Fibrose rénale
What's new?

Camille Cohen,

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Nephrology department hôpital Bichat, junior group leader centre de recherche pour l'inflammation, INSERM U1149, hôpital Bichat

Epidémiologie de la malade rénale chronique

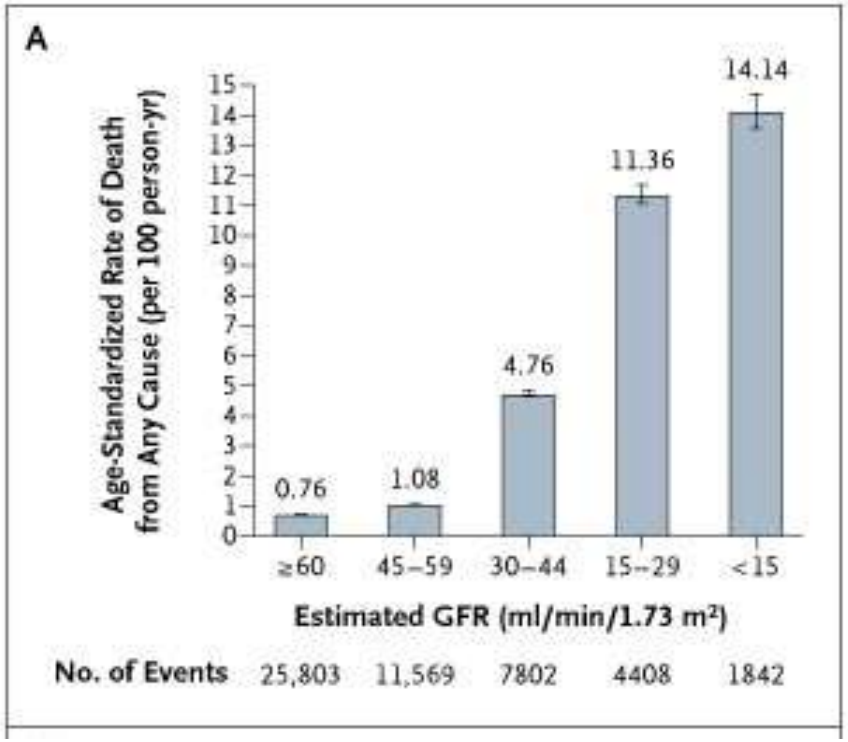
Chronic kidney disease

More than 2 millions of people in France

End-stage renal disease

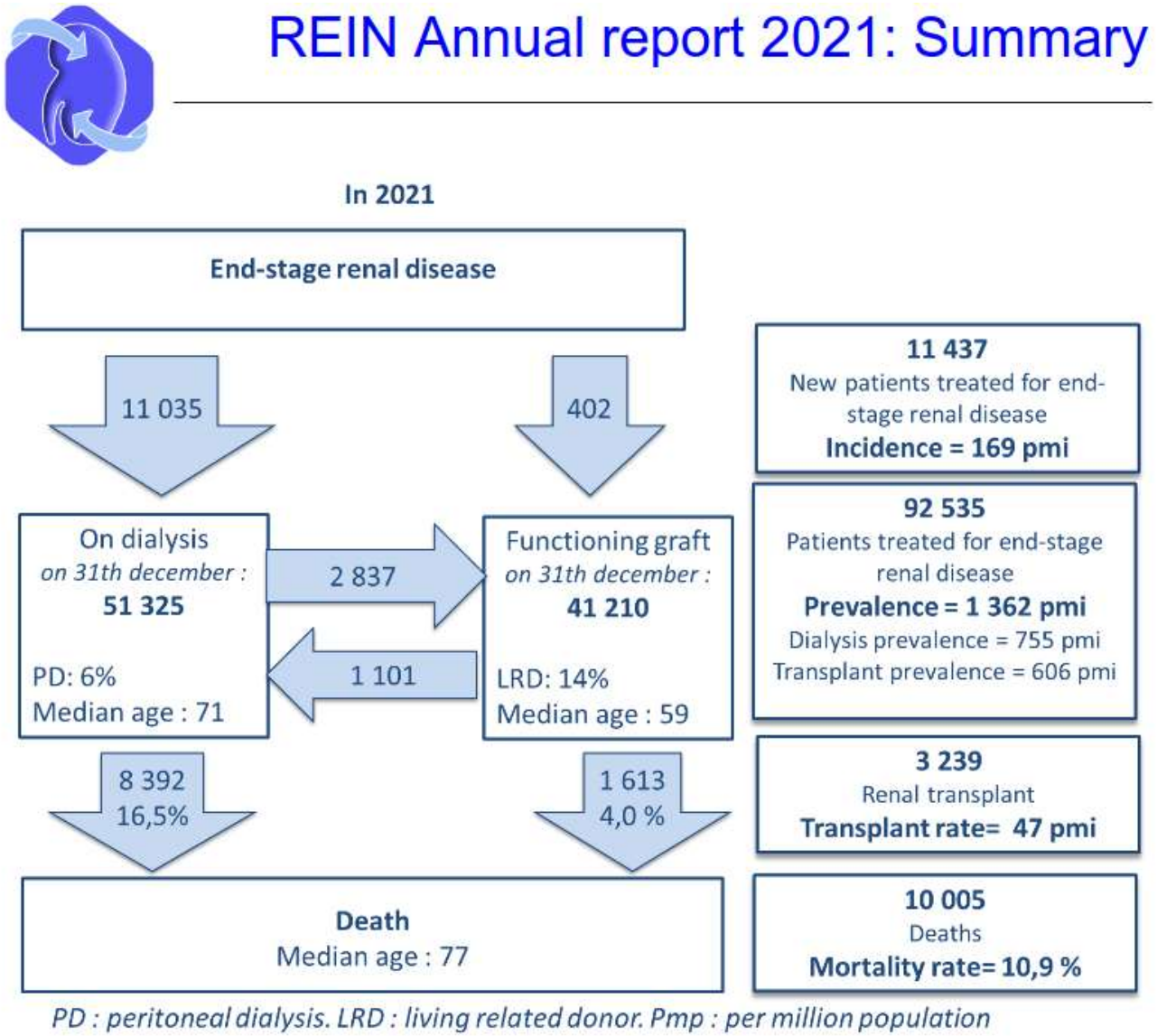
90 000 patients

Agence de la Biomédecine. *Rapport REIN 2021*



Go et al., NEJM 2004
Hill et al. Plos one 2016

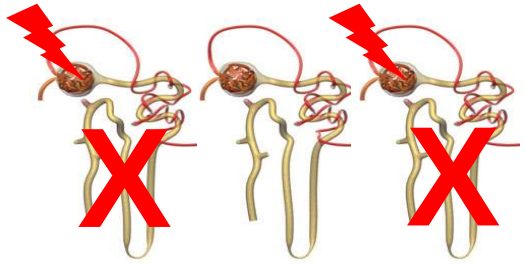
Epidémiologie de la malade rénale chronique en France



Registre REIN 2021

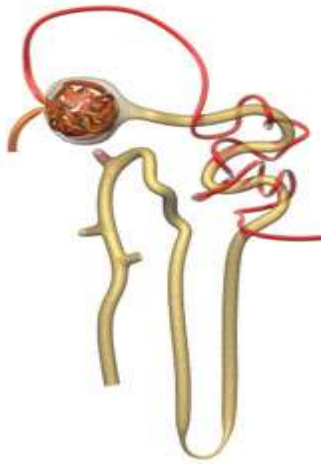
Histoire naturelle de la MRC

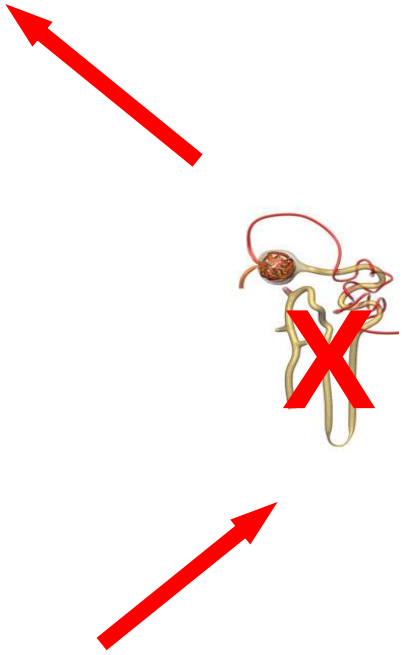
Nephron reduction



Compensatory growth

Functional adaptation



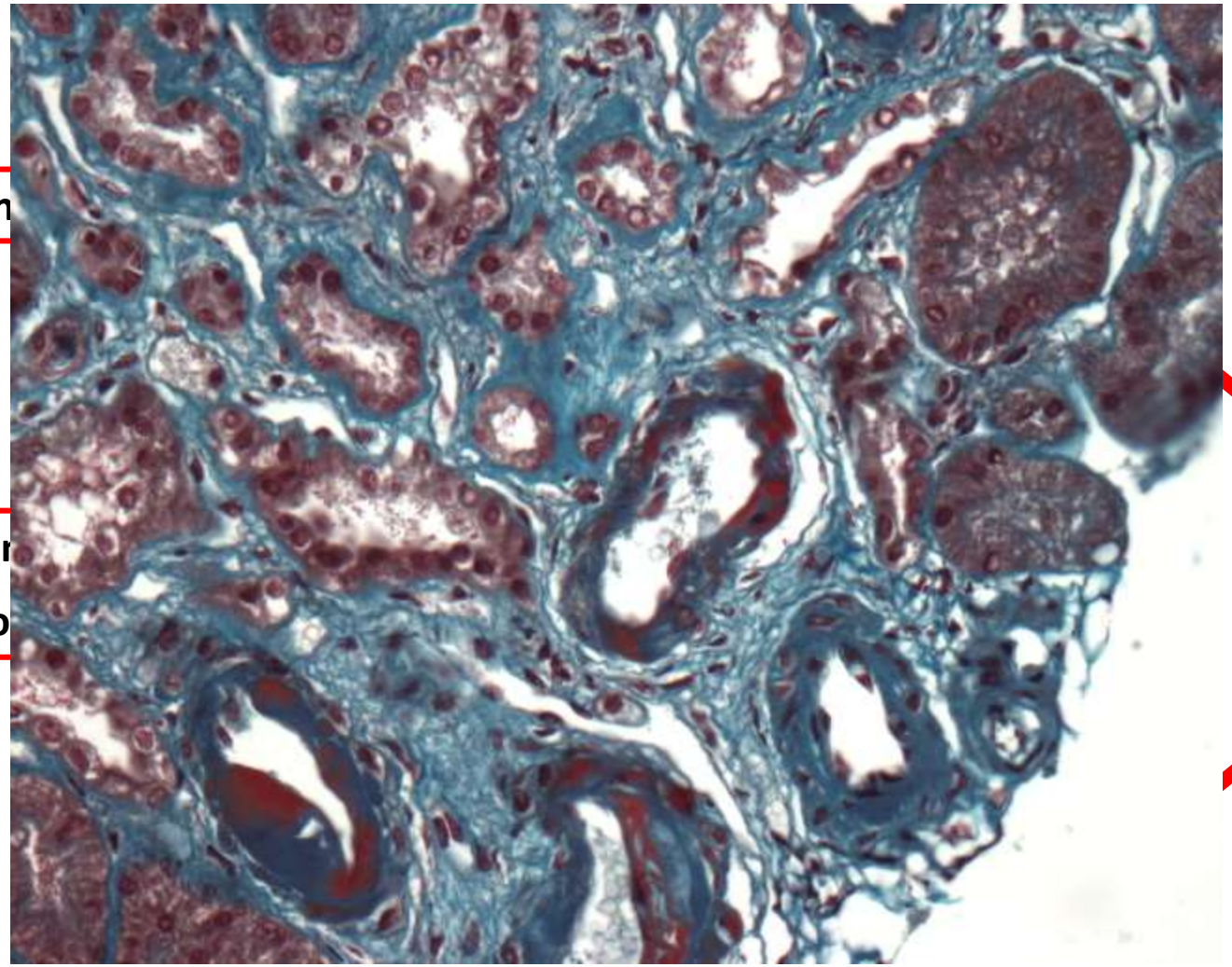


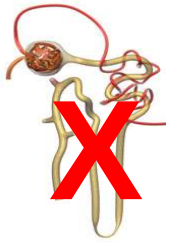
Histoire naturelle de la MRC

Neph

Compen

Functio





Introduction

- Malgré des événements précoces différents selon l'organe et/ou la pathologie, cela se termine par une **expansion et une activation des cellules sécrétrices de la MEC (les myofibroblastes).**

- Comprendre les mécanismes de développement de la fibrose = **comprendre comment apparaissent les myofibroblastes!**

- Des efforts importants ont été déployés pour trouver **l'origine des myofibroblastes dans le rein** : les péricytes et les fibroblastes résidents ont été considérés comme les principaux types cellulaires d'origine.

- Changement phénotypique et moléculaire chez les Fibroblastes = processus de différentiation

Kuppe et al. Nature 2020
Kramann et al. Semin Nephrol, 2014
Humphreys et al. Am J Pathol 2010

Introduction

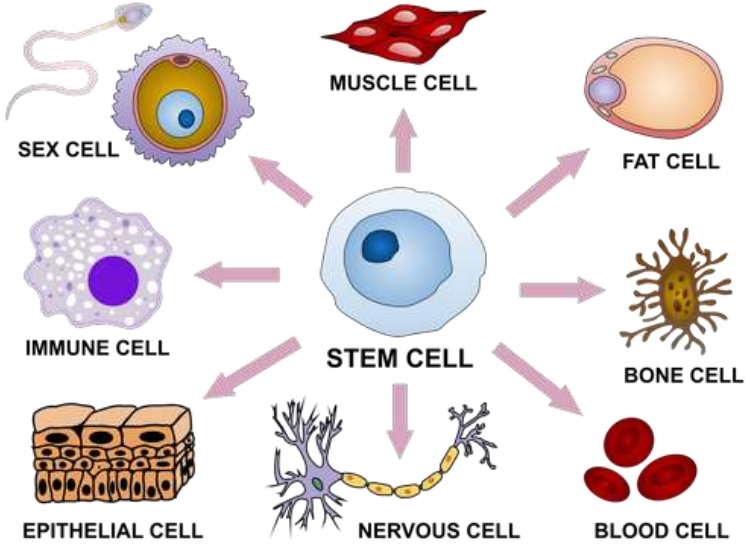
- Les avancées techniques ont permis de mieux comprendre ces processus

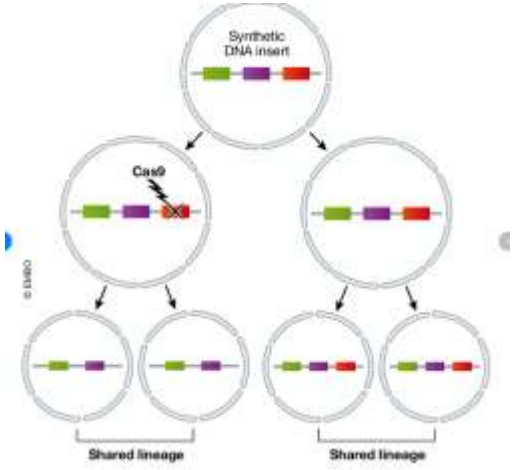
- En particulier les –Omics

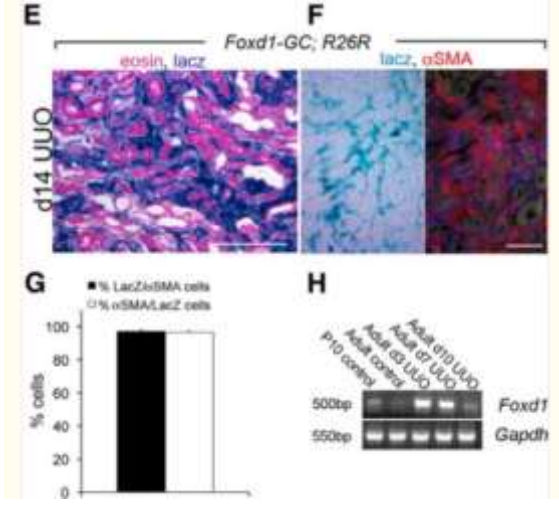
Origine cellulaire des myofibroblastes

- Historiquement : Cell lineage

- Mais pas chez l'homme.
- Approche candidate







Kramann et al. Semin Nephrol, 2014
Humphreys et al. Am J Pathol 2010

Origine cellulaire des myofibroblastes

- Evolution technique: Apport de la transcriptomique?
- Surtout le single cell RNAseq!

Bulk RNAseq

Single cell RNAseq

Origine cellulaire des myofibroblastes

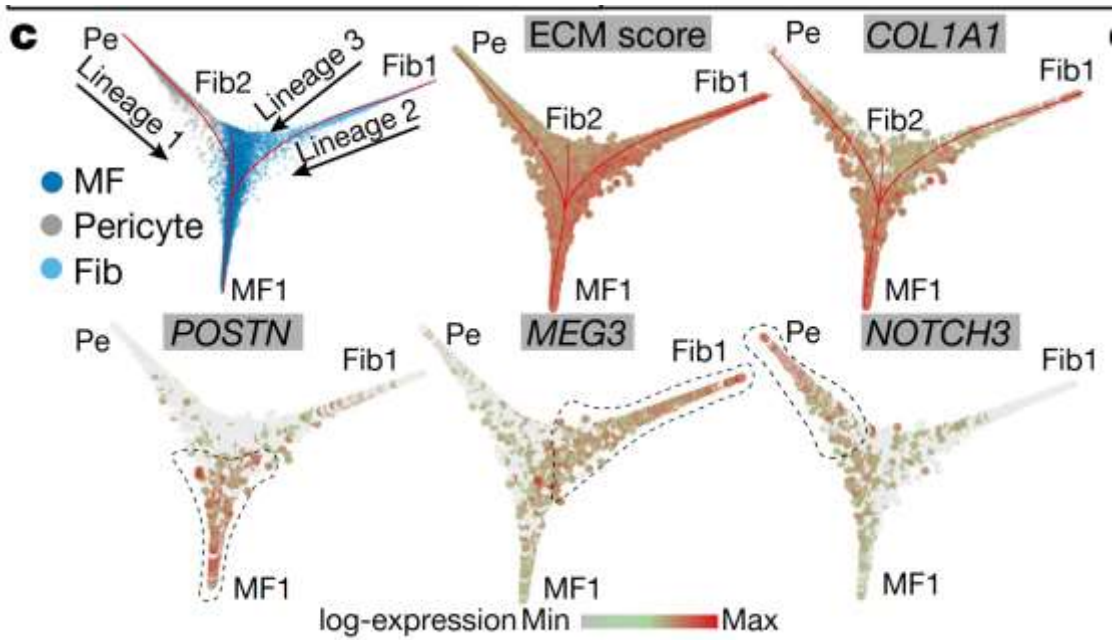
Article

Decoding myofibroblast origins in human kidney fibrosis

https://doi.org/10.1038/s41586-020-2941-1
Received: 30 January 2020
Accepted: 19 October 2020
Published online: 11 November 2020
Check for updates

Christoph Kuppe, Mahmoud M. Ibrahim, Jennifer Kranz, Xiaoting Zhang, Susanne Ziegler, Javier Perales-Patón, Jitske Jansen, Katharina C. Reimer, James R. Smith, Ross Dobie, John R. Wilson-Kanamori, Maurice Halder, Yaoxian Xu, Nazanin Kabgani, Nadine Kaesler, Martin Klaus, Lukas Gernhold, Victor G. Puelles, Tobias B. Huber, Peter Boor, Sylvia Menzel, Remco M. Hoogenboezem, Eric M. J. Bindels, Joachim Steffens, Jürgen Floege, Rebekka K. Schneider, Julio Saez-Rodriguez, Neil C. Henderson & Rafael Kramann

Les myofibro proviennent très majoritairement de fibroblastes résidents et de pericytes



La chute du mythe de la Transition épithélio-mésenchymateuse? oui mais non

JCI The Journal of Clinical Investigation

Epithelial-mesenchymal transition (EMT) in kidney fibrosis: fact or fantasy?

Wilhelm Kriz, … , Brigitte Kaissling, Michel Le Hir

J Clin Invest. 2011;121(2):468-474. https://doi.org/10.1172/JCI44595.

Pas de “vraie EMT” mais :
Dédifferentiation des cellules tubulaires: secretion de molecules profibrosantes et crosstalk avec les fibroblastes.

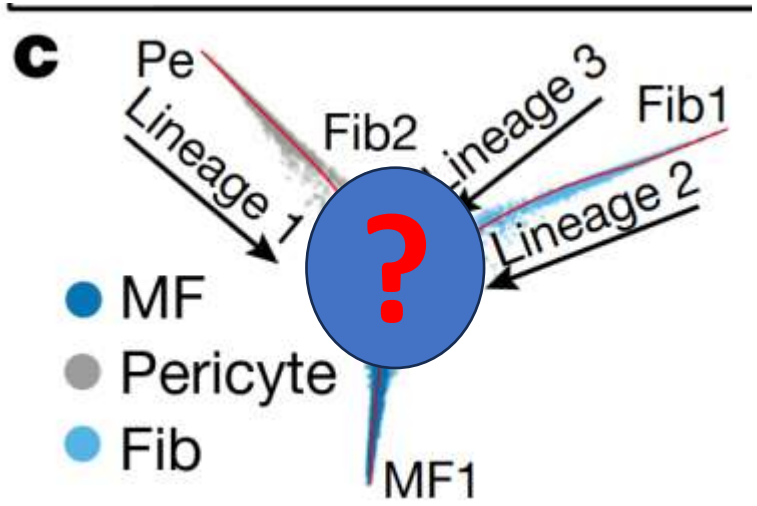
nature medicine

Snail1-induced partial epithelial-to-mesenchymal transition drives renal fibrosis in mice and can be targeted to reverse established disease

M Teresa Grande[1,5,6], Berta Sánchez-Laorden[1,6], Cristina López-Blau[1], Cristina A De Frutos[1,5], Agnès Boutet[1,5], Miguel Arévalo[2,3], R Grant Rowe[4,5], Stephen J Weiss[4], José M López-Novoa[2,3] & M Angela Nieto[1]

Mais que se passe-t-il entre l'origine et la fin?

- Heterogeneité fibroblastique



nature communications

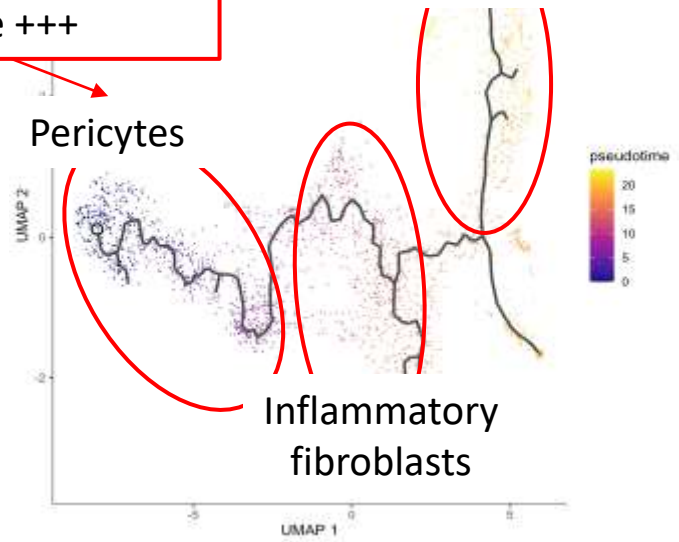
Article

WNT-dependent interaction between inflammatory fibroblasts and FOLR2+ macrophages promotes fibrosis in chronic kidney disease

Root of the trajectory
Litterature +++

ECM-secreting fibroblasts

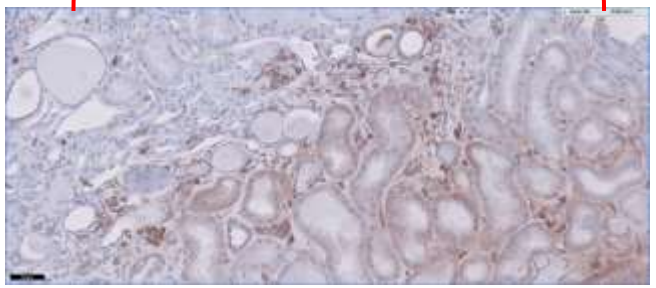
Pericytes



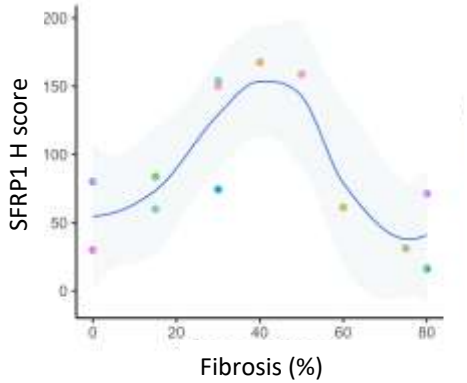
Inflammatory fibroblasts

Mais que se passe-t-il entre l'origine et la fin? Les fibroblastes inflammatoires?

Inflammatory Fibroblasts



Fibro inflammatoires



nature communications

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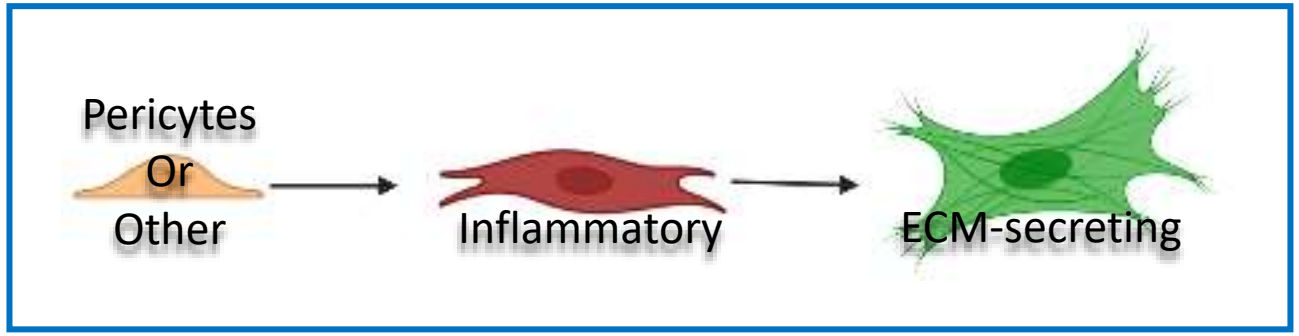


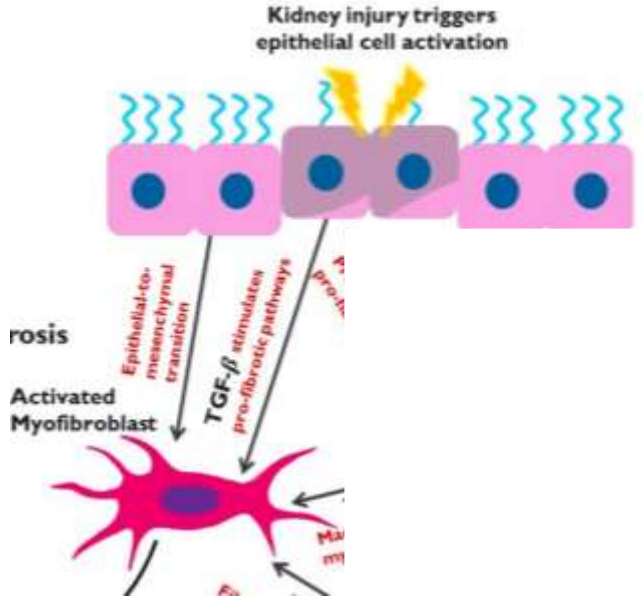
Probablement d'autres états de differentiation intermédiaires

QUESTION SUIVANTE?

Communication cellulaire? D'où viennent les signaux qui favorisent la differentiation des fibroblastes?

- Les fibro ne sont pas tout seul!

Communication cellulaire?
Le tubule?

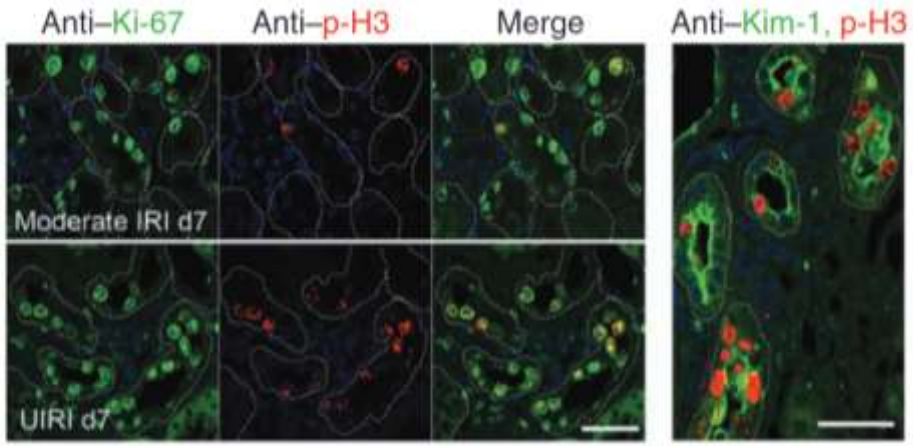


nature medicine

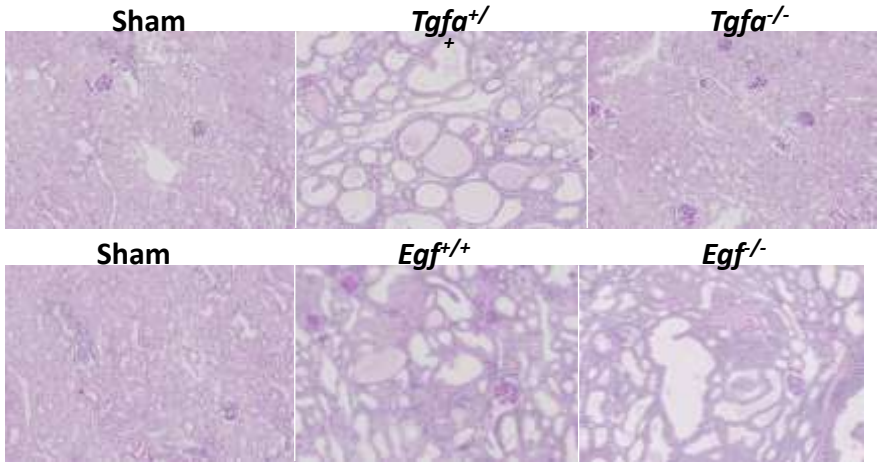
Blocage du cycle cellulaire

Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury

Li Yang[1,2], Tatiana Y Besschetnova[1,3], Craig R Brooks[1], Jagesh V Shah[1,3,4] & Joseph V Bonventre[1,4]



Activation de l'EGFR



Cohen Terzi unpublished

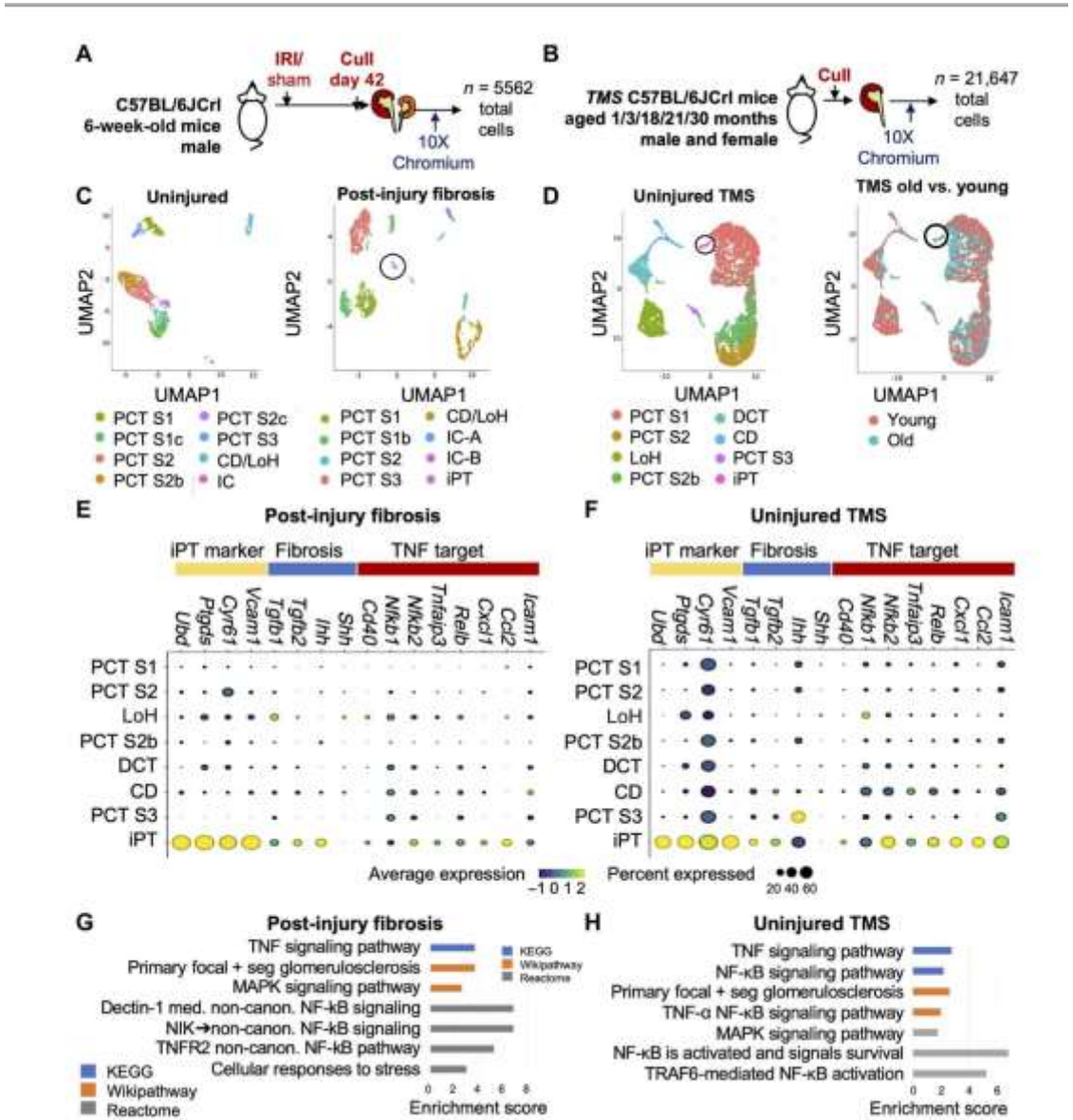
Communication cellulaire? Les cellules tubulaires pro-inflammatoires?

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

FIBROSIS

Indian Hedgehog release from TNF-activated renal epithelia drives local and remote organ fibrosis

Eoin D. O'Sullivan[1,2†], Katie J. Mylonas[1†], Cuiyan Xin[3†], David P. Baird[1], Cyril Carvalho[1], Marie-Helena Docherty[1], Ross Campbell[1], Kylie P. Matchett[1], Scott H. Waddell[4], Alexander D. Walker[4], Kevin M. Gallagher[1,5], Siyang Jia[1], Steve Leung[5], Alexander Laird[5], Julia Wilflingseder[3,6], Michaela Willi[7], Maximilian Reck[8], Sarah Finnie[8], Angela Pisco[9], Sabrina Gordon-Keylock[10], Alexander Medvinsky[10], Luke Boulter[4], Neil C. Henderson[1,4], Kristina Kirschner[11,12], Tamir Chandra[4], Bryan R. Conway[8], Jeremy Hughes[1], Laura Denby[8], Joseph V. Bonventre[3], David A. Ferenbach[1,3*]



Communication cellulaire? Les cellules tubulaires pro-inflammatoires secretent IHH qui favorise la fibrose

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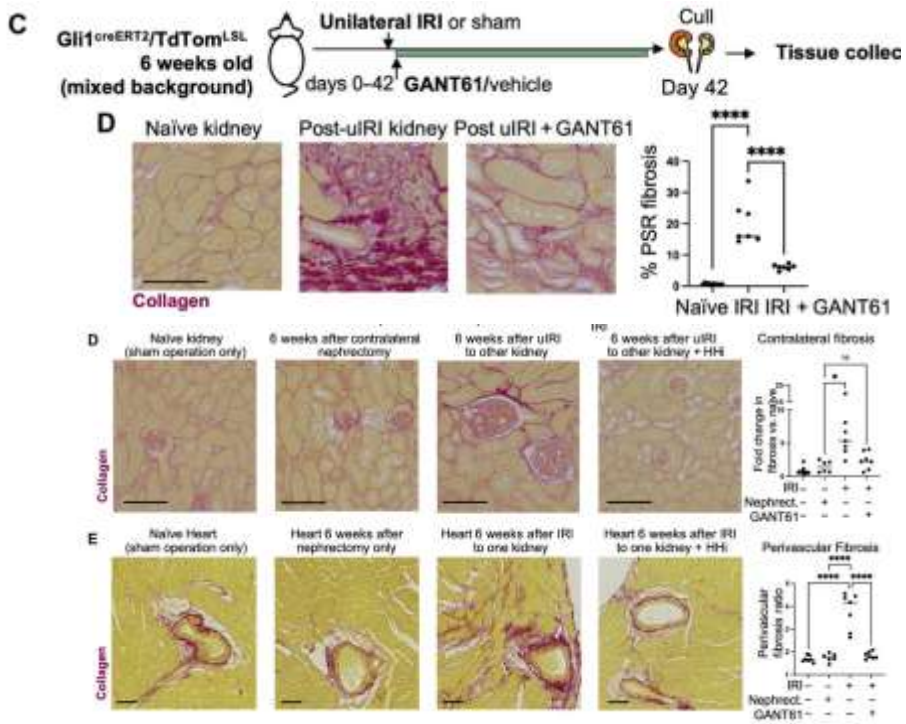
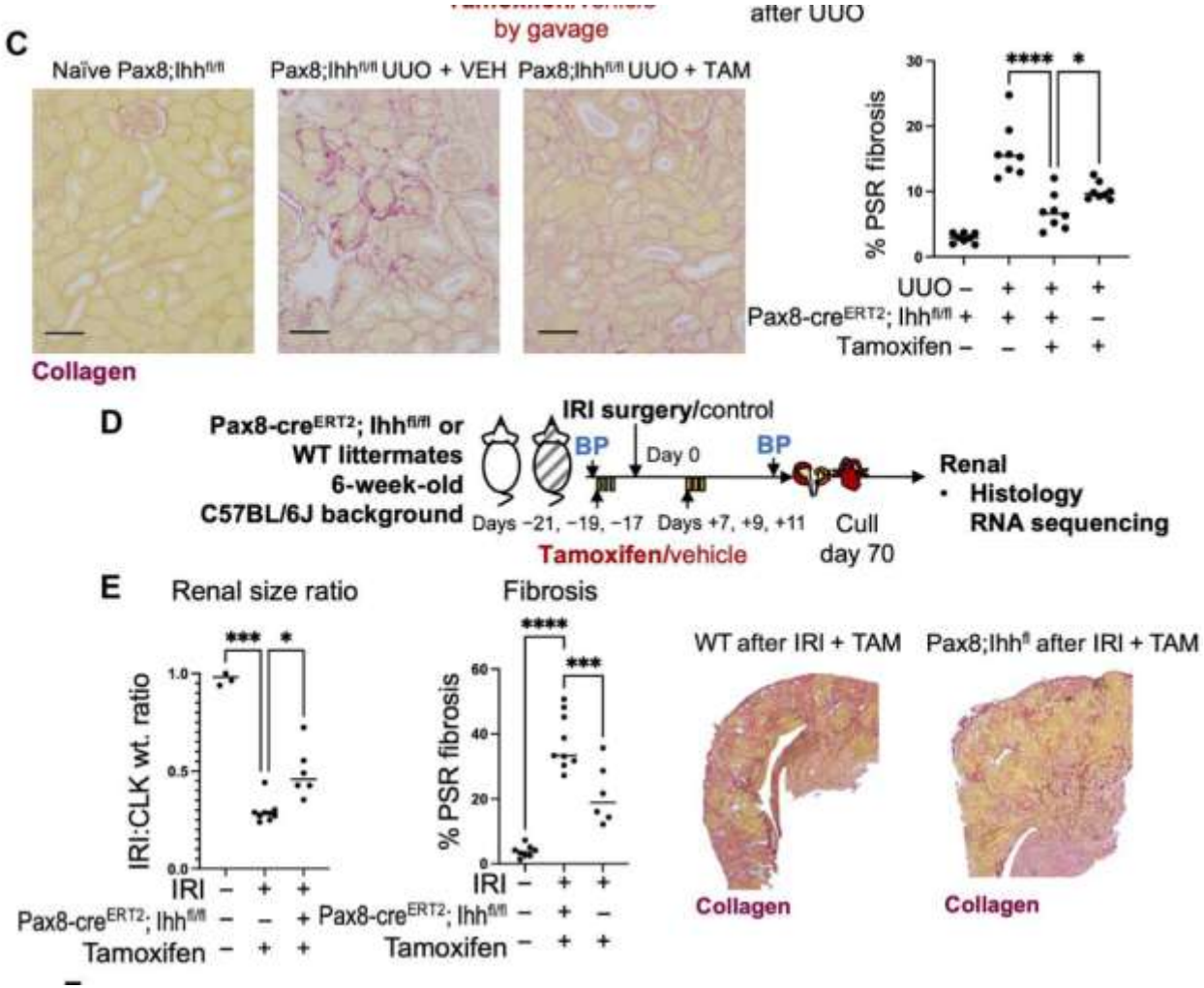


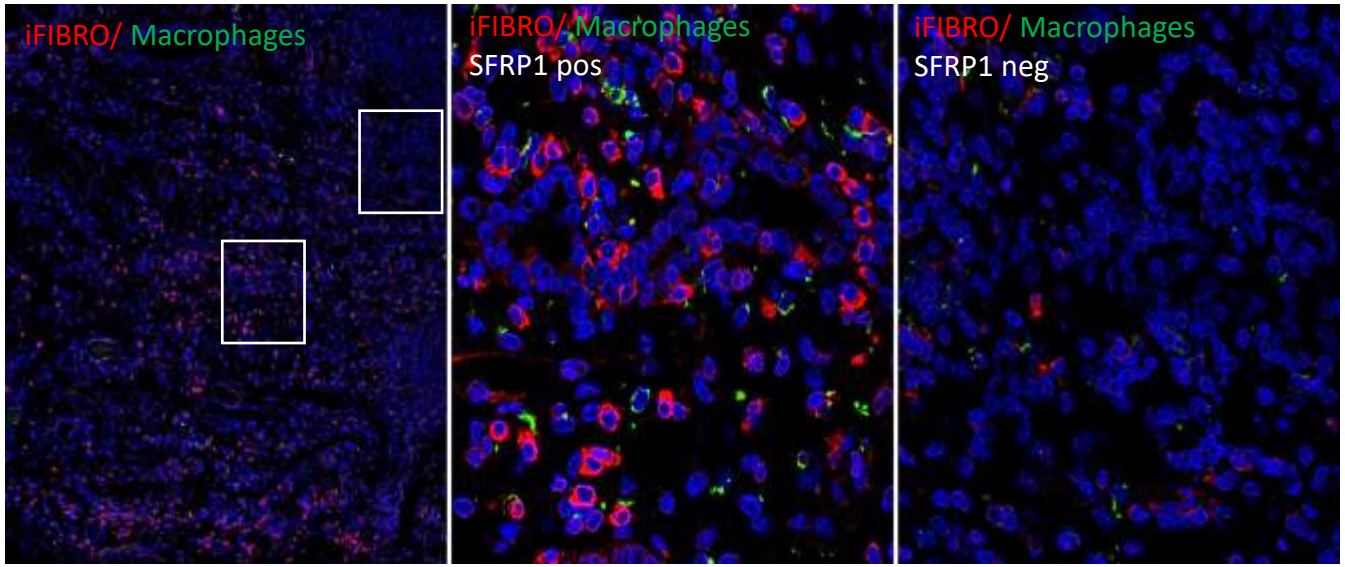


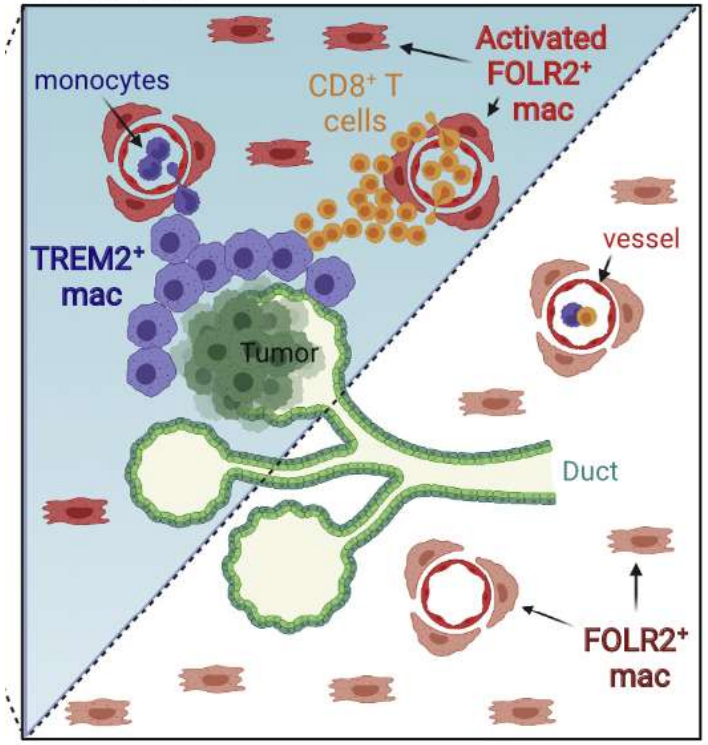
Communication cellulaire? Les cellules immunes?

nature communications

Article

WNT-dependent interaction between inflammatory fibroblasts and FOLR2+ macrophages promotes fibrosis in chronic kidney disease



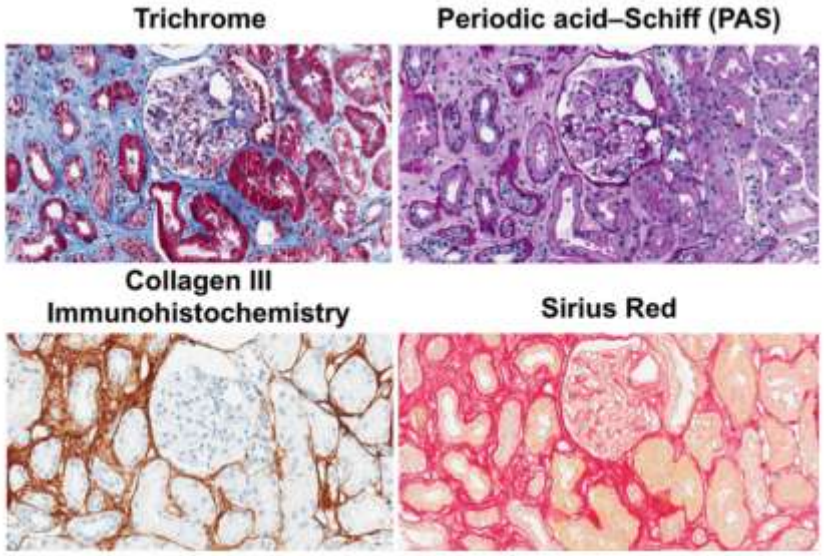


Cell

Article

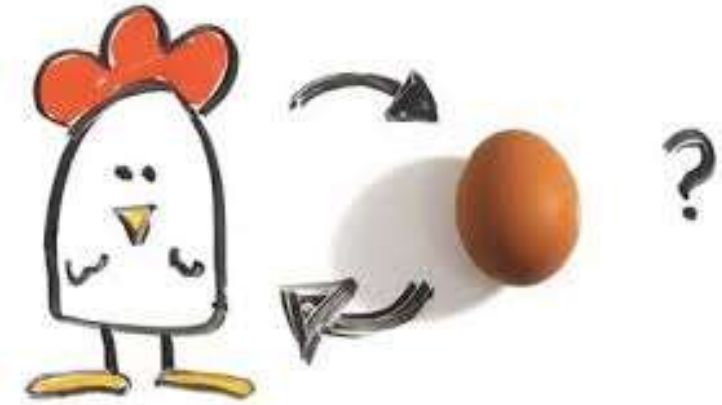
Tissue-resident FOLR2+ macrophages associate with CD8+ T cell infiltration in human breast cancer

Résumé intermédiaire



- Une origine des fibroblastes mieux comprise
- Des étapes de differentiation fibroblastiques mieux comprises
- Plusieurs acteurs cellulaires

- Mais qui interagit avec qui? Dans quel ordre?
  - Concept de la niche fibrotique
    - Basée sur l'observation de la fibrose "patchy"
  - Apport de la transcriptomique spatiale?

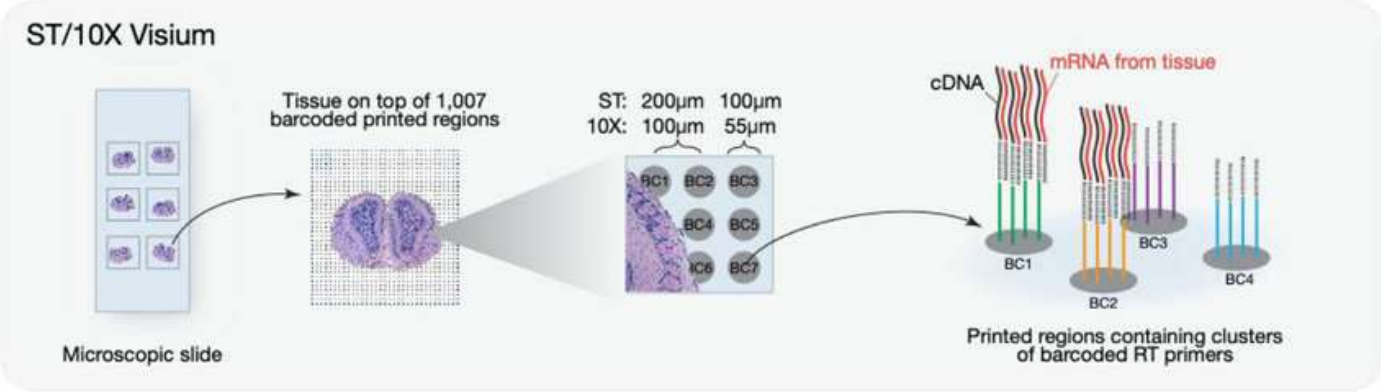


La niche fibrotique, apport de la transcriptomique spatiale

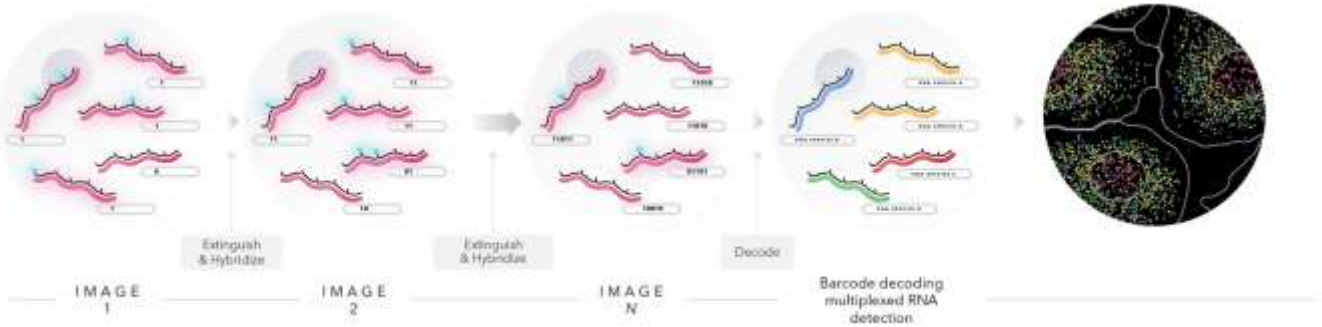
Single cell RNAseq

Spatial transcriptomic

Differentes techniques de spatiale



Spot based: transcriptome mais plusieurs cellules par spot



Hybridation in situ haut debit
Résolution subcellulaire mais panel de qq centaines de gènes

La niche fibrotique

Article

An atlas of healthy and injured cell states and niches in the human kidney

https://doi.org/10.1038/s41586-023-05769-3

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Check for updates

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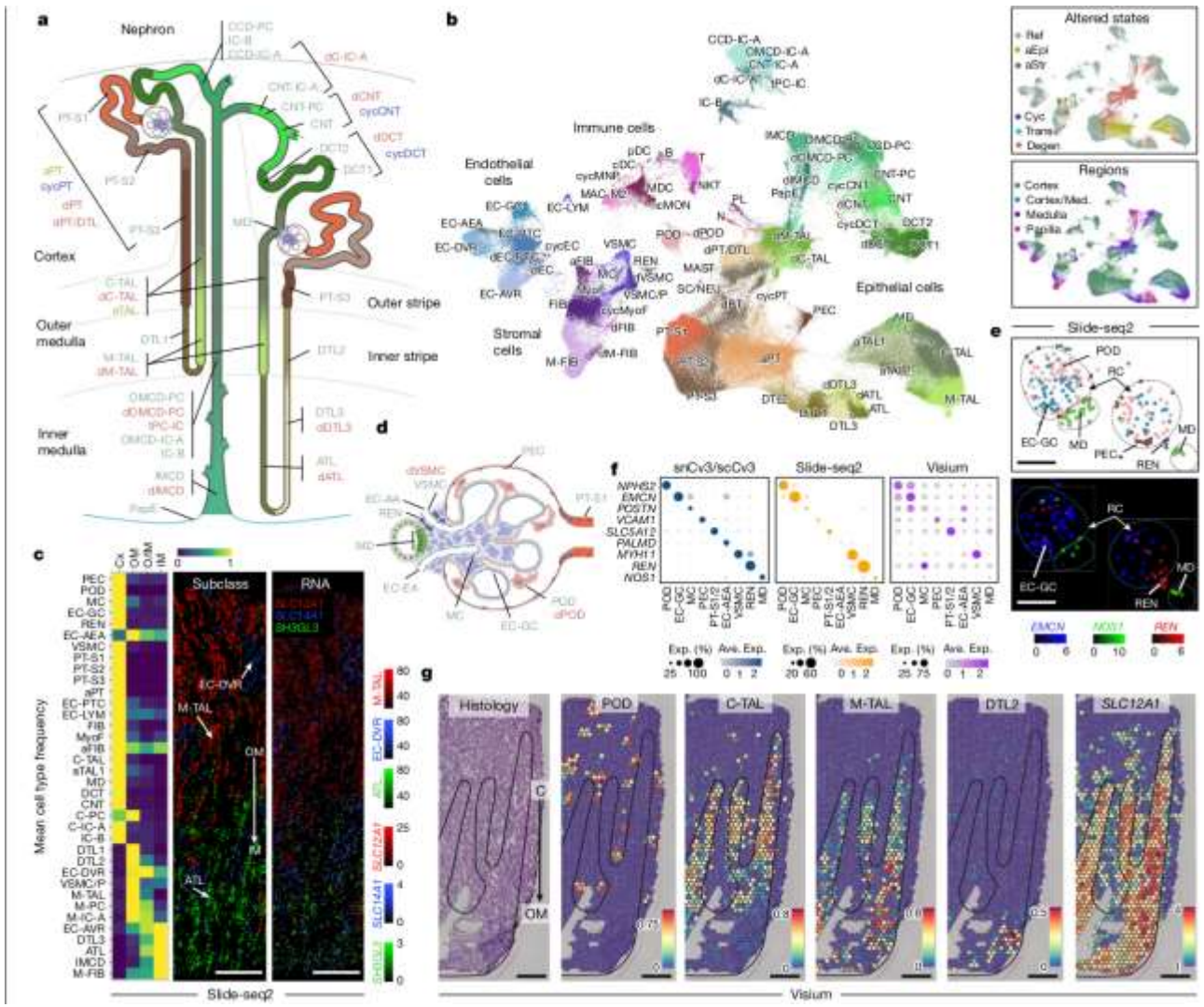

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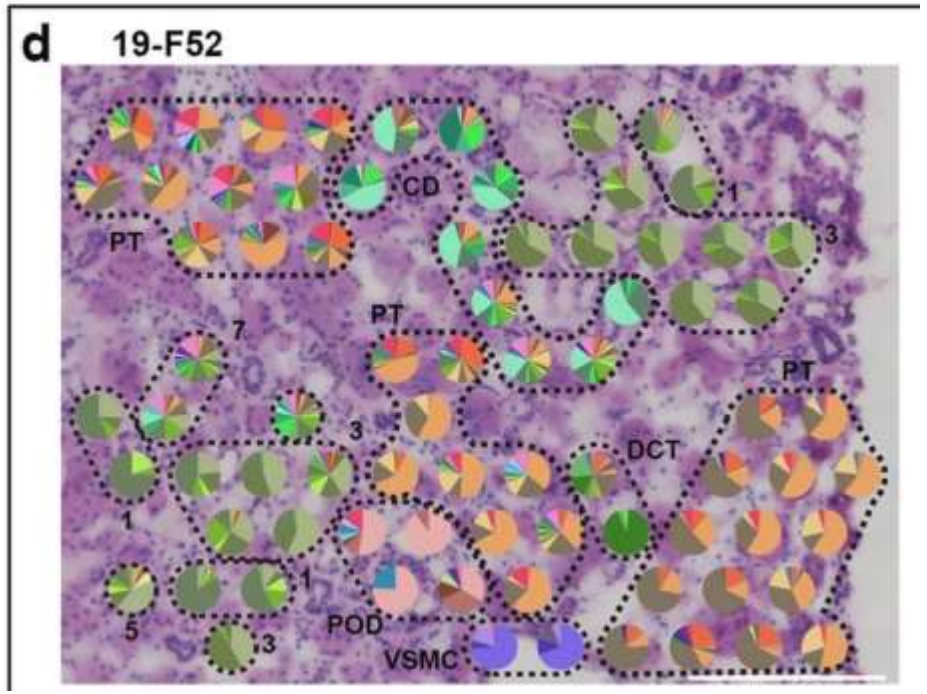
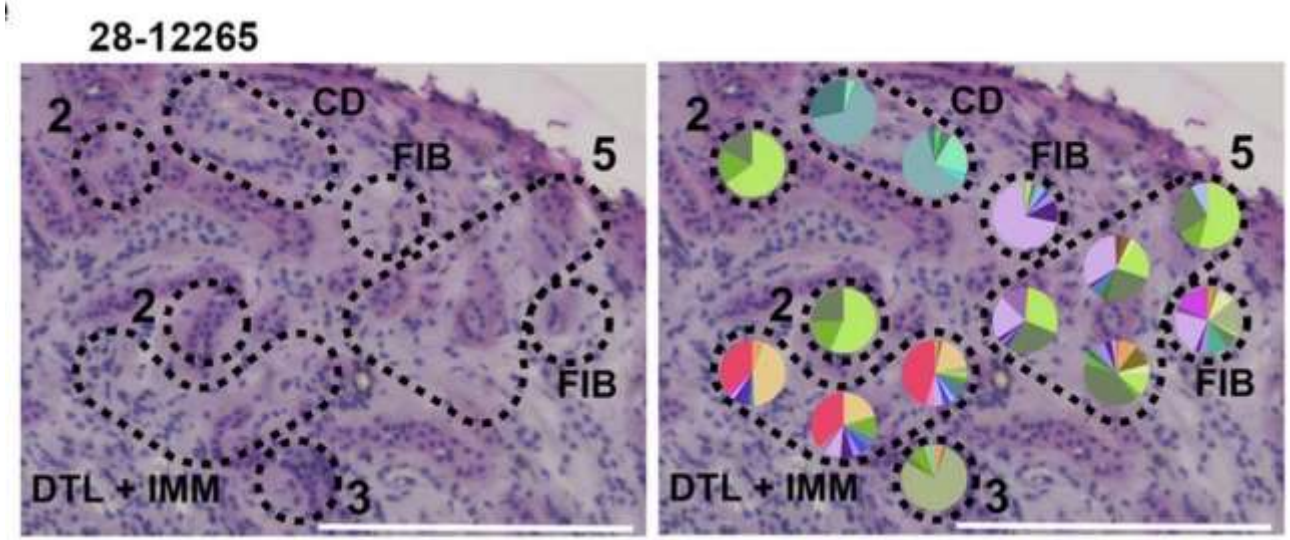
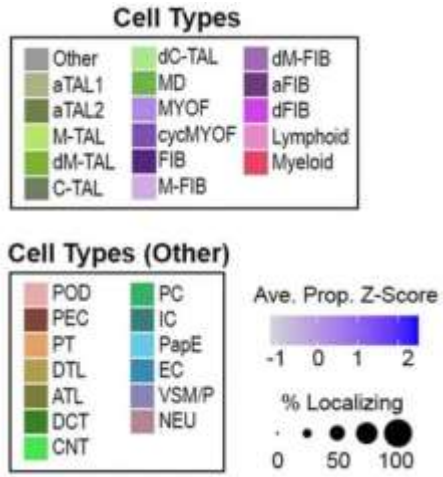
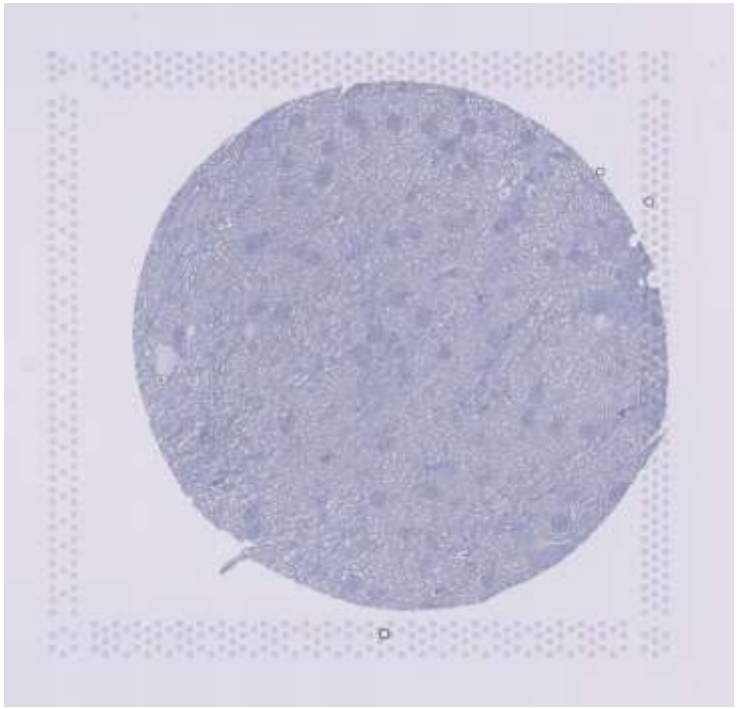


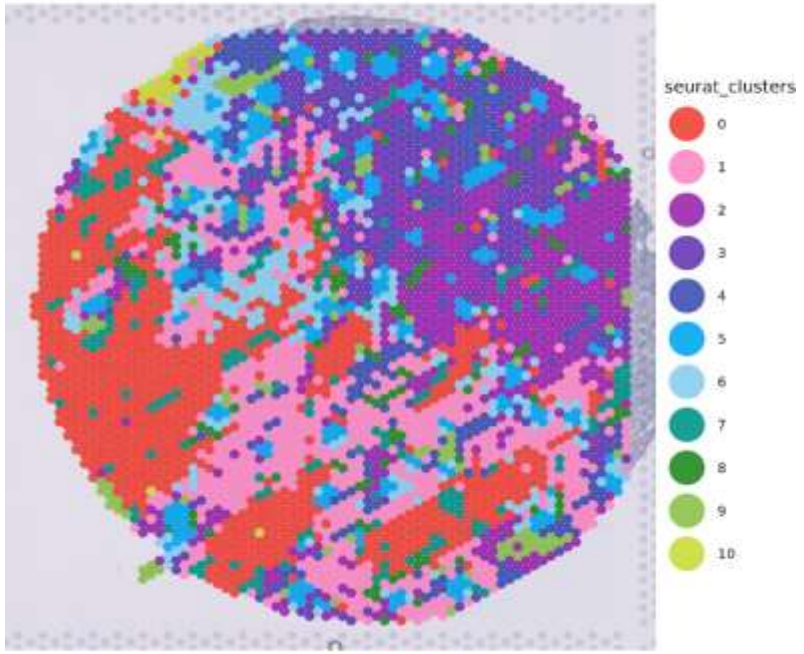




La niche fibrotique

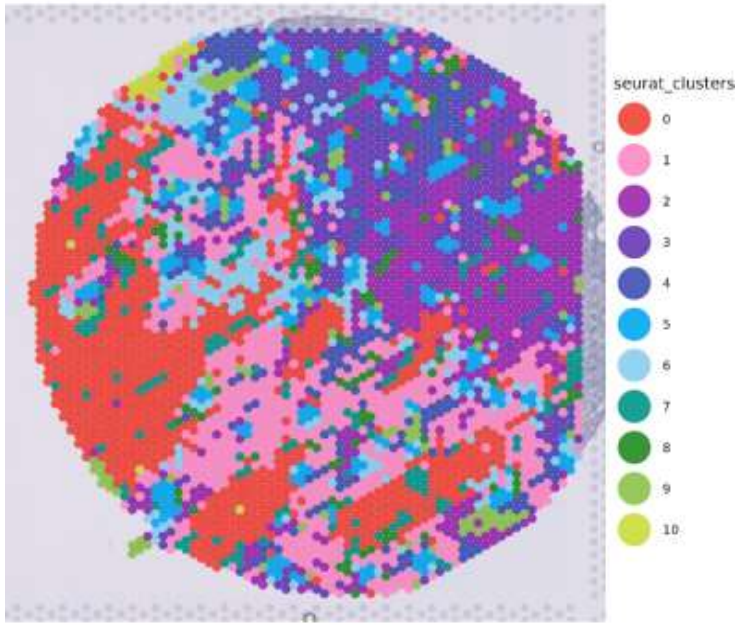
	Pt #1
Age	53
Gender	M
Serum creatinine at Nx (µM)	114
eGFR at Nx (mL/min/1.73m2)	62
HTN	Yes
Diabetes mellitus	Yes
Cause of CKD	Vascular and diabetic nephropathy

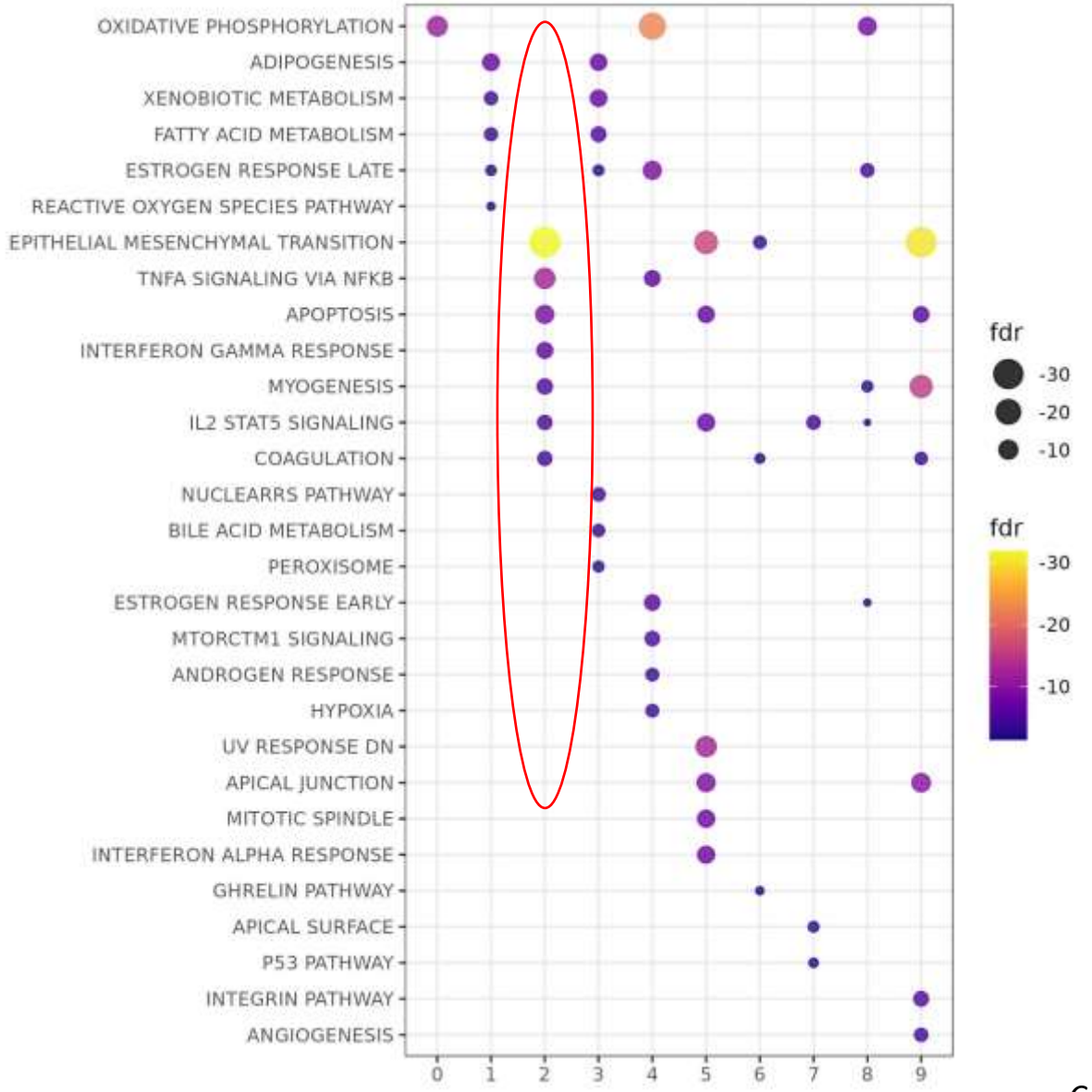




Cohen Unpublished

La niche fibrotique





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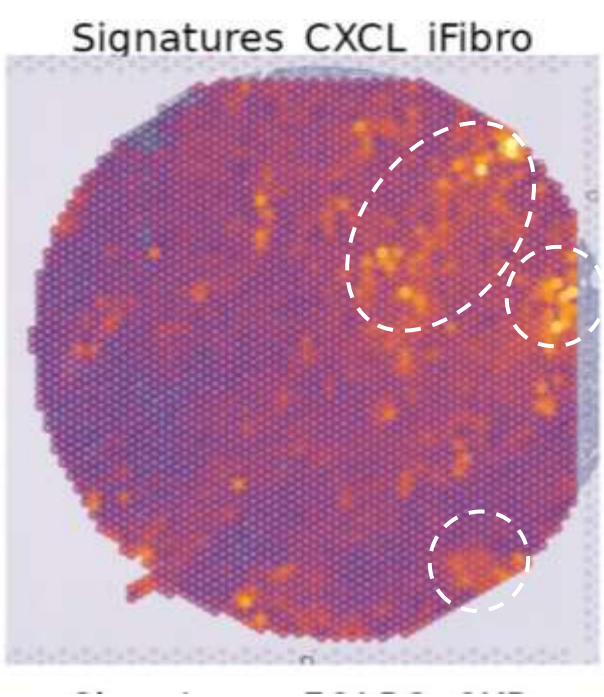
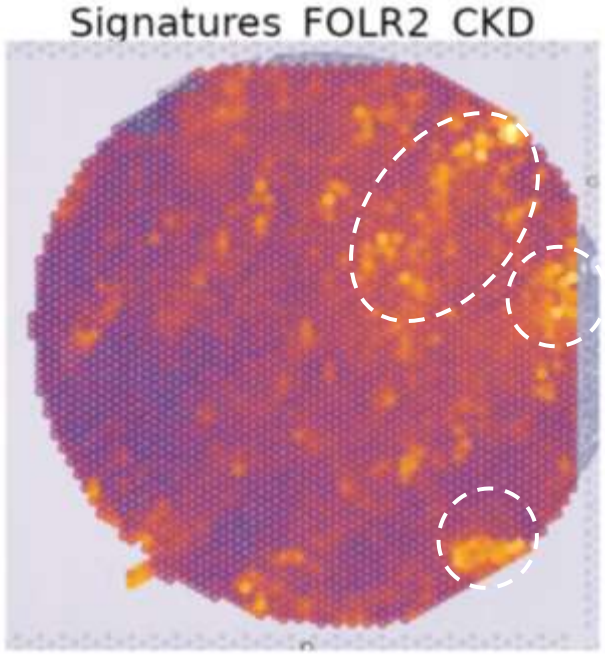
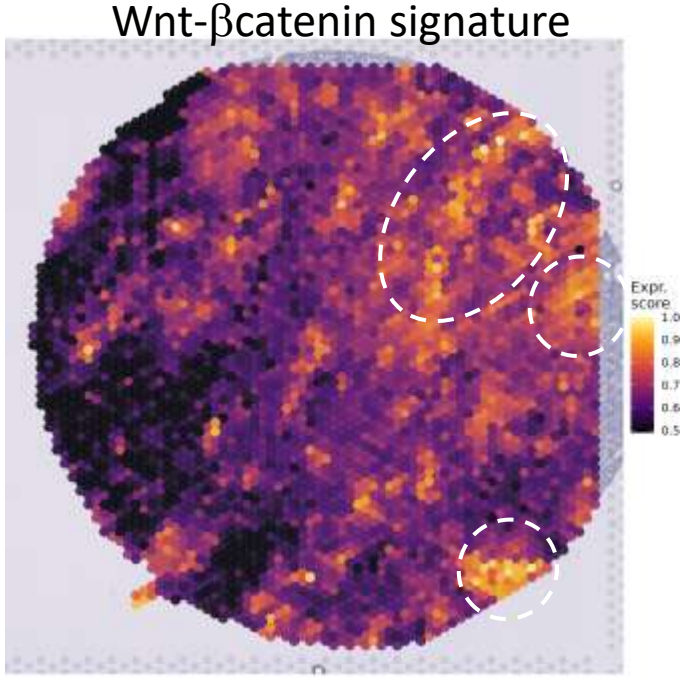
La niche fibrotique, vers un peu plus de méchanistique?





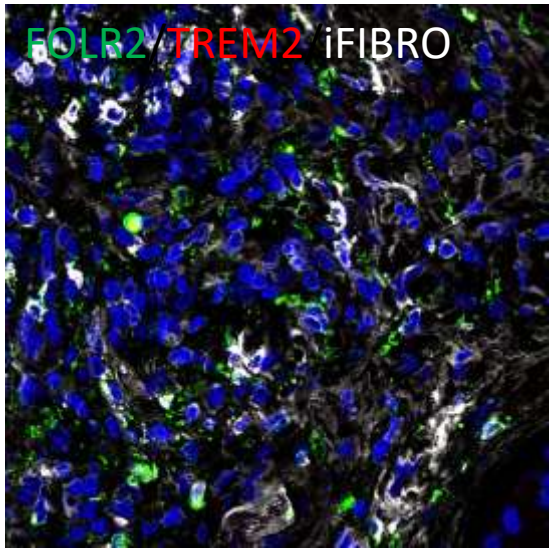


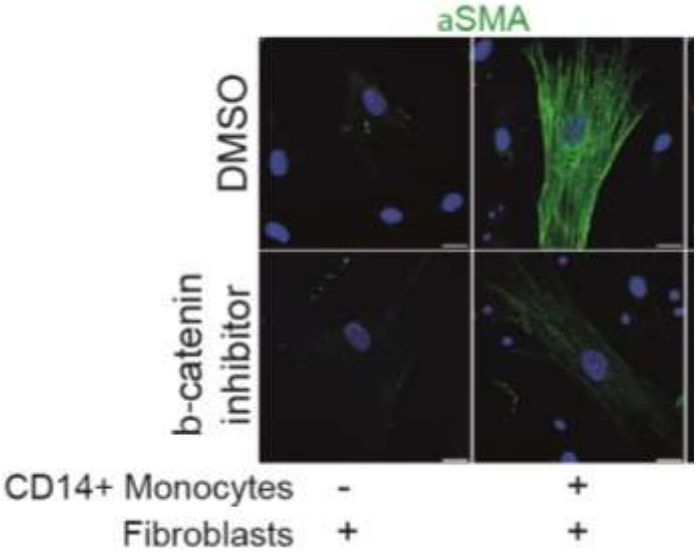
La niche fibrotique, vers un peu plus de méchanistique?

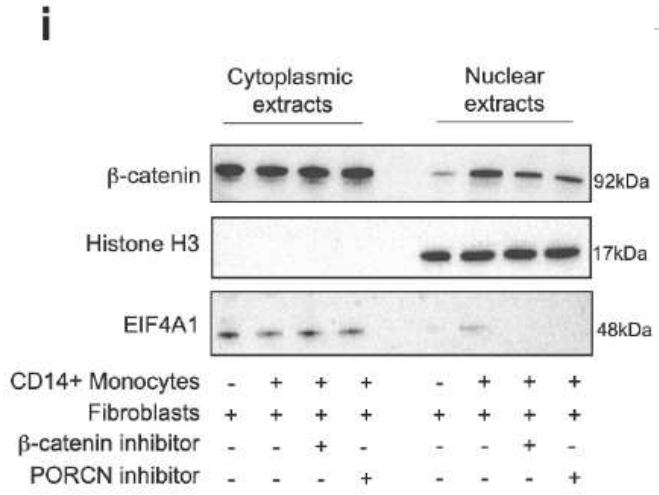
nature communications

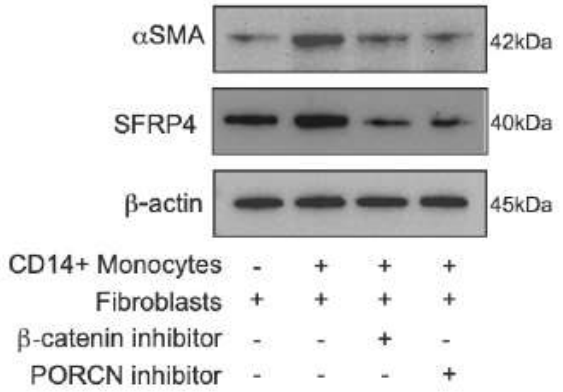
Article

WNT-dependent interaction between inflammatory fibroblasts and FOLR2+ macrophages promotes fibrosis in chronic kidney disease









La niche fibrotique, vers un peu plus de méchanistique?

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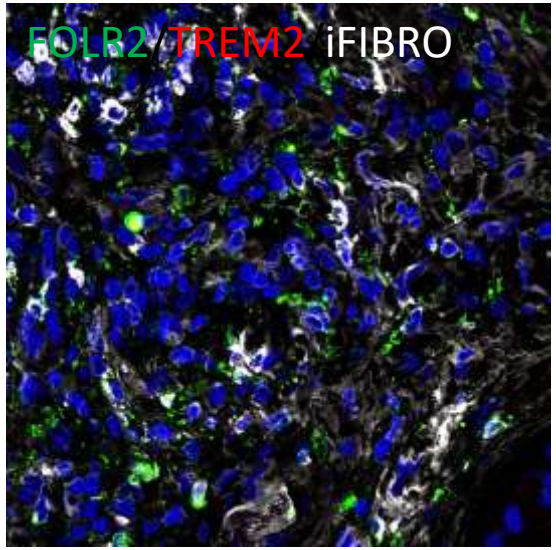
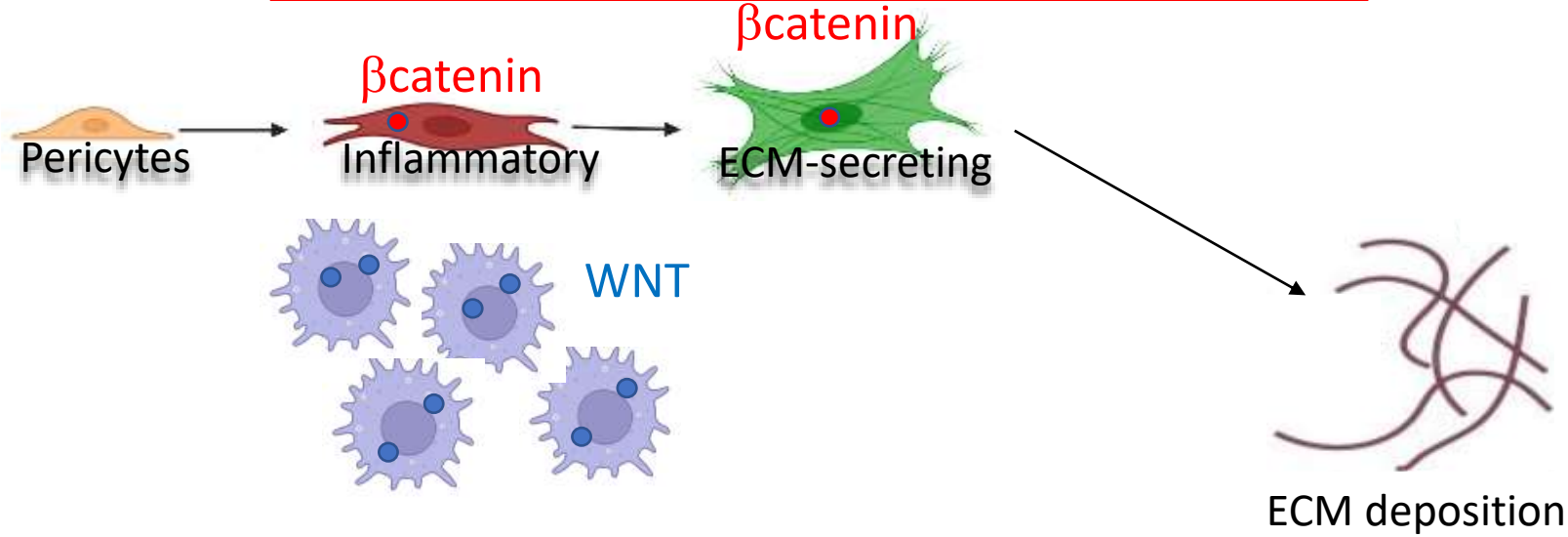


Role of macrophages in phenotypic switch in fibroblasts



QUESTION SUIVANTE

Et la pertinence clinique?

Pertinence clinique?

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Article

https://doi.org/10.1038/s41467-024-44886-

WNT-dependent interaction between inflammatory fibroblasts and FOLR2+ macrophages promotes fibrosis in chronic kidney disease

Article

An atlas of healthy and injured cell states and niches in the human kidney

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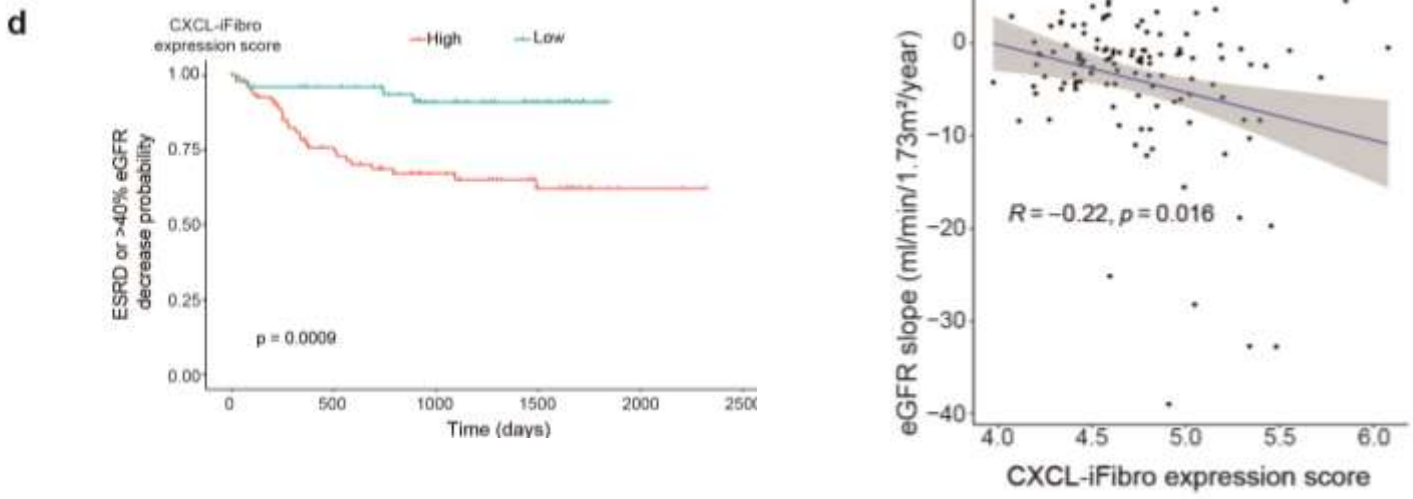
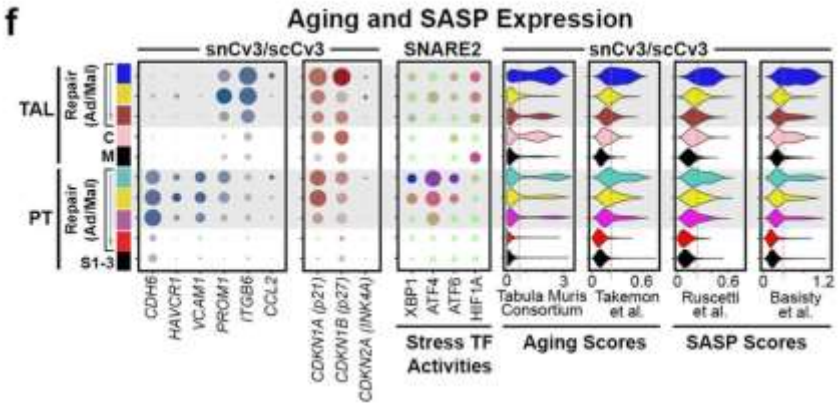
Blue B. Lake[1,40,41], Rajasree Menon[2,40], Seth Winfree[3,41], Qiwen Hu[4,41], Ricardo Melo Ferreira[5,41], Kian Kalhor[1,41], Daria Barwinska[3], Edgar A. Otto[4], Michael Ferkowicz[3], Dinh Diep[1,42], Nongluk Plongthongkum[1], Amanda Knoten[1], Sarah Urata[1], Laura H. Mariani[6], Abhijit S. Naik[6], Sean Eddy[4], Bo Zhang[1], Yan Wu[1,43], Diane Salamon[1], James C. Williams[3], Xin Wang[4], Karol S. Balderrama[3], Paul J. Hoover[3], Evan Murray[4], Jamie L. Marshall[6], Teia Noel[6], Anitha Vijayan[7], Austin Hartman[3], Fei Chen[8], Sushrut S. Waikar[10], Sylvia E. Rosas[11,12], Francis P. Wilson[13], Paul M. Palevsky[14], Krzysztof Kiryluk[15], John R. Sedor[16], Robert D. Toto[17], Chirag R. Parikh[18], Eric H. Kim[19], Rahul Satija[3], Anna Greka[4], Evan Z. Macosko[3], Peter V. Kharchenko[4,44], Joseph P. Gaut[20], Jeffrey B. Hodgin[21], KPMP Consortium*, Michael T. Eadon[9,22], Pierre C. Dagher[9,22], Tarek M. El-Achkar[9,23], Kun Zhang[1,44,45], Matthias Kretzler[8,22] & Sanjay Jain[9,22,24]





QUESTION SUIVANTE

Perspective thérapeutiques?

Perspective thérapeutiques?

Table 1. Treatment approaches for kidney fibrosis.

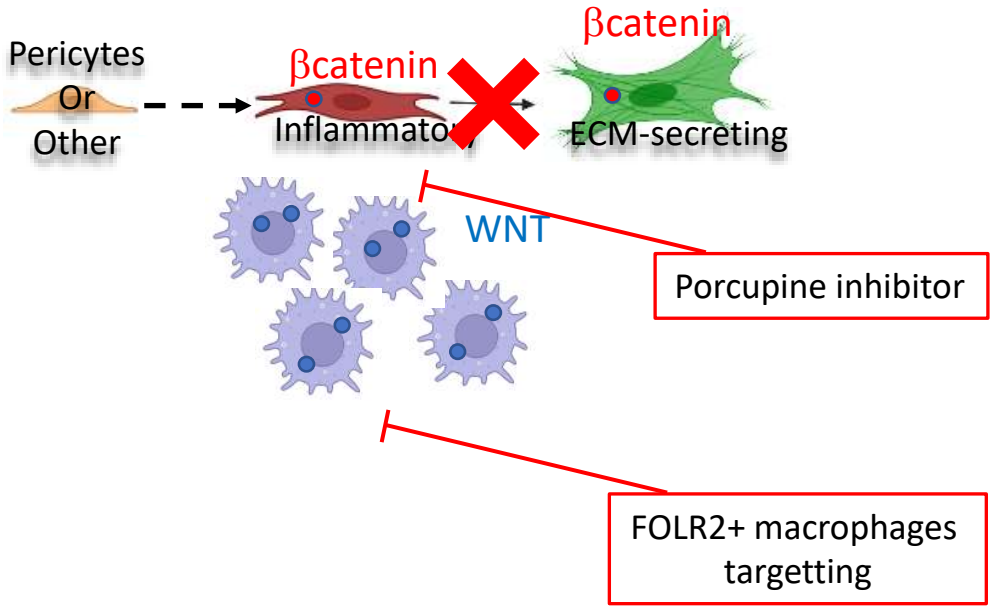
Current Status	Treatment	Description	References
In clinical use	Renin-angiotensin blockers	Inhibit the RAAS, slowing CKD progression and kidney fibrosis; also reduces the activity of TGF-β, PAI1, and PDGF, all molecules involved in promoting glomerular damage.	[168–172,183]
In clinical use	Mineralocorticoid receptor (MR) antagonists	Inhibit the activation of aldosterone at the MR, reducing inflammation and proteinuria; block the transcription of various inflammatory mediators that contribute to kidney fibrosis such as PAI1, TGF-β, NF-κβ, and IL-6.	[194–204]
In clinical use	Sodium-glucose cotransporter-2 (SGLT-2) inhibitors	Inhibit glucose reuptake by the kidney via SGLT-2 transporters located in the proximal tubules; promote lower macrophage-mediated inflammation and cytokines such as IL-6, TNF-α, IFNγ, NF-κβ, TLR-4, and TGF-β, thus reducing glomerular fibrosis. They also lower glomerular pressure and improve renal hemodynamics. Protective against ESRD even in patients without type 2 diabetes.	[205–211,219–222]
Experimental	Pirfenidone	Antifibrotic orally administered drug; works mainly via inhibition of TGF-β and MAPK signalling. Has anti-inflammatory and antioxidant activity.	[223–225,230–236]
Experimental	MicroRNA silencing	Antisense oligonucleotides that silence specific fibrosis-related microRNAs are being explored. Lademirsen, an anti-microRNA-21 drug, failed in human studies, even though microRNA21 is deregulated in kidney fibrosis. Antisense oligonucleotides that silence other microRNAs may be a viable treatment.	[245–253]
Experimental	Mesenchymal stem cells (MSC)	Multi-potent adult stem cells that demonstrate anti-fibrotic and anti-inflammatory abilities and can induce repair and regeneration.	[272,279]

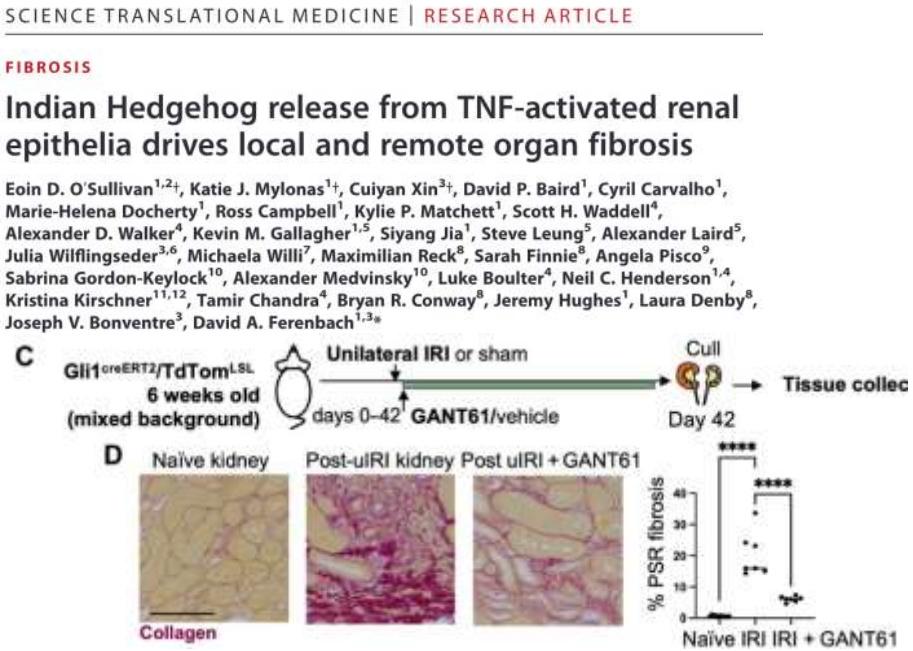
Plutot décevant pour le moment

Perspective thérapeutiques?

La meilleure comprehension des mécanismes pourra permettre d'identifier des cibles thérapeutiques

Blocage de molecules secrétées, comme IHH?

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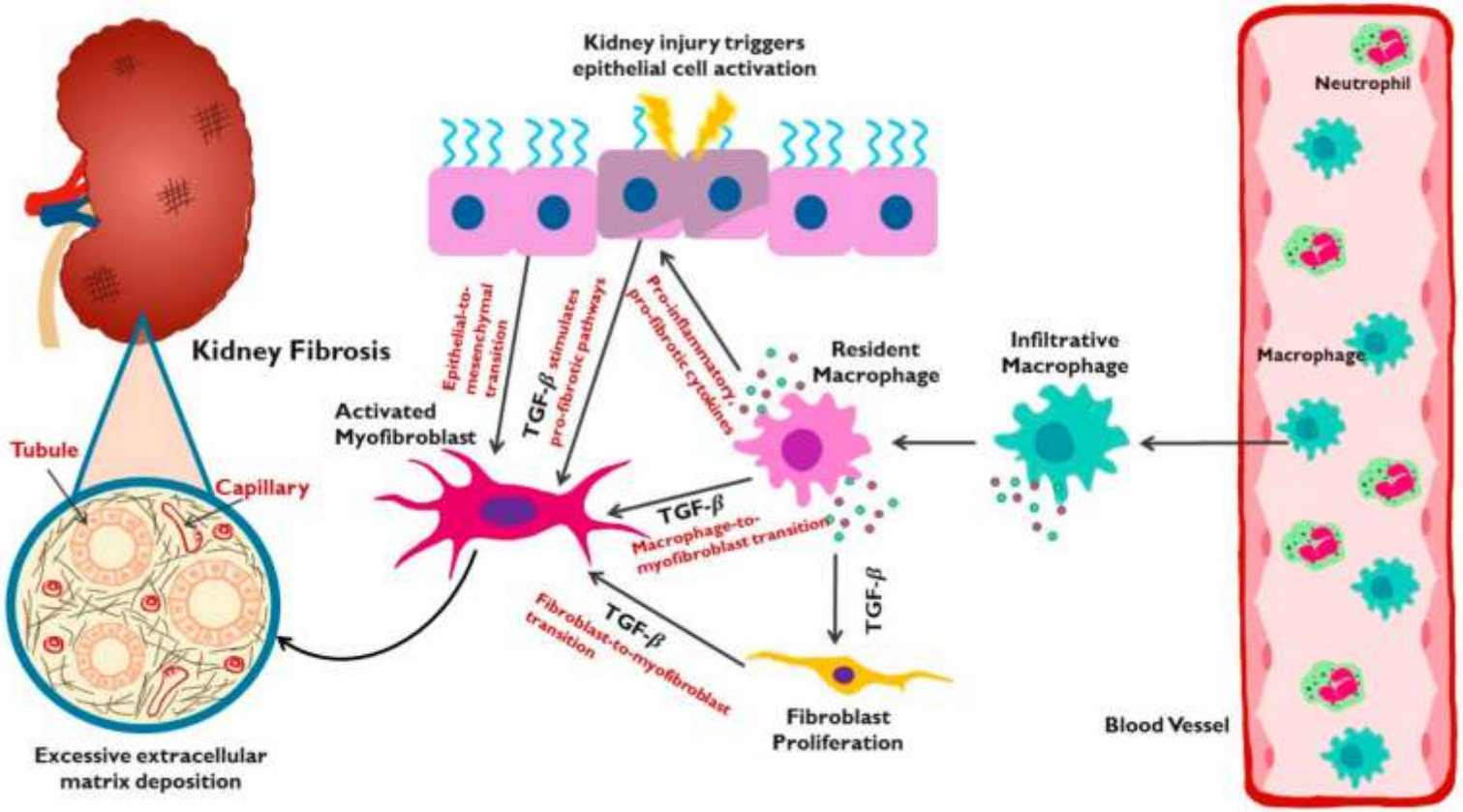
FIBROSIS

Indian Hedgehog release from TNF-activated renal epithelia drives local and remote organ fibrosis

Eoin D. O'Sullivan[1,2†], Katie J. Mylonas[1†], Cuiyan Xin[3†], David P. Baird[1], Cyril Carvalho[1], Marie-Helena Docherty[1], Ross Campbell[1], Kylie P. Matchett[1], Scott H. Waddell[4], Alexander D. Walker[4], Kevin M. Gallagher[1,5], Siyang Jia[1], Steve Leung[5], Alexander Laird[5], Julia Wilflingseder[3,6], Michaela Willi[7], Maximilian Reck[8], Sarah Finnie[8], Angela Pisco[9], Sabrina Gordon-Keylock[10], Alexander Medvinsky[10], Luke Boulter[4], Neil C. Henderson[1,4], Kristina Kirschner[11,12], Tamir Chandra[4], Bryan R. Conway[8], Jeremy Hughes[1], Laura Denby[8], Joseph V. Bonventre[3], David A. Ferenbach[1,3*]

Conclusion


Kidney injury triggers
epithelial cell activation
Neutrophil
Macrophage
Blood Vessel
Kidney Fibrosis
Tubule
Capillary
Excessive extracellular
matrix deposition
Activated
Myofibroblast
Epithelial-to-
mesenchymal
transition
TGF-β stimulates
pro-fibrotic pathways
Pro-inflammatory,
pro-fibrotic cytokines
Resident
Macrophage
Infiltrative
Macrophage
TGF-β
Macrophage-to-
myofibroblast transition
TGF-β
TGF-β
Fibroblast-to-myofibroblast
transition
Fibroblast
Proliferation

Bioinformatician is the new cool guy in the lab!

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