GROUPE FRANÇAIS D'ÉTUDE DES VASCULARITES Disease Tolerance as a Defence Strategy against Kidney Disease

Glomérulonéphrites rapidement progressives: mécanismes physiopathologiques et perspectives

erapeutiques

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Tissue Damage Control: Disease Tolerance & Resistance



(2014). Trends in Immunology, 1–12.









Genetic Variation For Disease Tolerance



Altered disease curves = > Ageing?



"The normal man is the normative man, being able to introduce new standards, even organic," depending on the environment and livelihoods

 \Rightarrow pathological = "another normal ?"

Georges Canguilhem "Le normal et le pathologique", Paris, PUF, 1966



Integrating Resistance & Disease Tolerance in Disease Curves



Adapted from Schneider, D. S. (2011). PLoS Biology, 9(9), e1001158.

The Glomerular Filtration Barrier



Human vasculitides



2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides.

Long-term patient survival in a Swedish population-based cohort of patients with ANCA-associated vasculitis



Heijl C, et al. RMD Open 2017;3:e000435

Survival of GPA: Population Based Study in UK

Z.S. Wallace et al. / Seminars in Arthritis and Rheumatism 45 (2016) 483-489



Fig. Survival according to the presence of granulomatosis with polyangiitis.

Crescentic Rapidly Progressive Glomerulonephritis (RPGN)

Pauci-immunes

ANCA Activated neutrophils

anti-GBM Abs

anti-α3NC1 / α5NC1 Autoreactive T Lymphocytes

Immune complexes

Auto-antibodies Complement activation Various Mechanisms (Lupus, IgA Nephropathy, infections...)



Common mechanisms causing loss of tolerance of glomerular epithelial cells to vasculitides?

Induction of Mitogenic Glomerular EGFR ligands in Crescentic RPGN ?



Untreated Human Microscopic Polyangiitis (MPA)



Masson

HB-EGF

De novo expression of HB-EGF in podocytes & PECs

MPA 2

Microscopic polyangiitis (MPA) 1 Endocarditis

Po Po Cr Po Pec Po EJJ Cr

MPA 3

MPA 4

MPA 5



Bollée G, Flamant M et al. Nat Med. 2011;17(10):1242-50



Autocrine HB-EGF induces a proliferative and migratory phenotype in podocytes *in vitro*



Primary podocyte outgrowth from decapsulated glomeruli

Conditional deletion of the Egfr gene in podocytes limits glomerular inflammatory destruction



Bollée G, Flamant M et al. Nat Med. 2011;17(10):1242-50



Acting Locally to Stop Crescent Formation?



Bollée G & Flamant M et al. **Nat Med. 2011**;17(10):1242-50. Harris R **Nat Med. 2011**;17(10):1188-9. Editorial. Flamant M, Bollée G, Hénique C, Tharaux PL **Nephrol Dial Transplant. 2012**;27(4):1297-04.

Activation of STAT3 in glomeruli during CGN

Carole Henique

Isolated glomeruli

CT
NTS

p-STAT3
Image: Compared to the second secon





Sustained increase in STAT3 phosphorylation in podocytes 10 days after NTS injection into mice



STAT3 activity is Required for Proliferation of Primary Podocytes



Deletion of *Stat3* in podocytes only is sufficient to limit fatal renal destruction during CGN

Carole Henique



STAT3 Inhibition Blunts Progression of Glomerular Damage and Interstitial Fibrosis





anti-HB-EGF?, anti-IL-6?, anti-STAT3?







A Role for the Epithelial Metabolism In Glomerular Cells Phenotype Switch?

Free fatty oxidation to glycolysis mode?

How does the disease spread to the whole organ?



Nature Medicine doi:10.1038/nm.3159



Healthy Glomerular Epithelial Cells express PPARγ constitutively





RPGN (MPA)





СТ





Is Constitutive PPARγ Kidney Epithelial Expression A Tonic Cytoprotective Mechanism?

François Gaillard



Disturbances of PPAR γ and p-STAT3 Expressions are Widespread and Anti-correlated during late stage of NTS-induced RPGN and TIF





Regulation of PPARγ during Chronic Interstitial Fibrosis?

Control

NTS



PPARγ agonism limits apoptosis in **PAN-injured podocytes**



Protective effects of PPARy agonist in acute nephrotic syndrome



Nephrol Dial Transplant. 2011;27(1):174-181.

Pioglitazone Enhances the Beneficial Effects of Glucocorticoids in Experimental Nephrotic Syndrome



S. Agrawal, M. A. Chanley, D. Westbrook, X. Nie, T. Kitao, A. J. Guess, R. Benndorf, G. Hidalgo & W. E. Smoyer *Scientific Reports* **volume 6**, : 24392 (2016)

PPARy expression in Glomerular Epithelial cells is lost in CGN



Henique et al. J Am Soc Nephrol. 2016;27(1):172-88

Podocyte Selective PPARy Deficiency Aggravates Crescentic RPGN





Pioglitazone Alleviates RPGN in WT mice BUT NOT in Podocyte Selective PPARγ Deficiency



Pioglitazone Alleviates RPGN in WT mice BUT NOT in Podocyte Selective PPARγ Deficiency



Delayed PPARy Agonism Halts Crescentic RPGN



PPARγ AGONISM: A SAFE WAY TO INHIBIT STAT3-DEPENDENT INFLAMMATION AND FIBROSIS?

Integrating Resistance & Disease Tolerance for Therapy



Immunosuppressants

(anti-CD20, CYC, Corticosteroids, MTX, AZA...)