

Nouveaux concepts dans l'HTA

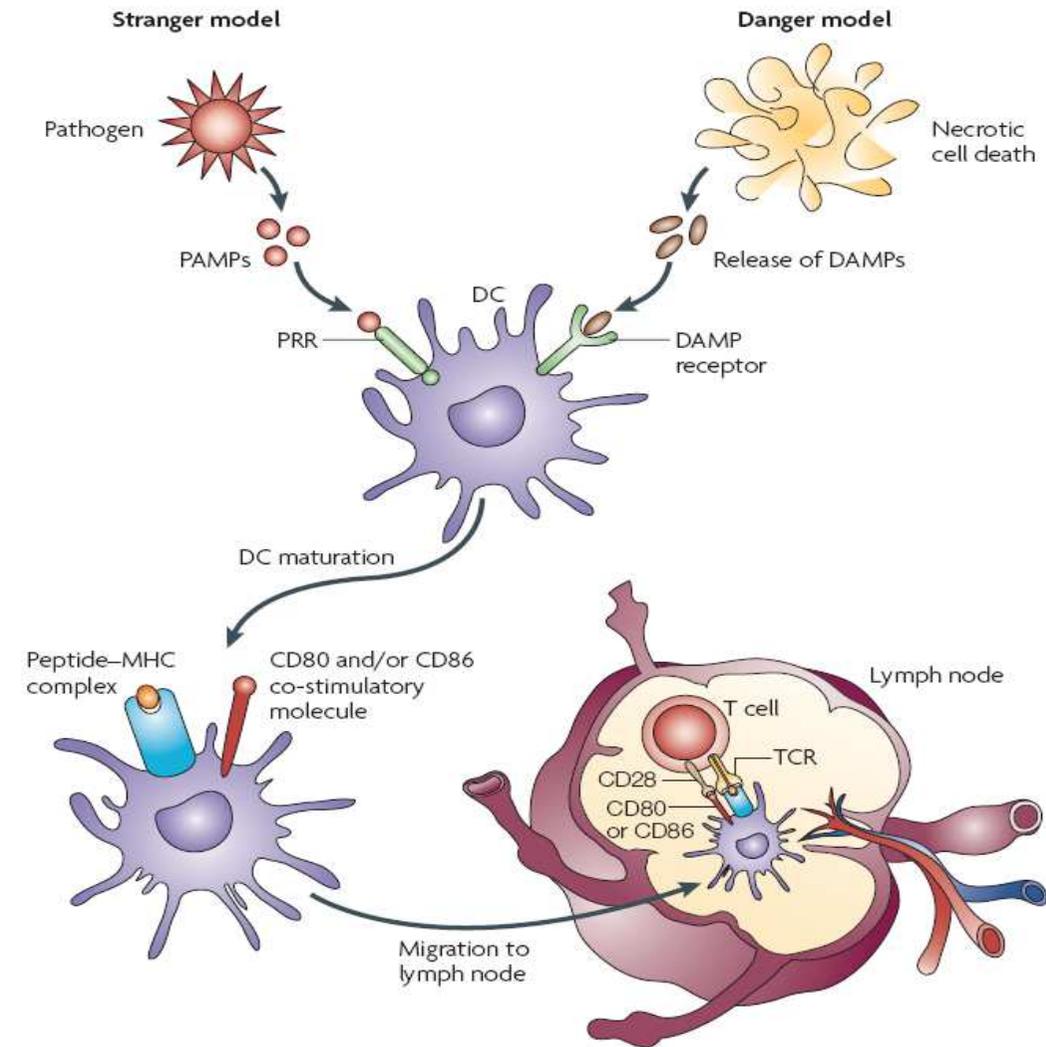
1. Rôle des cellules dendritiques / lymphocytes

Pr Jean-Michel Halimi, Tours

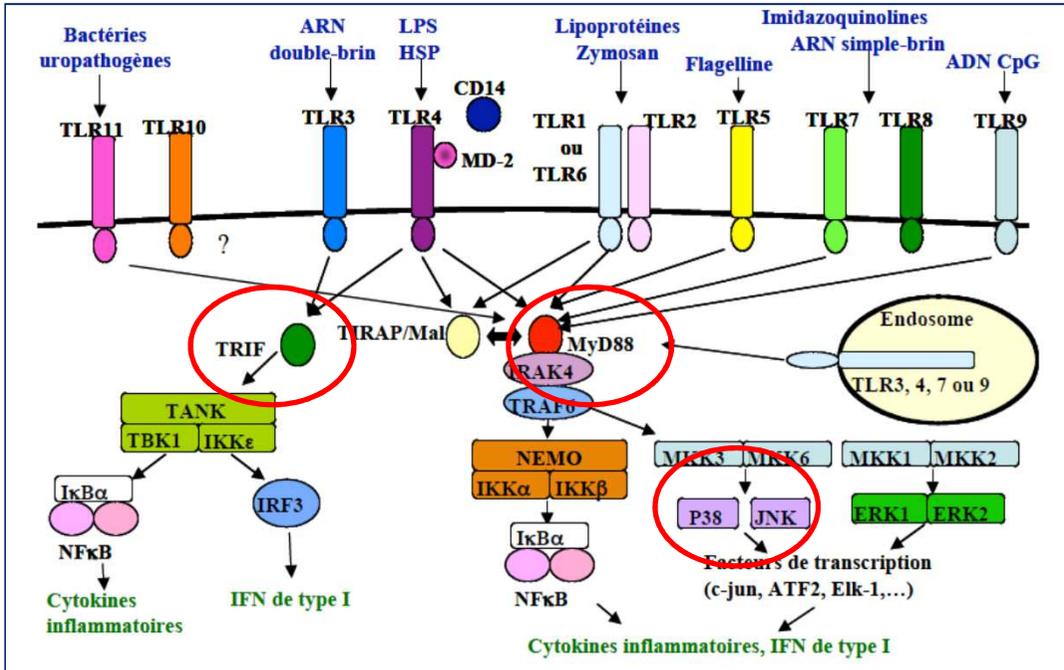
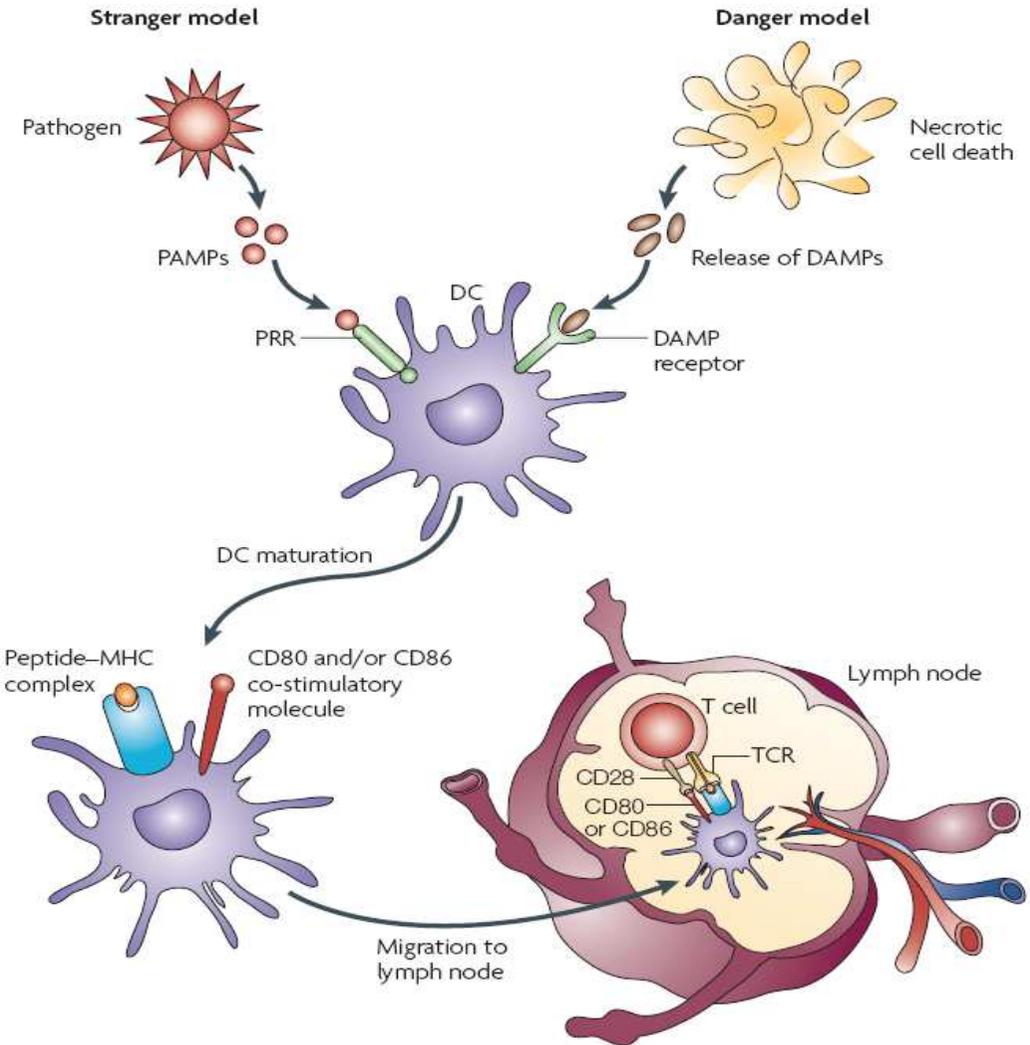
DC = cellules dendritiques

DIU HTA, 7 décembre 2017

Les cellules dendritiques (DC) reconnaissent les signaux « stranger/danger »
(alarmines: ATP, HSP70, IL33; PAMPs: LPS, peptidoglycane)

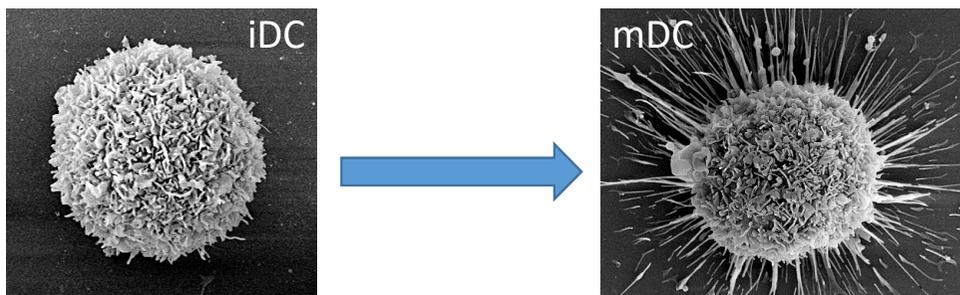


Les cellules dendritiques (DC) reconnaissent les signaux « stranger/danger »
 (ex: alarmines: ATP, HSP70, IL33; PAMPs: LPS, peptidoglycane) grâce à des récepteurs (ex: TLR)



Après activation par DAMP/alarmines:

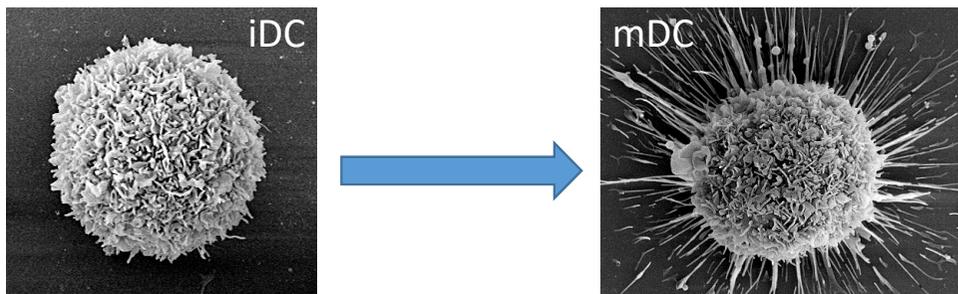
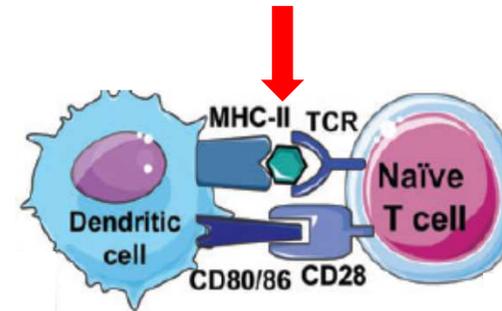
1. Maturation des DC immatures => mDC



Après activation par DAMP/alarmines:

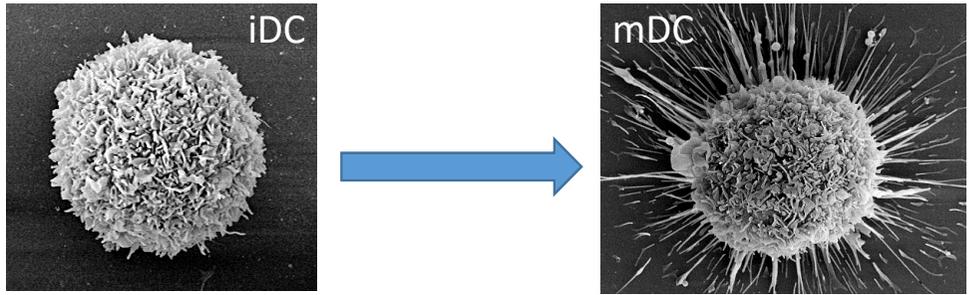
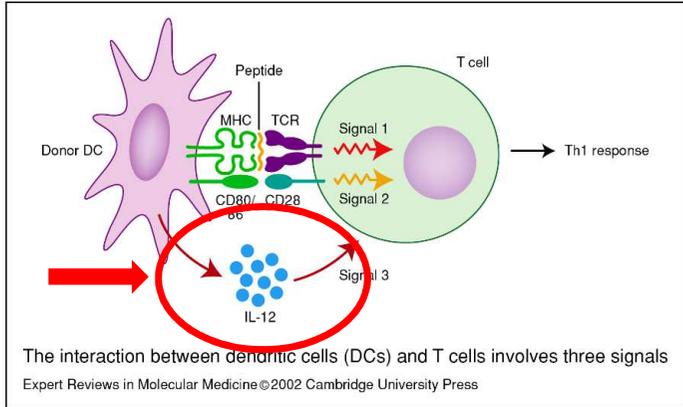
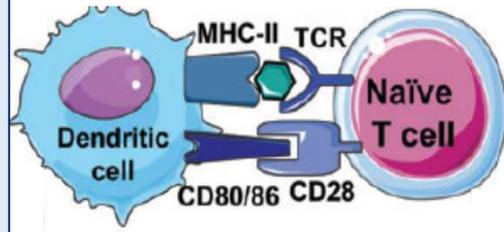
1. Maturation des DC immatures => mDC

2. mDC: présentent l'Ag au lympho T



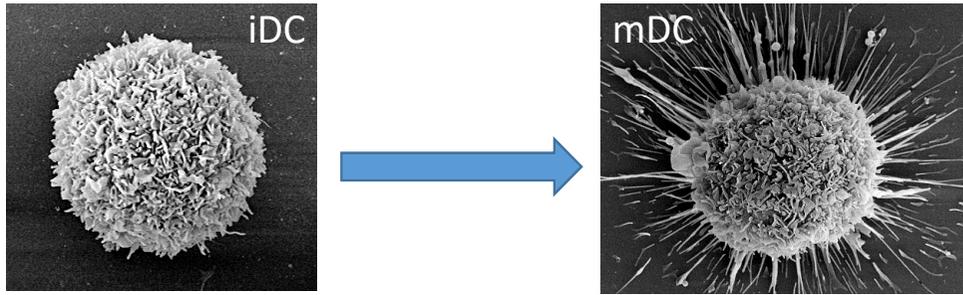
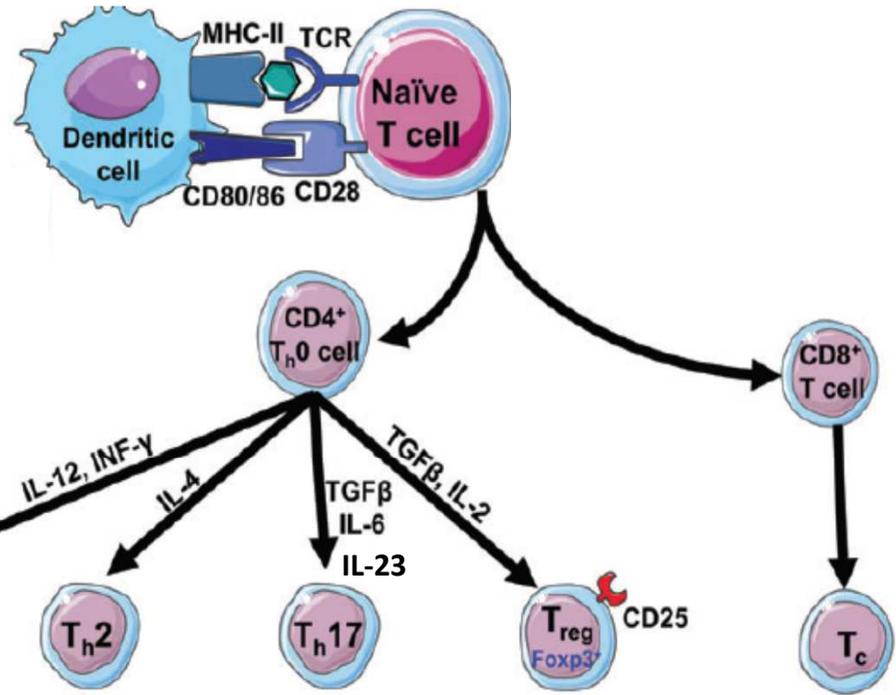
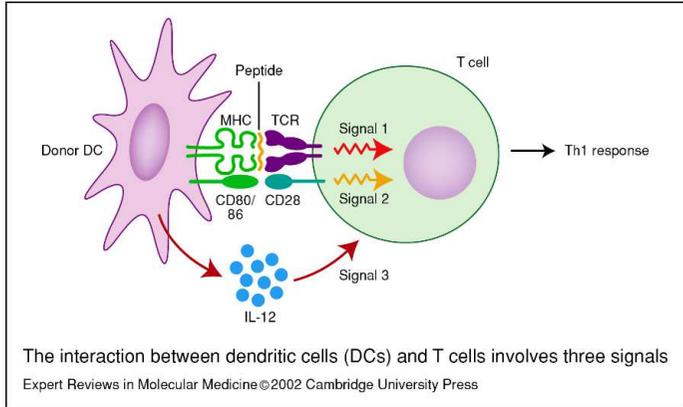
Après activation par DAMP/alarmines:

- 1. Maturation des DC: immatures (iDC) => matures (mDC)
- 2. mDC: présentent l'Ag au lympho T
- 3. mDC: synthétisent des cytokines



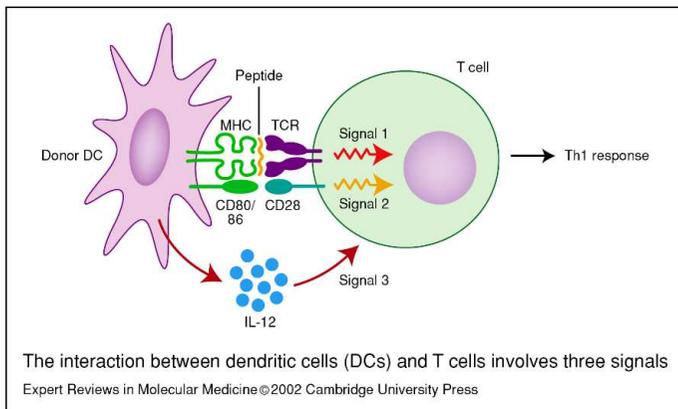
Après activation par DAMP/alarmines:

- 1. Maturation des DC immatures => mDC
- 2. mDC: présentent l'Ag au lympho T
- 3. mDC: synthétisent des cytokines
- => Orientation la réponse Lympho T (Th1, Th2, Treg, Th17)
- => Prolifération des Lympho T

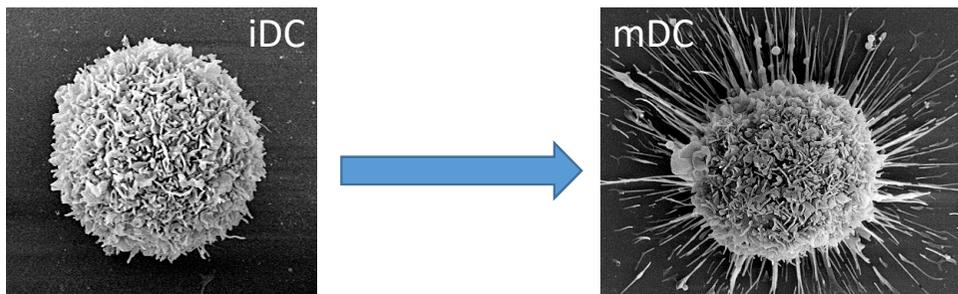
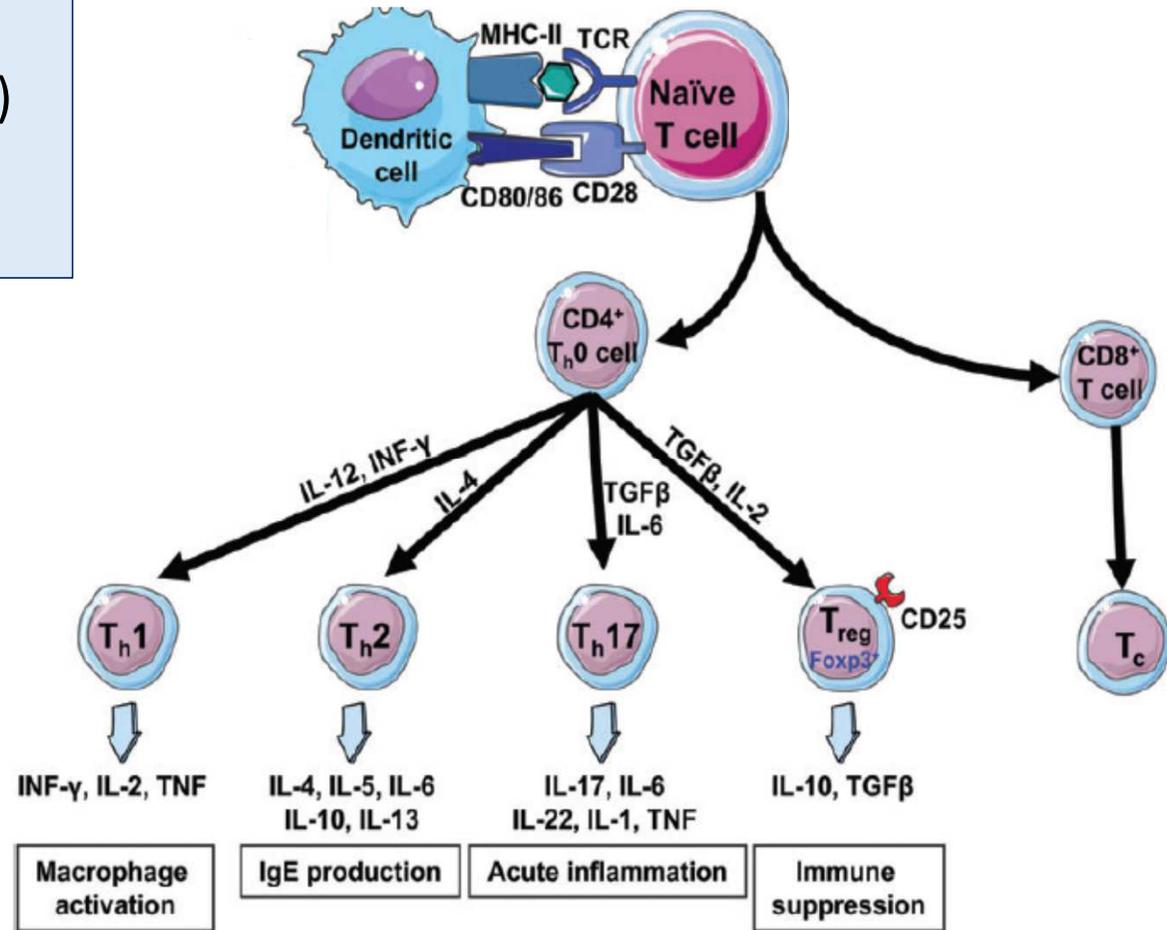


Après activation par DAMP/alarmines:

1. Maturation des DC immatures => mDC
 2. mDC: présentent l'Ag au lympho T
 3. mDC: synthétisent des cytokines
- ⇒ Orientation la réponse (Th1, Th2, Treg, Th17)
 ⇒ Prolifération des Lympho T
 ⇒ Synthèse de cytokines par les lympho T



DC = organise la réponse immunitaire

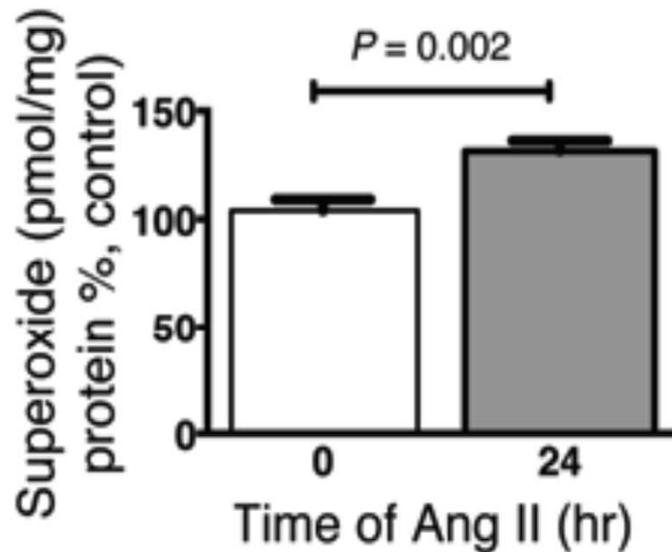


DC isoketal-modified proteins activate T cells and promote hypertension

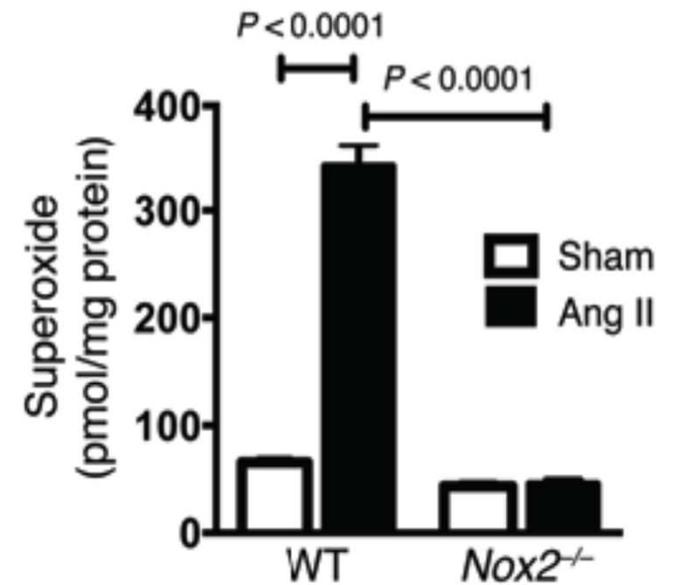
Annet Kirabo,¹ Vanessa Fontana,² Ana P.C. de Faria,² Roxana Loperena,¹ Cristi L. Galindo,³ Jing Wu,^{1,4} Alfiya T. Bikineyeva,¹ Sergey Dikalov,¹ Liang Xiao,¹ Wei Chen,¹ Mohamed A. Saleh,^{1,5} Daniel W. Trott,¹ Hana A. Itani,¹ Antony Vinh,⁶ Venkataraman Amarnath,⁷ Kalyani Amarnath,⁷ Tomasz J. Guzik,⁸ Kenneth E. Bernstein,⁹ Xiao Z. Shen,⁹ Yu Shyr,¹⁰ Sheau-chiann Chen,¹⁰ Raymond L. Mernaugh,¹¹ Cheryl L. Laffer,¹ Fernando Elijovich,¹ Sean S. Davies,^{1,4} Heitor Moreno,² Meena S. Madhur,¹ Jackson Roberts II,^{1,4} and David G. Harrison^{1,4}

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Angio II => O₂^{•-} dans les DC provenant de la rate,
sauf en l'absence de Nox2

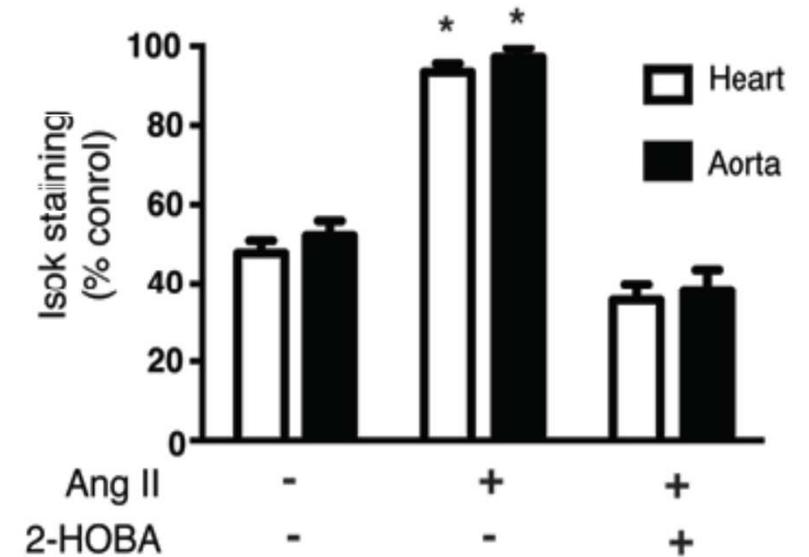
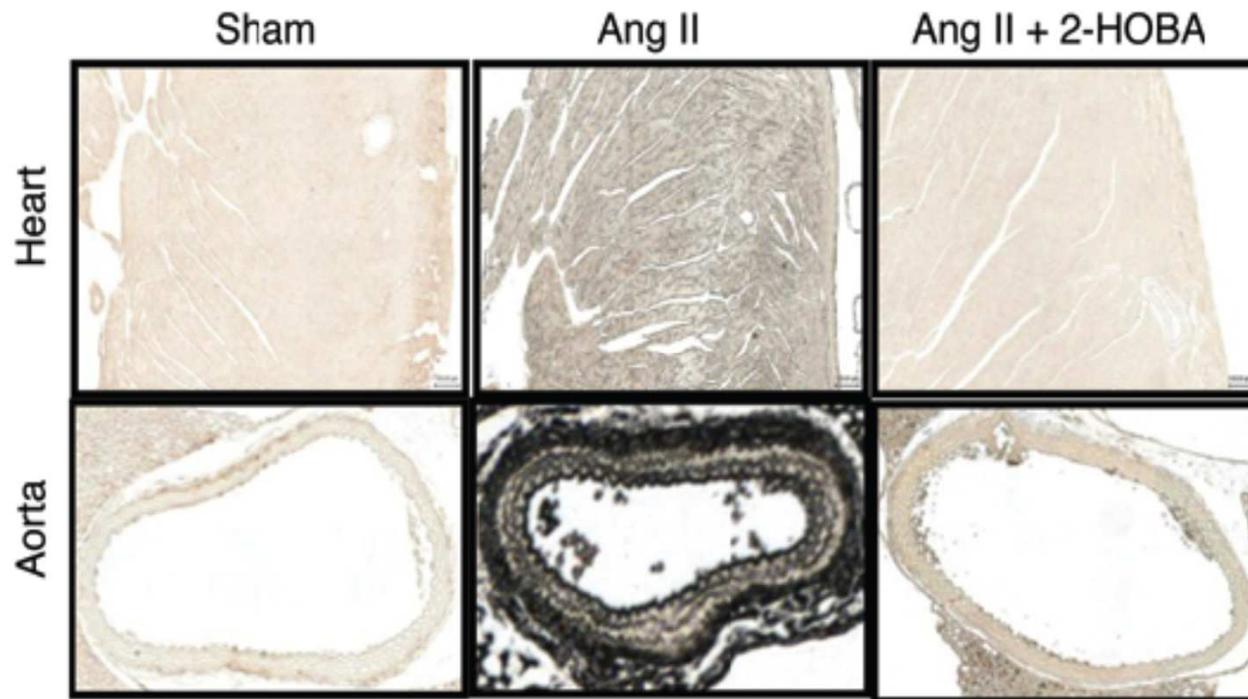


Baseline A 24h AII
In vitro, 100 nM pdt 24h



AII=> O₂^{•-} par une processus NOX2 dépendant

Angio II => accumulation d'isoketals dans cœur et vaisseaux, prévenue par l'adm. d'2-HOBA



immunohistochimie

Angio II => production Il-1b, Il-6 et Il-23 dans DC

Cytokine	Sham	Ang II
IL-1 α	7.82 \pm 3.74	5.86 \pm 2.19
IL-1 β	136.21 \pm 60.00	253.47 \pm 83.03 ^A
IL-2	9.75 \pm 1.03	10.45 \pm 1.77
IL-6	920.98 \pm 501.21	2385.13 \pm 1017.10 ^B
IL-12p40	0.00 \pm 0.00	0.00 \pm 0.00
IL-12p70	0.87 \pm 0.25	0.19 \pm 0.03
IL-23	23.30 \pm 17.17	85.13 \pm 36.69 ^B
GM-CSF	80.43 \pm 28.01	132.21 \pm 34.62
TGF- β 1	596.91 \pm 53.55	697.89 \pm 28.97
TGF- β 2	213.09 \pm 46.99	295.57 \pm 18.56
TGF- β 3	6.70 \pm 0.52	7.09 \pm 0.36

^A*P* < 0.05, ^B*P* < 0.001.

Angio II => prod. Il-1b, Il-6, Il-23 dans DC,
prévenue par l'administration d'un anti-oxydant (2-HOBA)

Cytokine	Sham	Ang II	Ang II + 2-HOBA
IL-1 α	7.82 \pm 3.74	5.86 \pm 2.19	0.00 \pm 0.00
IL-1 β	136.21 \pm 60.00	253.47 \pm 83.03 ^A	95.25 \pm 10.80
IL-2	9.75 \pm 1.03	10.45 \pm 1.77	10.164 \pm 3.63
IL-6	920.98 \pm 501.21	2385.13 \pm 1017.10 ^B	214.87 \pm 143.61
IL-12p40	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00
IL-12p70	0.87 \pm 0.25	0.19 \pm 0.03	0.16 \pm 0.06
IL-23	23.30 \pm 17.17	85.13 \pm 36.69 ^B	14.80 \pm 7.56
GM-CSF	80.43 \pm 28.01	132.21 \pm 34.62	110.48 \pm 65.12
TGF- β 1	596.91 \pm 53.55	697.89 \pm 28.97	681.63 \pm 11.92
TGF- β 2	213.09 \pm 46.99	295.57 \pm 18.56	309.85 \pm 7.13
TGF- β 3	6.70 \pm 0.52	7.09 \pm 0.36	6.99 \pm 0.23

^AP < 0.05, ^BP < 0.001.

Angio II => ↗ PAS, modulation par les scavengers d'isoketals

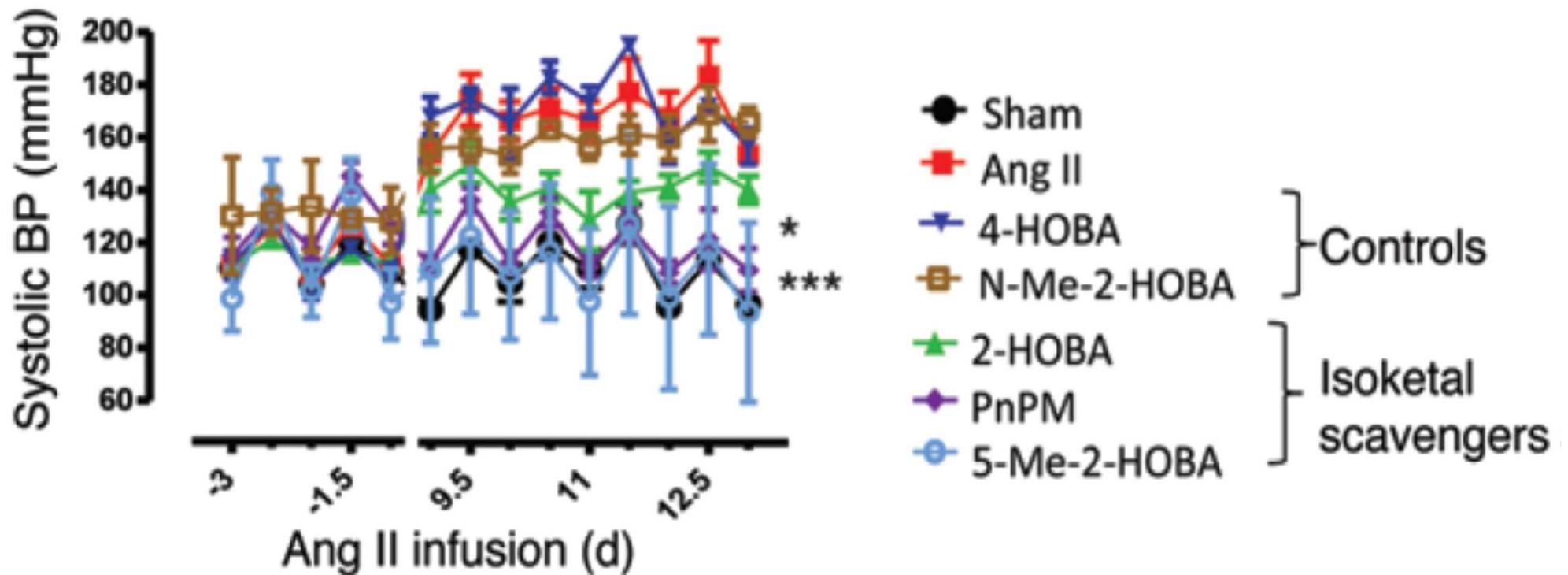


Figure 2. Isoketals contribute to angiotensin II hypertension and kidney damage. (A) Effect of isoketal scavengers 2-HOBA, 5-methyl-2-HOBA (5-Me-2-HOBA), and pentylpyridoxamine (PnPM) and control compounds N-methyl-2-HOBA (N-Me-2-HOBA) and 4-HOBA on the hypertensive

re: **Reference information:** *J Clin Invest.* 2014;124(10):4642-4656. doi:10.1172/JCI74084.

Angio II => fibrose rénale, modulation par les scavengers d'isoketals

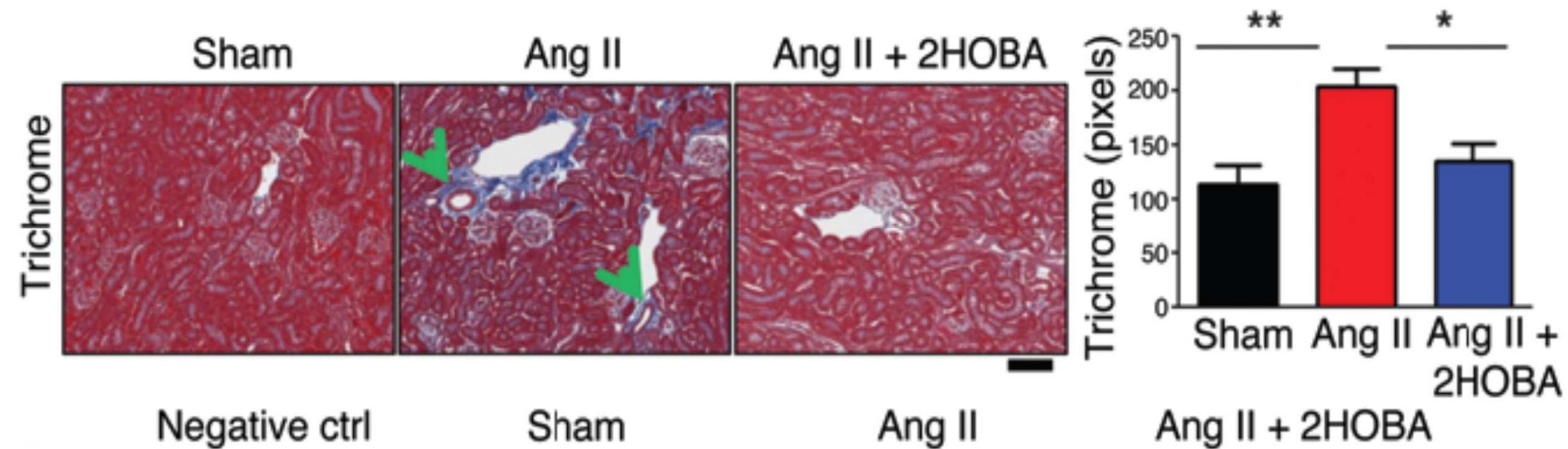
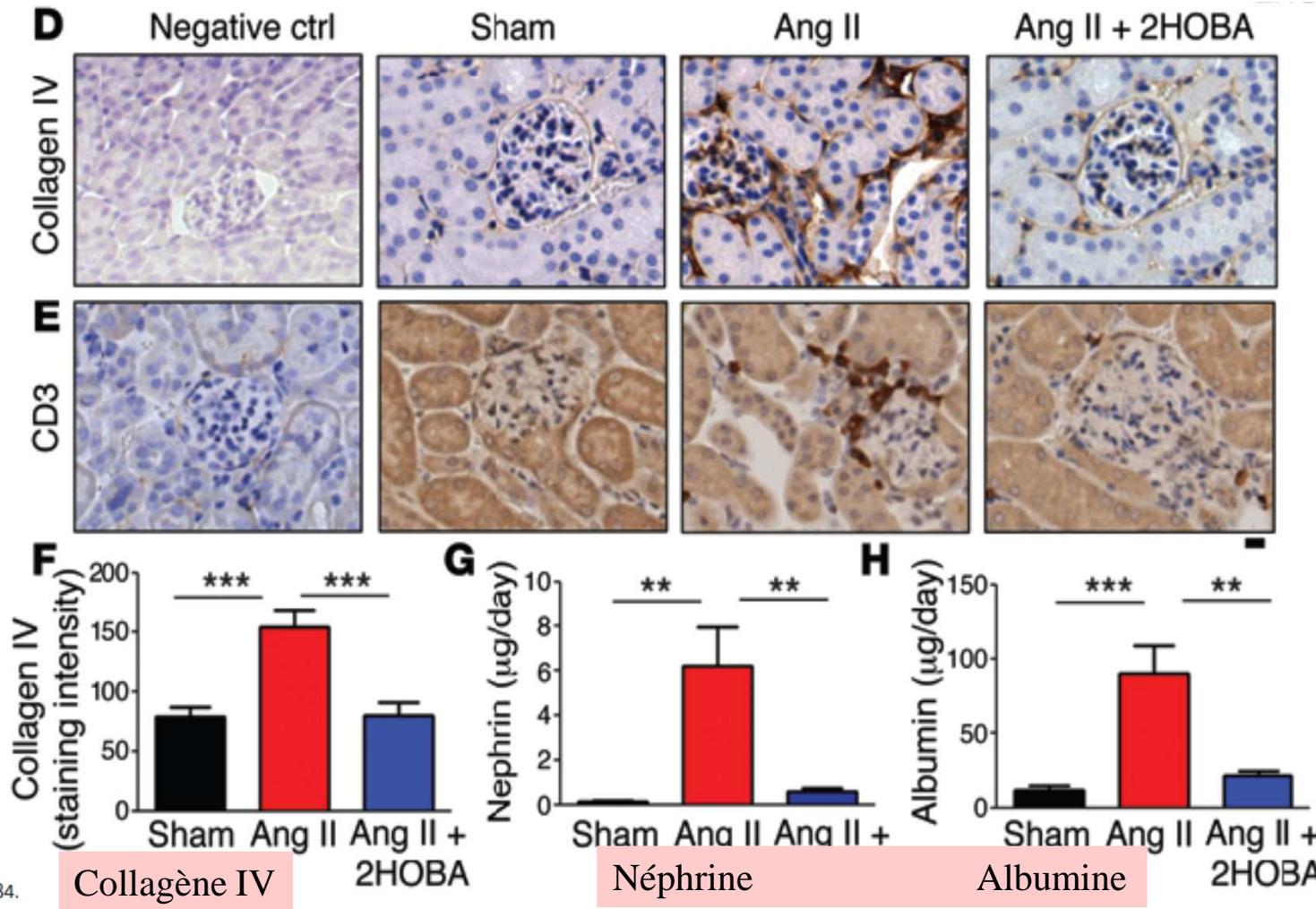


Figure 2. Isoketals contribute to angiotensin II hypertension and kidney damage. (A) Effect of isoketal scavengers 2-HOBA, 5-methyl-2-HOBA (5-Me-2-HOBA), and pentylpyridoxamine (PnPM) and control compounds N-methyl-2-HOBA (N-Me-2-HOBA) and 4-HOBA on the hypertensive

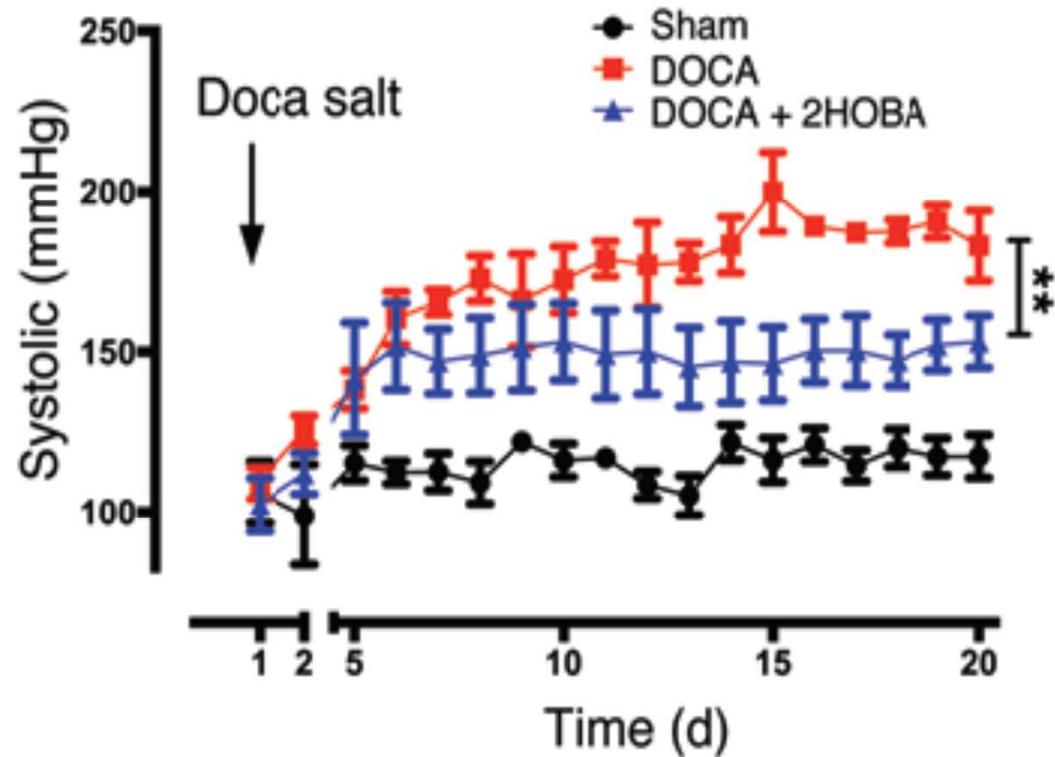
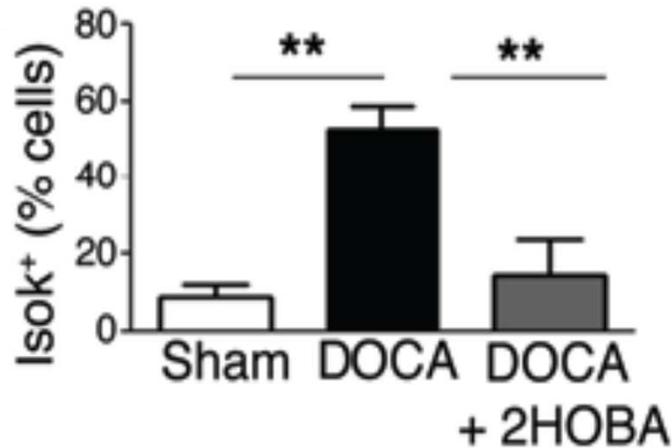
re: **Reference information:** *J Clin Invest.* 2014;124(10):4642-4656. doi:10.1172/JCI74084.

Angio II => coll. IV, infiltration CD3+, néphrinurie, d'albuminurie, modulation par les scavengers d'isoketals

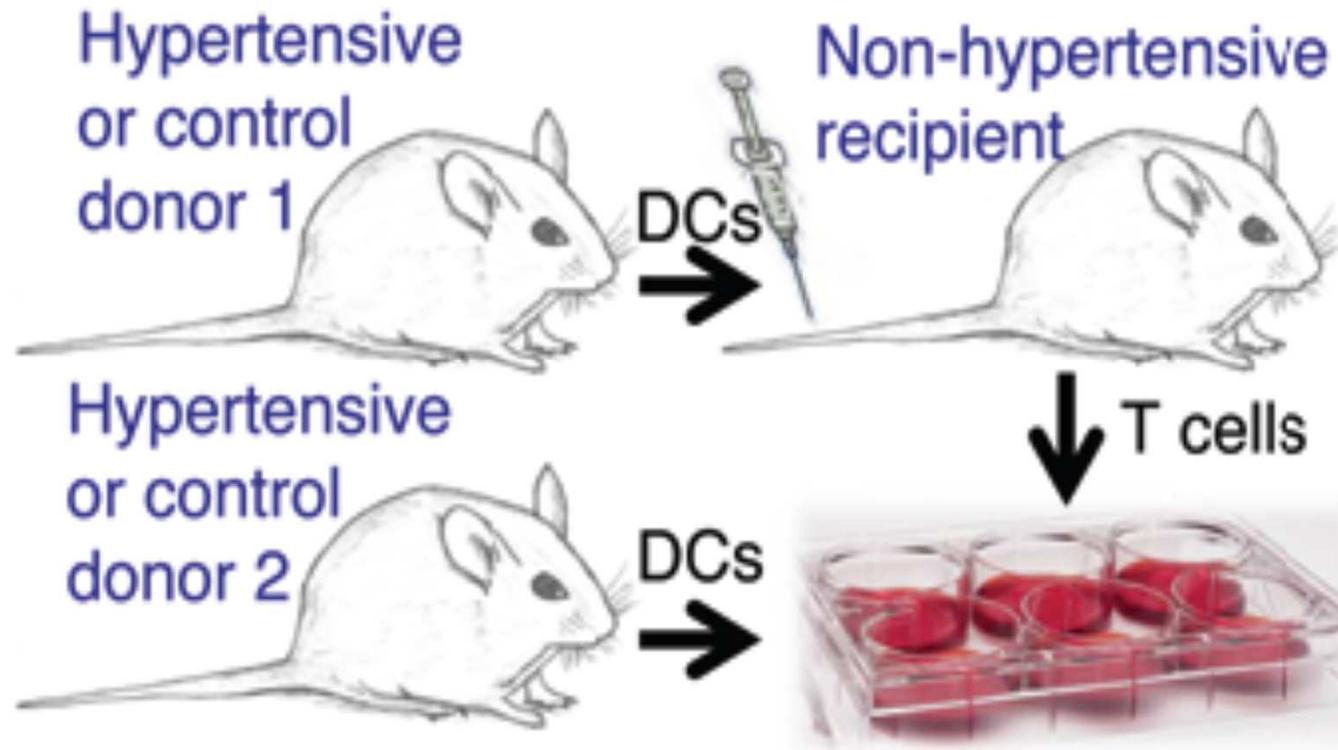


Quantification of total renal fibrosis. (D) Collagen IV staining in kidney sections (scale bar: 10 µm). (E) Anti-CD3 staining showing T cell infiltration in kidney sections from angiotensin II-infused mice (scale bar: 10 µm). (F) Quantification of collagen IV staining. (G) Nephrine and (H) albumin concentrations were measured in urine using an ELISA-based

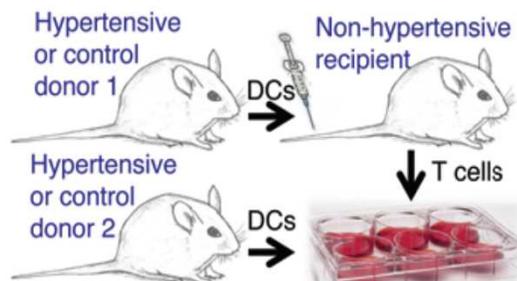
Résultat identique dans modèle DOCA-salt: effet sur PAS et isoketals dans CD11c+



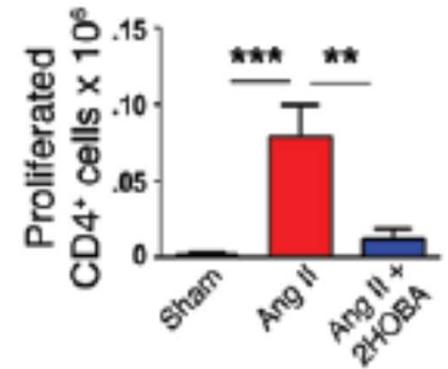
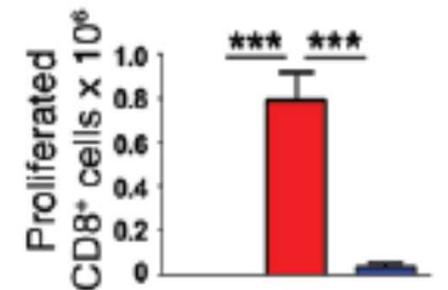
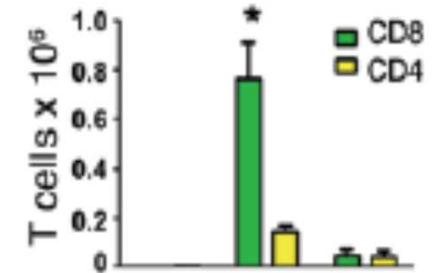
Ces effets sont-ils observés en transférant les DC des animaux HT aux NT?



Transfert des DC d'HT -> NT => prolifération des CD8+

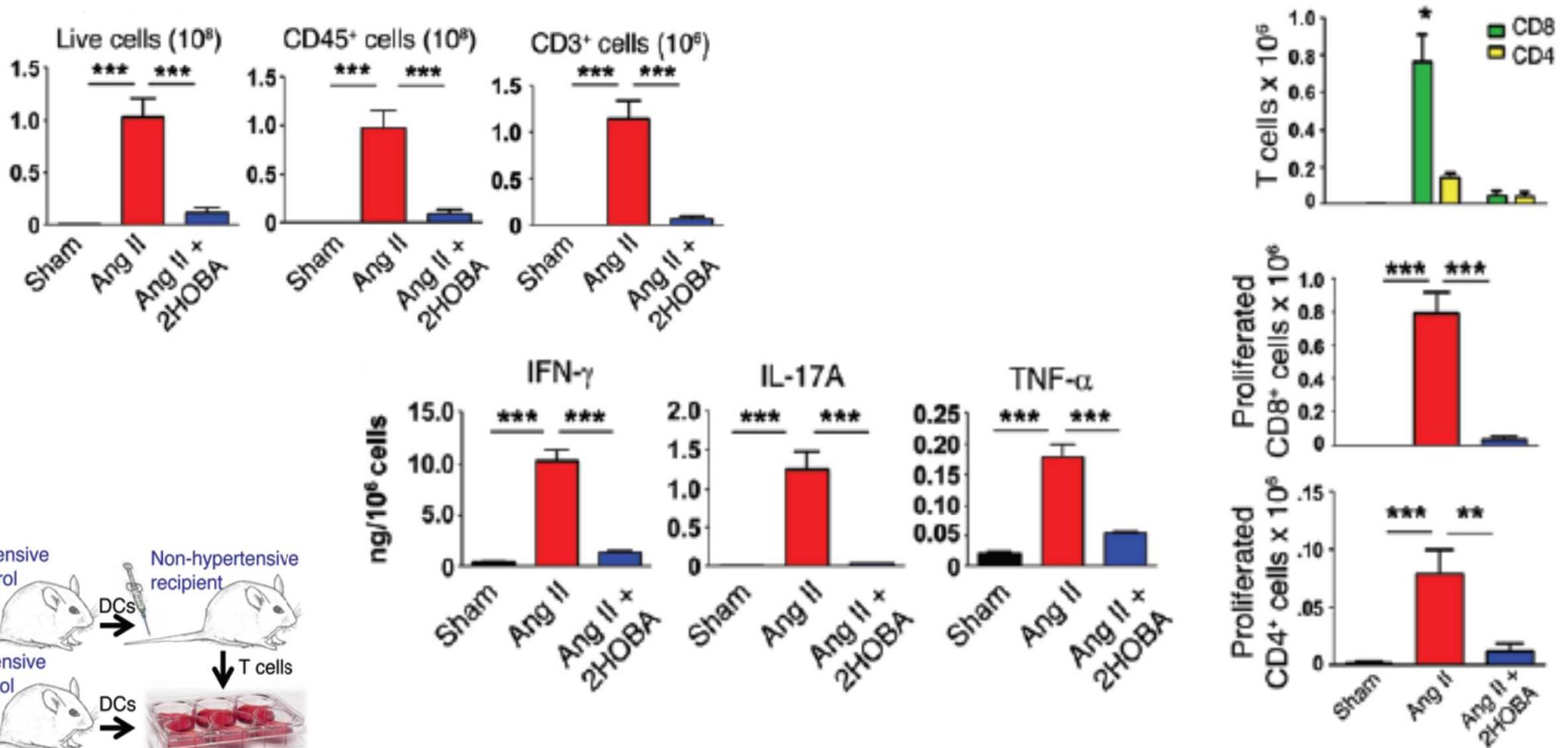


Reference information: *J Clin Invest.* 2014;124(10):4642-4656. doi:10.1172/JCI74084.

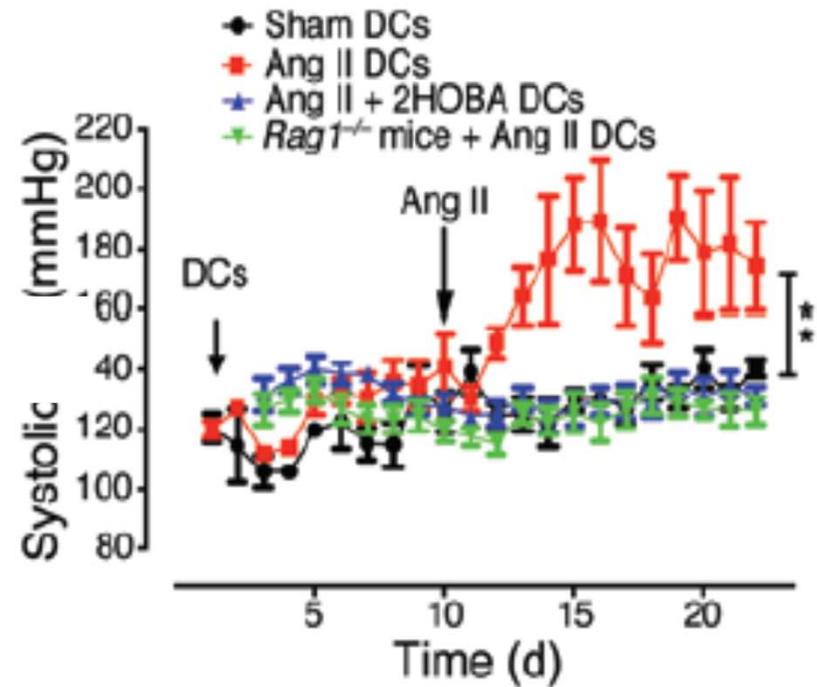
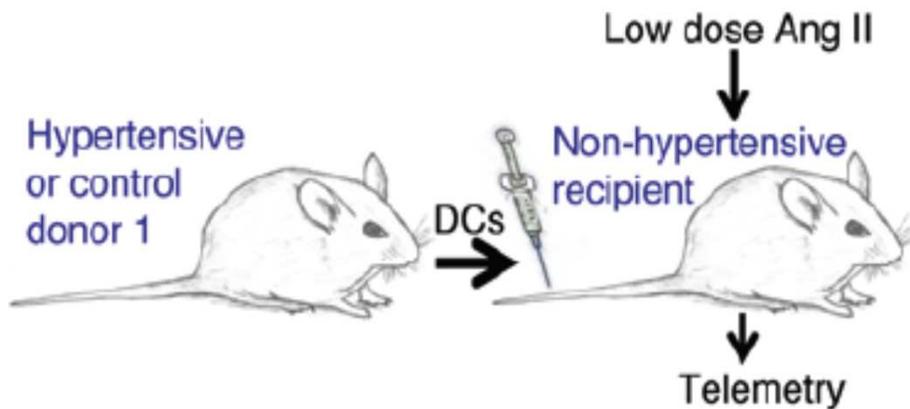


Transfert des DC d'HT -> NT

=> ces CD8+ synthétisent IL-17, Inf-g et TNF-a



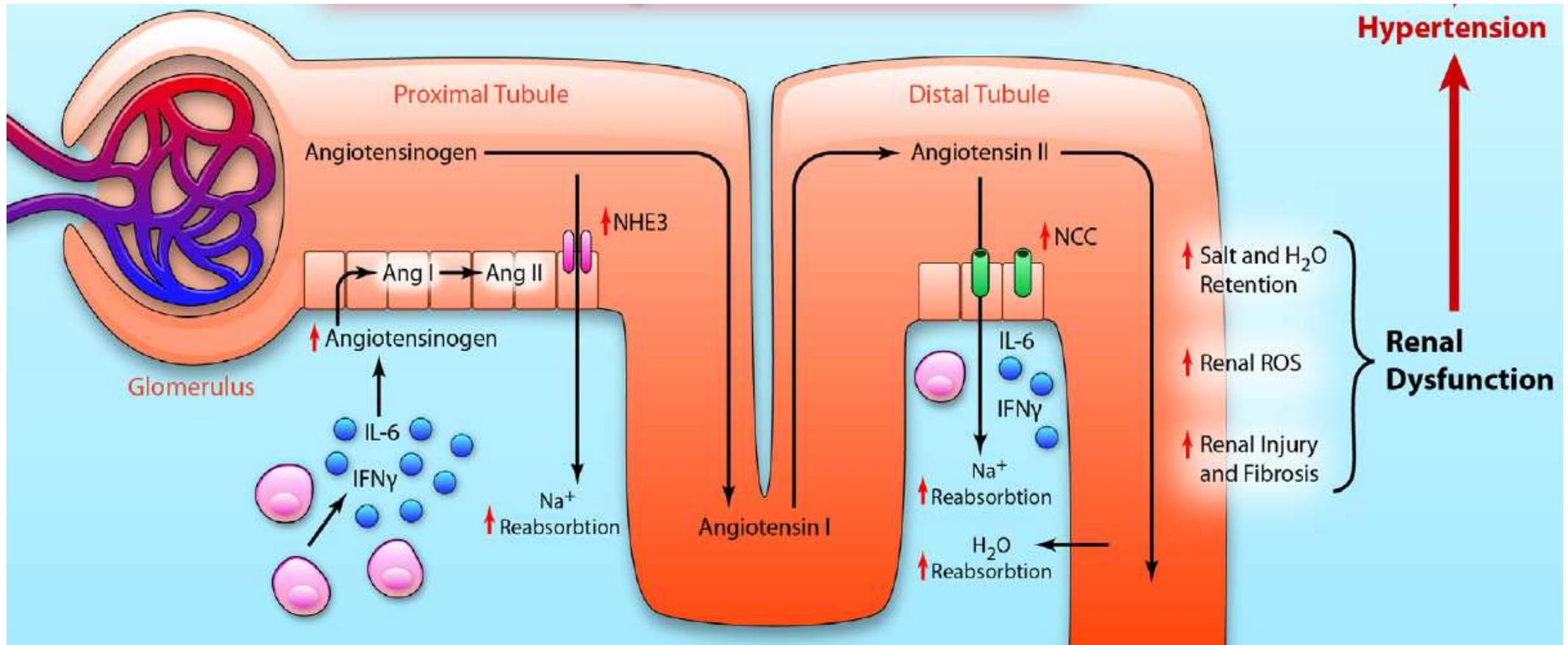
Transfert des DC d'HT -> NT => ↗ PA
sauf en l'absence de lymphocytes



HTA: réponse inflammatoire rénale à un stress oxydatif dans DC

- Angio II /DOCA-salt => $O_2^{\cdot-}$ dans DC
- $O_2^{\cdot-}$ dans DC => peroxydation lipidique (AA) => isoketals
- Isoketals => modification de protéines (liaisons covalentes sur résidus azotés)
- Protéines modifiées => se comportent comme des néo-Ag du soi modifié
- Néo-Ag => activation/maturation DC
 - ↗ CD80 et CD86
 - Cytokines: Il-6, Il-1 β , Il-23 -> activation lymphocytes CD8+ (mémoires)
- Activation lymphocytes CD8+
 - CD8+: prolifération (± CD4+ mémoires)
 - CD8+ => If γ , IL17 α , TNF α => shift rel. PA-Na+u
- ↗ PA transférable par DC d'animaux HT (DC se fixent dans rate, Ao, reins)

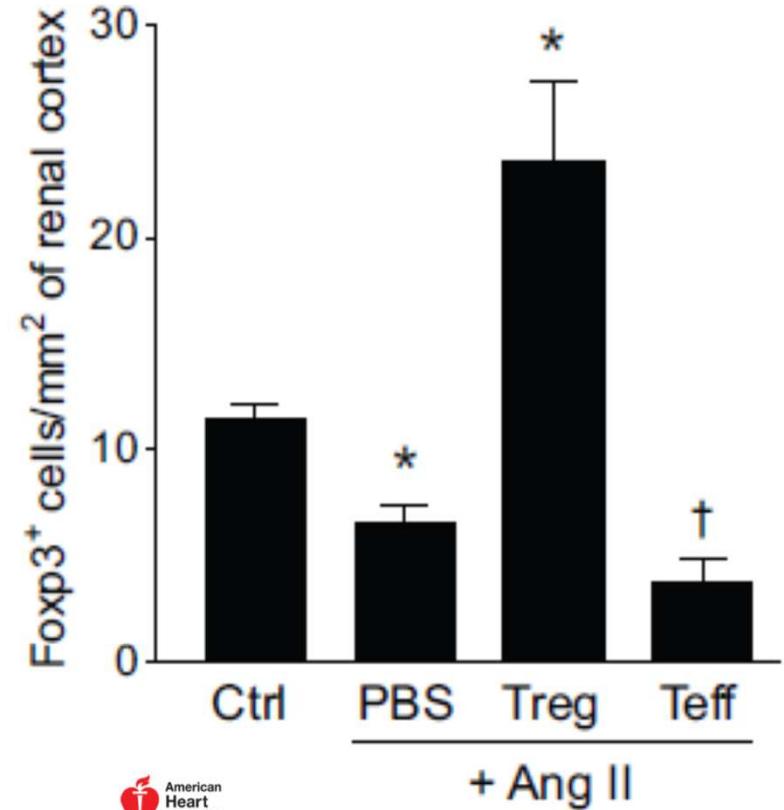
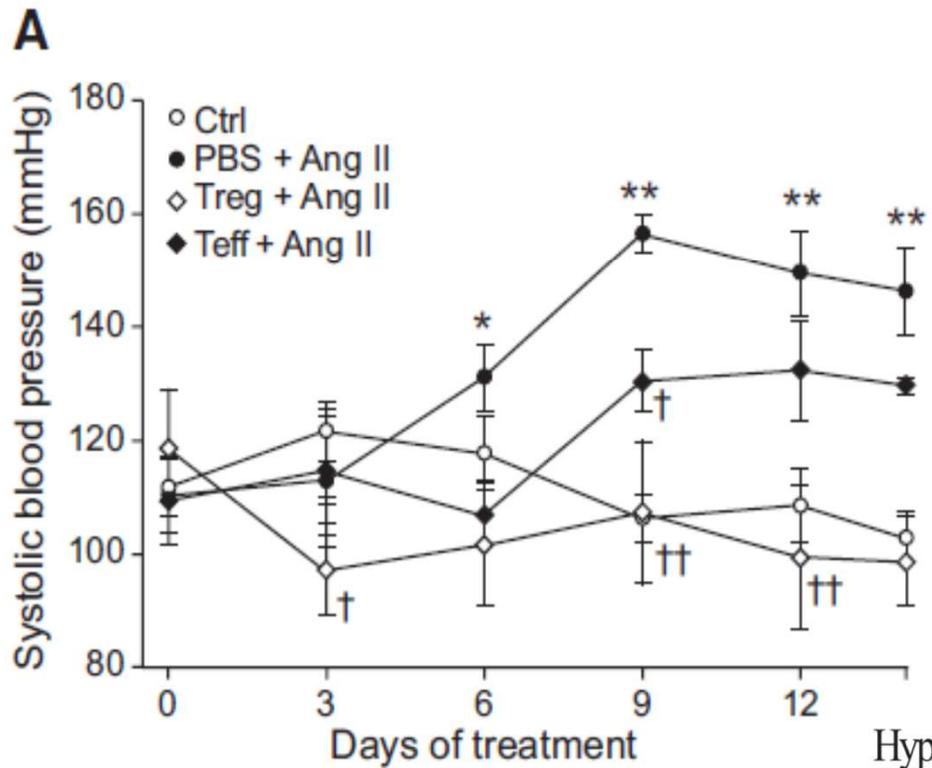
Processus NADPH-oxidase dép., en partie prévenu par des anti-oxydants spécifiques



Shift de la relation PA-natriurèse

Comment marchent les
médicaments?

Les lymphocytes T-reg \searrow PA (modèle d'HTA induite par angio II)



Lympho T-Reg \Rightarrow \searrow PA

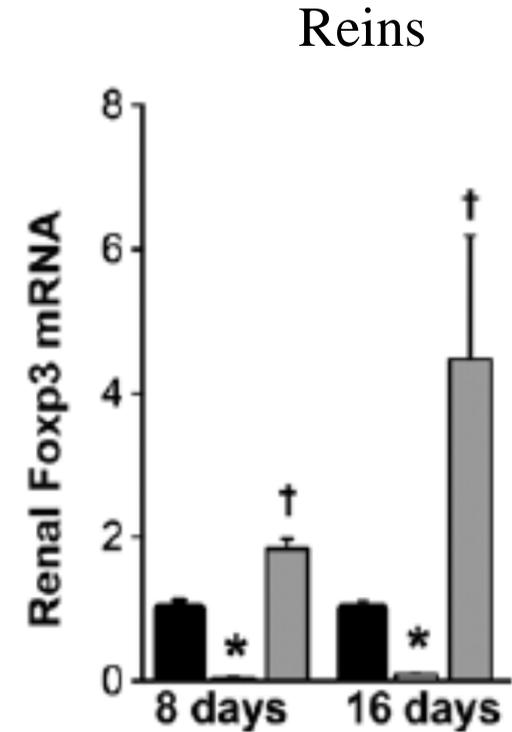
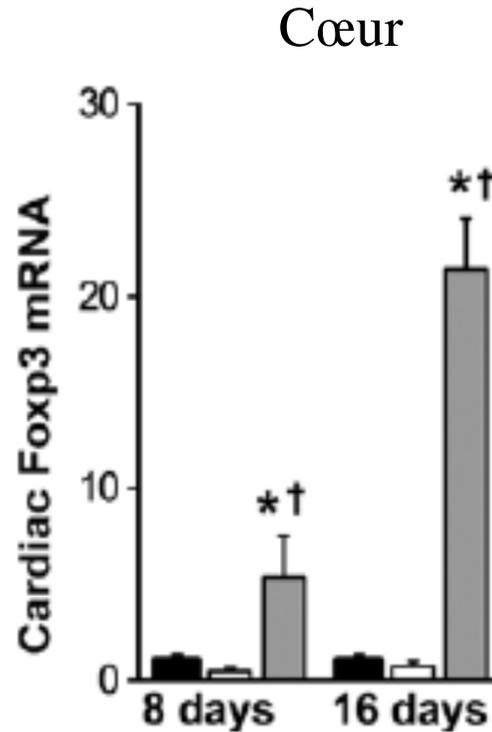
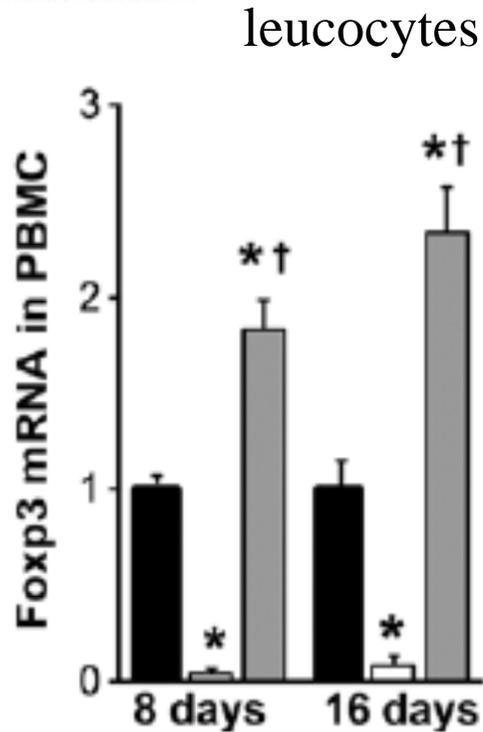
Hypertension



T Regulatory Lymphocytes Prevent Angiotensin II-Induced Hypertension and Vascular Injury
Tlili Barhoumi, Daniel A. Kasal, Melissa W. Li, Layla Sibat, Pascal Laurant, Mario F. Neves, Pierre Paradis and Ernesto L. Schiffrin

Hypertension. 2011;57:469-476; originally published online January 24, 2011;
doi: 10.1161/HYPERTENSIONAHA.110.162941

La spironolactone ↗ production Lympho T-Reg

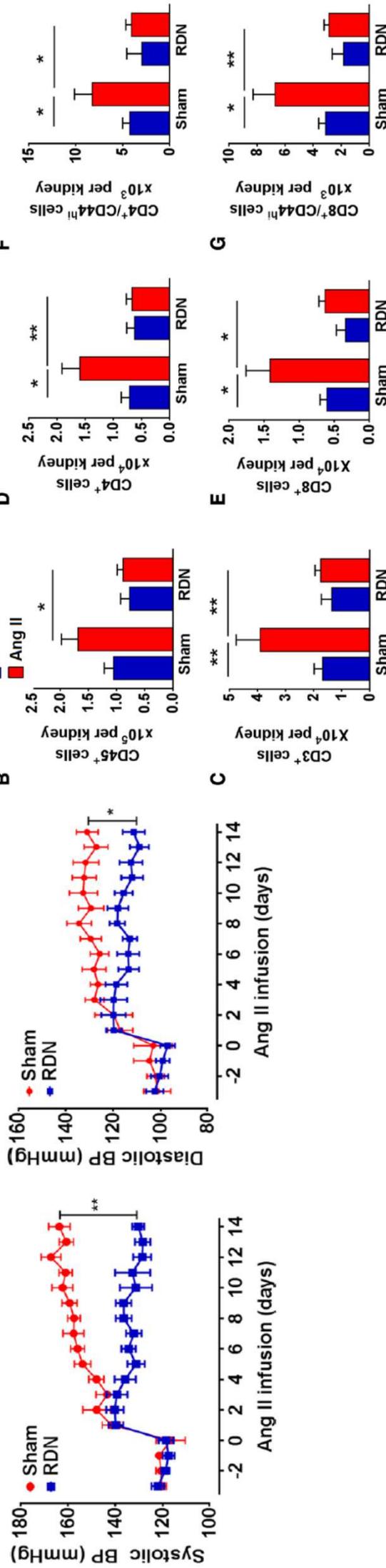
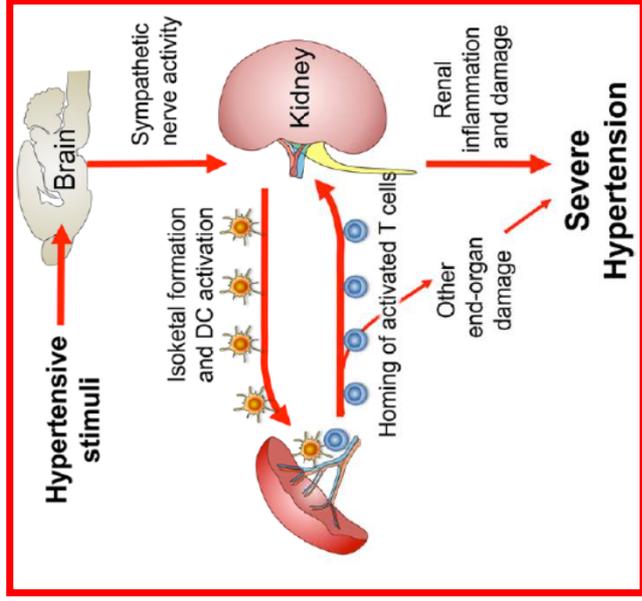


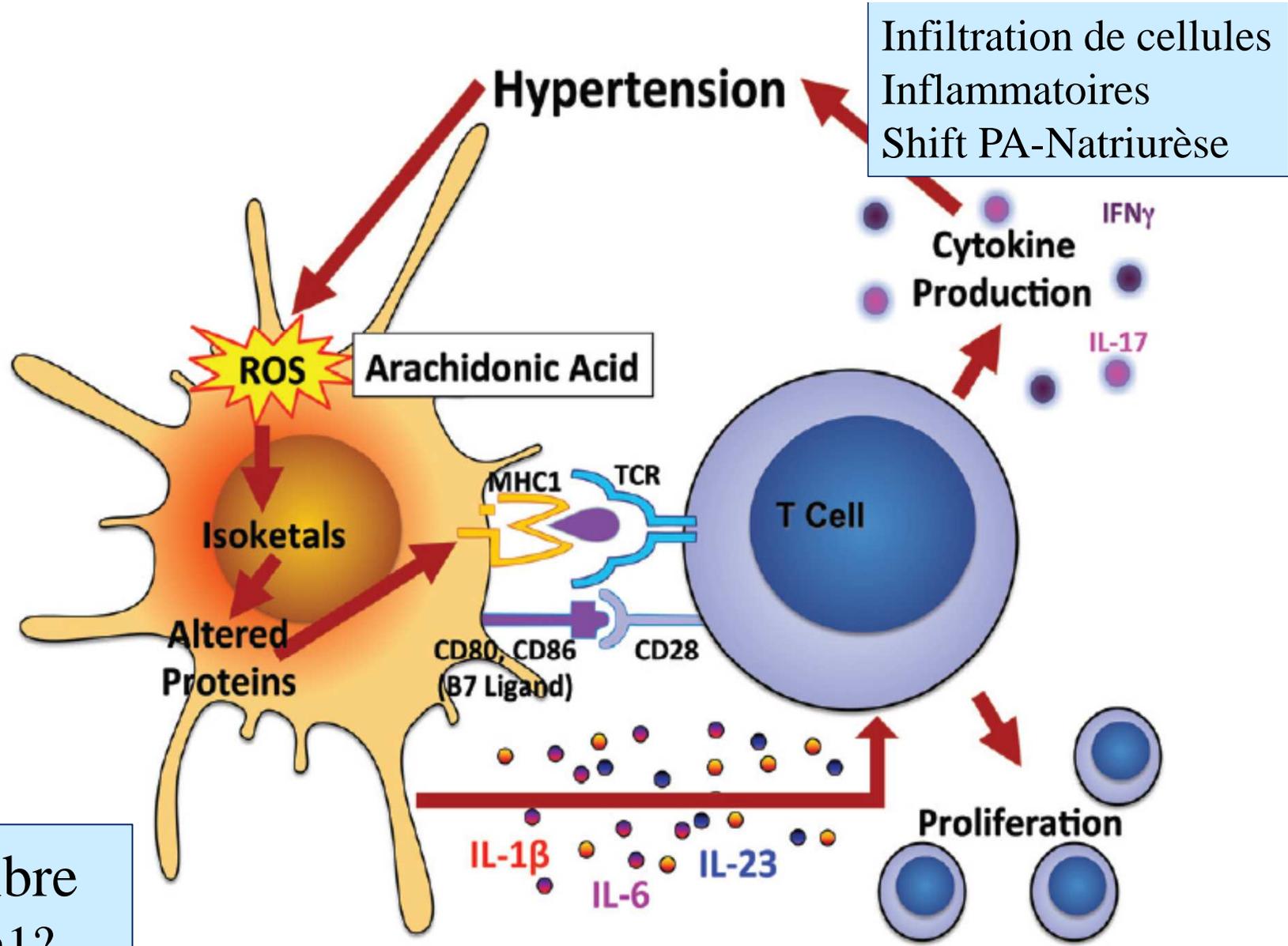
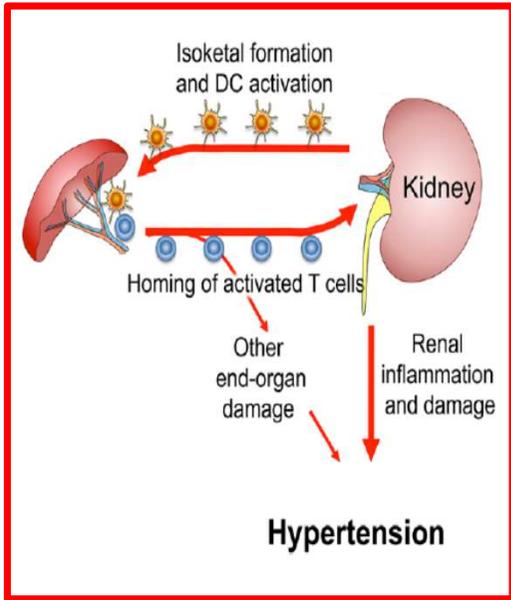
Comment marche la dénervation?
(si/quand ça marche)

Renal Denervation Prevents Immune Cell Activation and Renal Inflammation in Angiotensin II-Induced Hypertension

Liang Xiao, Annet Kirabo, Jing Wu, Mohamed A. Saleh, Linjue Zhu, Feng Wang, Takamune Takahashi, Roxana Loperena, Jason D. Foss, Raymond L. Mernaugh, Wei Chen, Jackson Roberts II, John W. Osborn, Hana A. Itani, David G. Harrison

Conclusions: Renal sympathetic nerves contribute to DC activation, subsequent T-cell infiltration and end-organ damage in the kidney in the development of hypertension. (*Circ Res.* 2015;117:547-557. DOI: 10.1161/CIRCRESAHA.115.306010.)





HTA \Leftrightarrow déséquilibre Th2/T-reg – Th17/Th1?