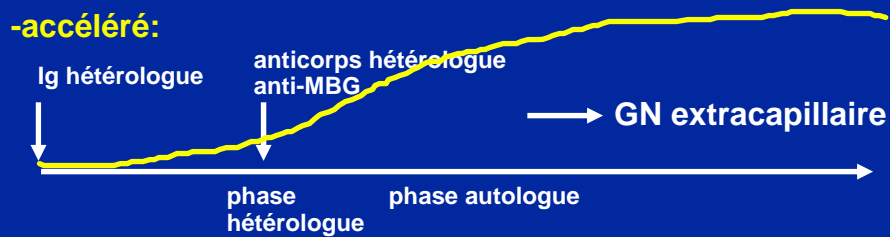


Modèle expérimental: GN par anticorps anti-MBG

2) modèles passifs
-simple:



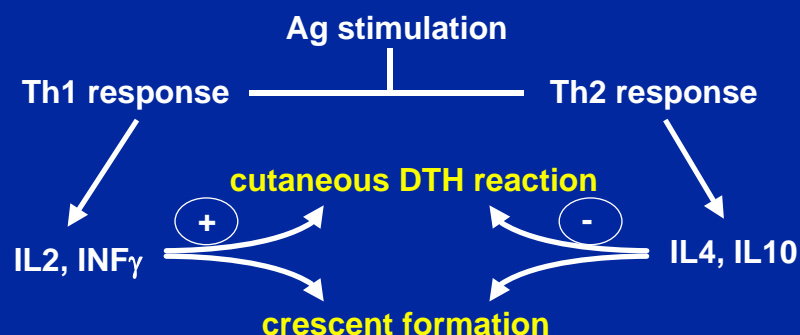
-accélééré:



T cells in crescents: a delayed-type hypersensitivity mechanism

- Evidence of IL2R⁺ mononuclear cells in RPGN
- T cell infiltration correlates with Bowman's capsule disruption
- Inhibition of crescent formation by CTLA-4-Ig, blocking CD28/B7 co-signal for T cell activation
- MAb-induced depletion in T cells demonstrate the requirement for CD4⁺ T cells
- Th1 responsiveness to nephritogenic antigens determines susceptibility to crescent formation

T cells in crescents: a delayed-type hypersensitivity mechanism

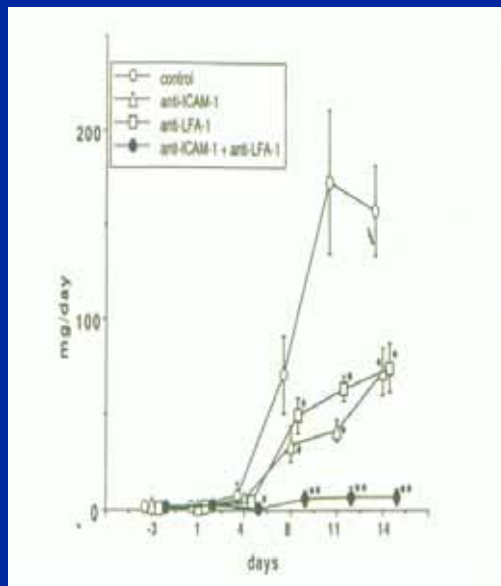
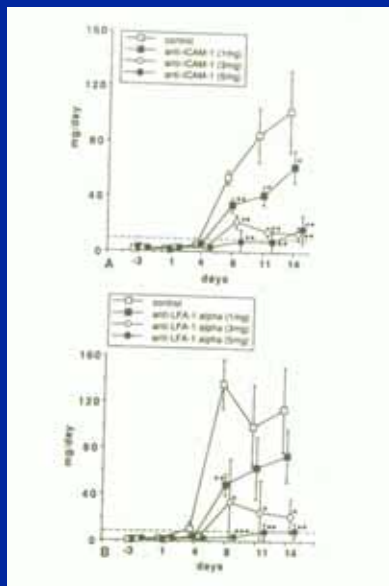


Physiopathologie des croissants (3)

- Médiateurs impliqués:

- complément, dérivés réactifs de O₂,
proteases
- facteurs de la coagulation / fibrinolyse
- cytokines
 - » IL1 α , IL1 β , TNF α
 - » balance INF γ - IL2 versus IL4 - IL10
 - » chémokines: MCP1, MIF, MIP1 α , MIP1 β
- facteurs de croissance: FGFb, PDGF, TGF β
- métalloproteinases et inhibiteurs

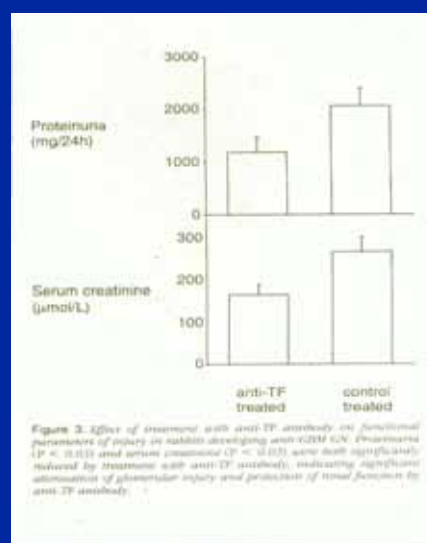
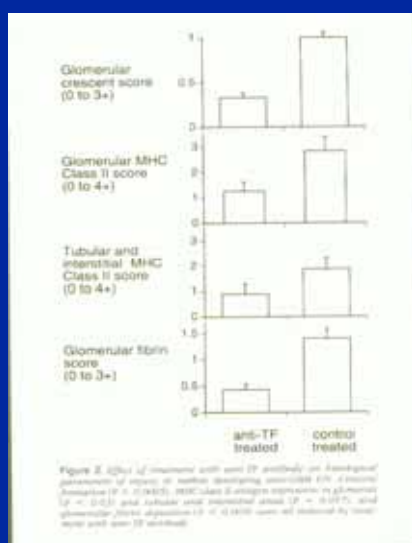
Rôle des molécules d'adhésion



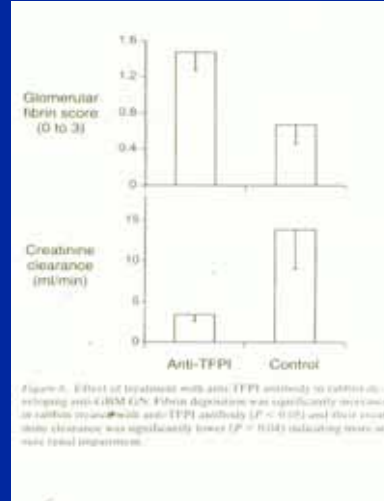
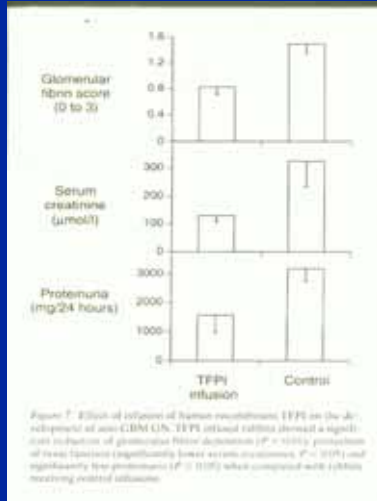
Physiopathologie des croissants Rôle de IL1 et de TNF α

- Synthèse glomérulaire d'IL1+++
- Principale source d'IL1: macrophages
- IL-1 β aggrave la GN par anticorps anti-MBG
- IL-1 ra inhibe la formation des croissants
- IL-1 augmente l'infiltration macrophagique et favorise la progression vers la fibrose
- pas d'effet additif du blocage de IL1 et de TNF α

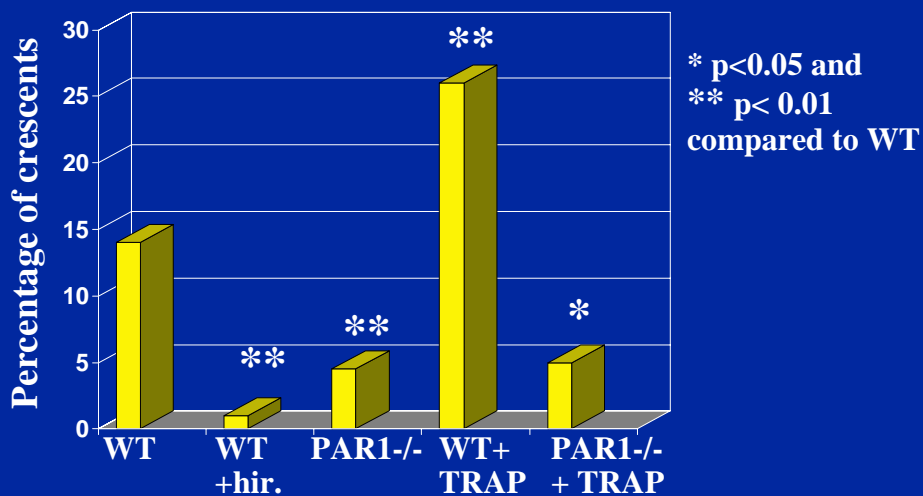
Coagulation et croissants: TF



Coagulation et croissants: TFPI



Crescent Formation in PAR1^{-/-} Mice



Fibrinolyse et croissants

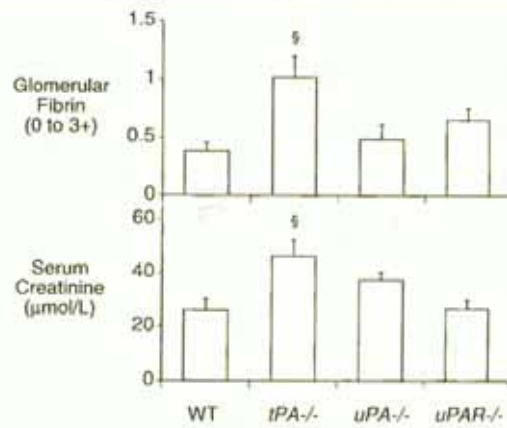


Figure 3. Glomerular fibrin deposition and renal function (sCr) in *tPA*^{-/-}, *uPA*^{-/-}, *uPAR*^{-/-}, and WT mice. [§]*P* < 0.005 compared to WT control by Fisher's PLSD test.

Fibrinolyse et croissants

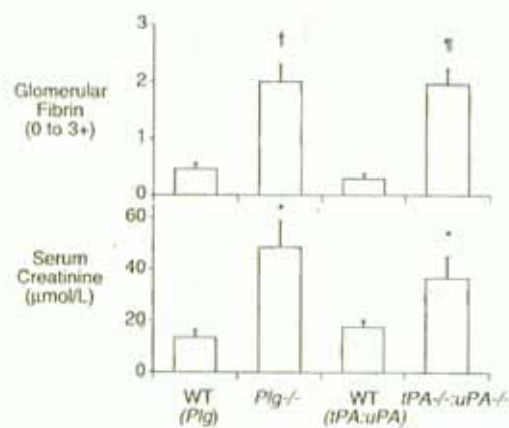


Figure 2. Glomerular fibrin deposition and renal function (sCr) in *Plg*^{-/-}, WT (*Plg*), *tPA*^{-/-}:*uPA*^{-/-} and WT (*tPA:uPA*) mice ([†] indicates *P* < 0.05, ^{*}*P* < 0.01, [‡]*P* < 0.001, compared to appropriate WT control by unpaired *t* test).

Role of leukocytes and intrinsic renal cells in nephrotoxic nephritis

- Leukocytes

- IL-1 β
- IFN- γ

- Intrinsic renal cells

- IL-1R I
- TNF- α
- TNF- α R
- IL-12
- IFN- γ
- MHC II
- CD40
- p27^{kip1}

Reversibility of cellular crescents

- Can reversibility be demonstrated?
YES
- Which factors control the reversibility of crescents?
 - integrity of the Bowman's capsule
 - epithelial cells / macrophages ratio in the Bowman's space
 - local balance between profibrinolytic and antifibrinolytic proteins
 - local balance between MMPs and TIMPs

Progression to Fibrotic Crescents

- **Infiltration and local proliferation of fibroblasts:** role of FGF1 and FGF2 produced by parietal epithelial cells, macrophages and fibroblasts
- **Production of collagen:** role of TGF β
- **Apoptosis:** gradual loss of macrophages, Tcells, and fibroblasts

Crescentic glomerulonephritis studied with knock out mice (1)

KO gene	Severity of GN (compared to WT mice)	Author, year
CD4	↓ ↓	Tipping, 1998
CD8	no change	Tipping, 1998
MHC II	↓ ↓	Li, 1998
μ chain	no change	Li, 1997
IL-10	↑	Kitching, 2000
IL-4	↑	Kitching, 1998

Crescentic glomerulonephritis studied with knock out mice (2)

KO gene	Severity of GN (compared to WT mice)	Author, year
TNF α / β	↓↓	Le Hir, 1998 Ruffel, 1998
IFN γ	no change	Haas, 1995
C3, C4	↓ (±)	Sheerin, 1997
FcR γ (CD40)	↓↓	Park, 1998 Wakayama, 2000
Mac 1 (CD11b/CD18)	↓	Tang, 1997
P selectin	↑ !	Mayadas, 1996

Crescentic glomerulonephritis studied with knock out mice (3)

KO gene	Severity of GN (compared to WT mice)	Author, year
eNOS (NOS1)	↑	Heeringa, 2000
iNOS (NOS2)	no change	Cattel, 1998
Elastase, cathepsin G	↓	Schrigver, 1989 Feith, 1993
PAR1	↓	Cunningham, 2000
t-PA	↑	Cunningham, 1998
Plasminogène	↑	Cunningham, 1998

Physiopathologie des croissants

Conclusions

- **Rôle de l'immunité cellulaire+++**
 - balance Th1 versus Th2
 - réaction de type hypersensibilité retardée
- **Rôle essentiel des cytokines $TNF\alpha$ et IL1**
- **Importance de l'effecteur coagulation et de la thrombine**
- **Réversibilité des lésions et intégrité de la capsule de Bowman**