Coups de cœur 2010

Ce qui influence la recherche en hypertension au Québec

Le Mandat

- Donner un aperçu de la recherche d'impact en hypertension au cours de la dernière année
- Méthodologie
  - Appel aux récipiendaires du Prix du Jeune chercheur de la SQHA
  - Quelle est l'étude qui vous a le plus impressionné en 2010 et pourquoi?

Johanne Tremblay

- La rénalase: une nouvelle cible thérapeutique dans l'hypertension et la protection cardiaque post ischemie-réperfusion.

http://www.kidney-international.org original article

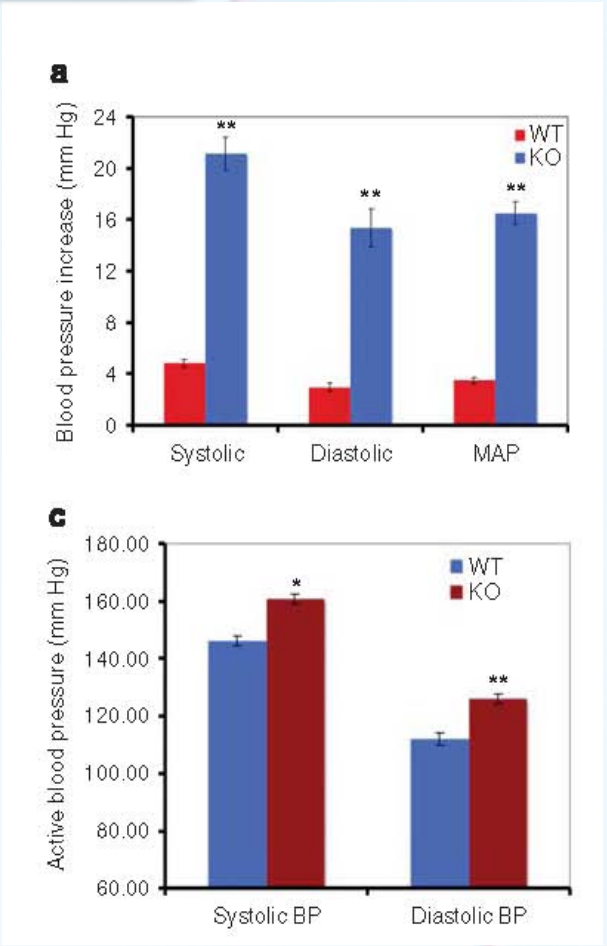
Renalase deficiency aggravates ischemic myocardial damage

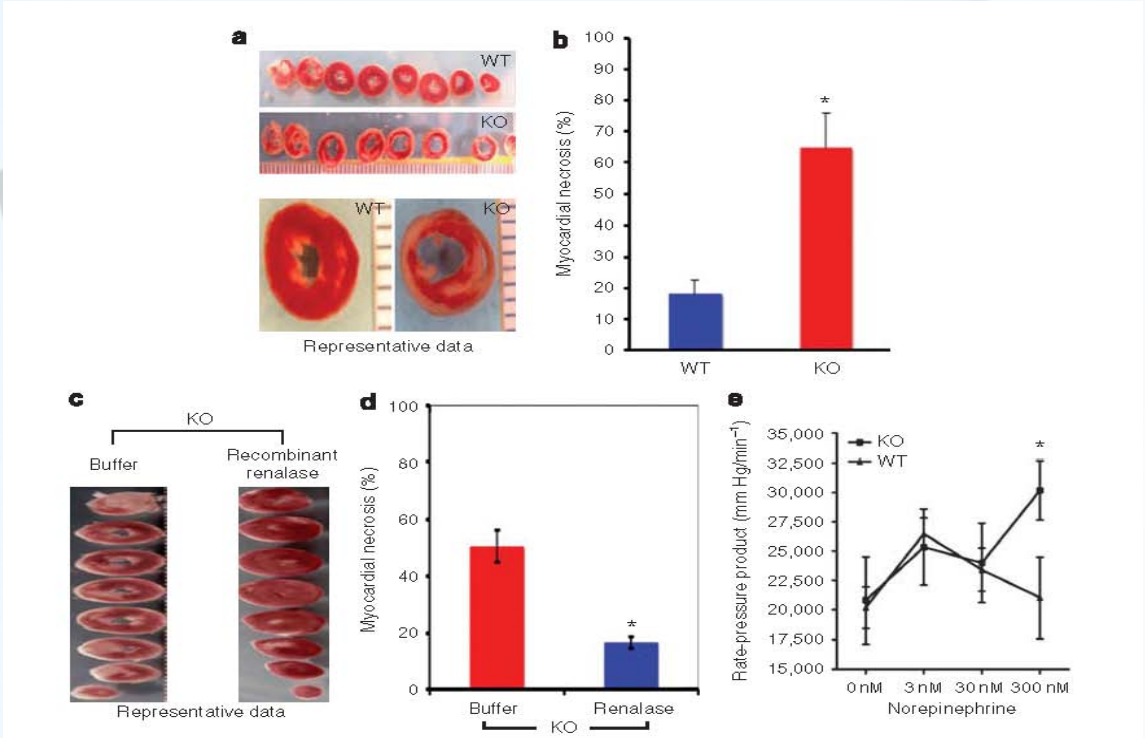
Yanling Wu[1,2,5], Jianchao Xu[1,2,5], Heino Velazquez[1,2], Peili Wang[1,2], Guoyong Li[1,2], Dinggang Liu[1], Benedita Sampaio-Maia[3], Janete Quelhas-Santos[3], Kerry Russell[1], Raymond Russell[1], Richard A. Flavell[4], Manuel Pestana[3], Frank Giordano[1] and Gary V. Desir[1,2]

[1]Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, USA; [2]VACHS Medical Center, West Haven, Connecticut, USA; [3]Nephrology Research and Development Unit, Faculty of Medicine, Hospital S. João, Porto, Portugal and [4]Department of Immunobiology, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, Connecticut, USA

Johanne Tremblay

La rénalase: une nouvelle cible thérapeutique dans l'hypertension et la protection cardiaque post ischemie-réperfusion





Yan Burelle

Integrative Physiology

DNA Damage Links Mitochondrial Dysfunction to Atherosclerosis and the Metabolic Syndrome

John R. Mercer, Kian-Kai Cheng, Nichola Figg, Isabelle Gorenne, Melli Mahmoudi, Julian Griffin, Antonio Vidal-Puig, Angela Logan, Michael P. Murphy, Martin Bennett

Rationale: **DNA damage is present in both genomic and mitochondrial DNA in atherosclerosis. However, whether DNA damage itself promotes atherosclerosis, or is simply a byproduct of the risk factors that promote atherosclerosis, is unknown.**

Objective: **To examine the effect of DNA damage on atherosclerosis, we studied apolipoprotein (Apo)$E^{-/-}$ mice that were haploinsufficient for the protein kinase ATM (ataxia telangiectasia mutated), which coordinates DNA repair.**

Methods and Results: **$ATM^{+/-}$/$ApoE^{-/-}$ mice developed accelerated atherosclerosis and multiple features of the metabolic syndrome, including hypertension, hypercholesterolemia, obesity, steatohepatitis, and glucose intolerance. Transplantation with $ATM^{+/+}$ bone marrow attenuated atherosclerosis but not the metabolic syndrome. $ATM^{+/-}$ smooth muscle cells and macrophages showed increased nuclear DNA damage and defective DNA repair signaling, growth arrest, and apoptosis. Metabolomic screening of $ATM^{+/-}$/$ApoE^{-/-}$ mouse tissues identified metabolic changes compatible with mitochondrial defects, with increased β-hydroxybutyrate but reduced lactate, reduced glucose, and alterations in multiple lipid species. $ATM^{+/-}$/$ApoE^{-/-}$ mouse tissues showed an increased frequency of a mouse mitochondrial "common" deletion equivalent and reduced mitochondrial oxidative phosphorylation.**

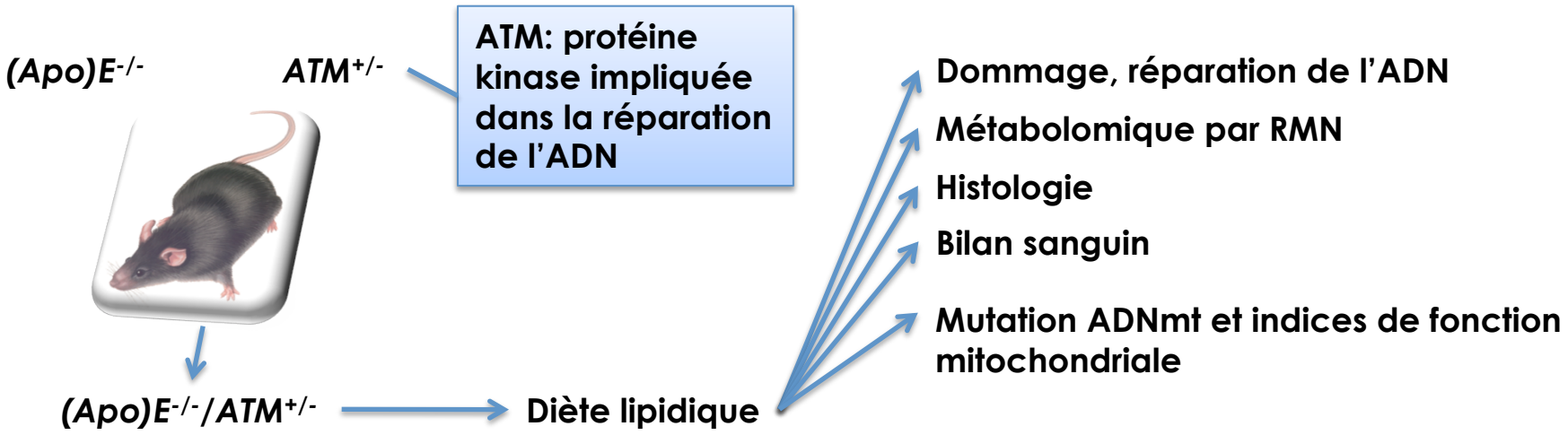
Conclusions: **We propose that failure of DNA repair generates defects in cell proliferation, apoptosis, and mitochondrial dysfunction. This in turn leads to ketosis, hyperlipidemia, and increased fat storage, promoting atherosclerosis and the metabolic syndrome. Prevention of mitochondrial dysfunction may represent a novel target in cardiovascular disease. (*Circ Res*. 2010;107:1021-1031.)**

Key Words: atherosclerosis ■ mitochondria ■ DNA damage ■ metabolic syndrome

Problématique:

Des mutations de l'ADN génomique et mitochondrial sont observés au cours de l'athérosclérose.

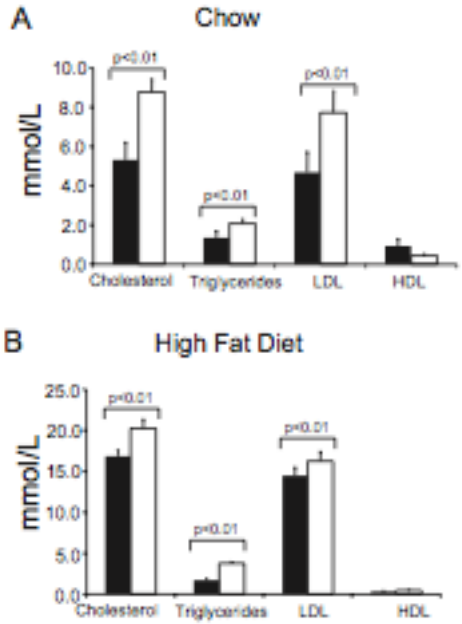
Cependant la question en suspens est de savoir si ces mutations sont causales dans la maladies ou simplement des conséquences de facteurs de risque qui favorisent l'athérosclérose.



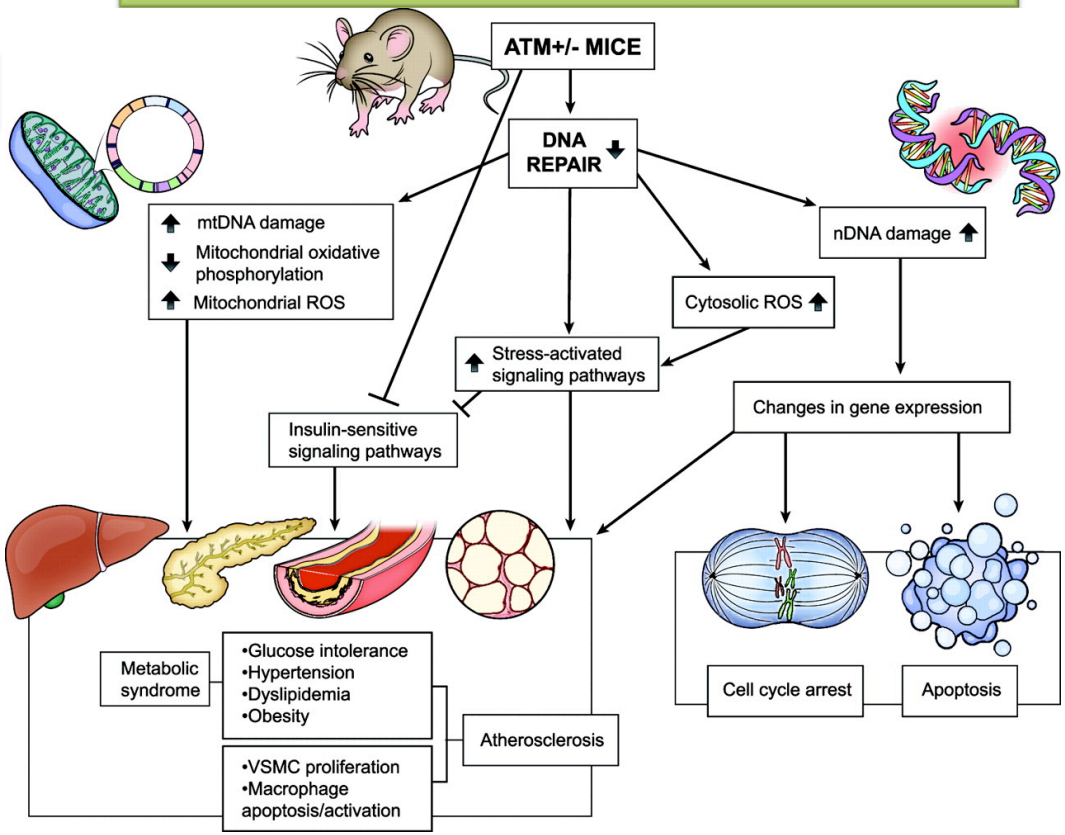
Athérosclérose accélérée chez las souris *ATM$^{+/-}$*

			Bone Marrow Transplant	
	ATM$^{+/+}$ (n=13)	ATM$^{+/-}$ (n=15)	ATM$^{+/+}$→ATM$^{+/+}$ (n=7)	ATM$^{+/+}$ →ATM$^{+/-}$ (n=8)
Aortic Plaque area (mm^2)	4.76±1.07	8.26±2.32*	2.78±0.73	2.03±0.91
Aortic Root per Plaque area (μm^2)	63.93±12.9	103.14±17.4*	81.94±22.5	114.17±22.4
SMA positive area (%)	5.68±1.72	4.23±0.83	13.92±6.94	11.9±2.92
MAC positive area (%)	39.81±3.53	32.42±4.63	46.47±10.14	58.66±6.99
Necrotic core area (%)	34.35±4.15	34.30±5.74	71.91±5.57	66.31±3.39
Ki67 positive cells (%)	0.68±0.10	0.29±0.1	0.89±0.20	2.15±0.55*
Cleaved caspase 3–positive cells (%)	0.55±0.07	0.22±0.07*	0.82±0.15	0.28±0.17*

Hyperlipidémie chez las souris *ATM$^{+/-}$*



Plusieurs mécanismes potentiels identifiés



Principaux aspects remarquables:

- Le modèle animal utilisé est original et permet de manipuler sélectivement le processus de réparation de l'ADN.

- Les approches expérimentales sont diversifiées.

- Cette étude est la première à démontrer de manière directe que les mutations non spécifiques de l'ADN nucléaire et mitochondrial sont suffisantes pour induire des dysfonctions mitochondriales, un syndrome métabolique et l'athérosclérose.

Mohsen Agharazii

BASIC RESEARCH www.jasn.org

Klotho Deficiency Causes Vascular Calcification in Chronic Kidney Disease

Ming Chang Hu,*†‡ Mingjun Shi,* Jianning Zhang,† Henry Quiñones,† Carolyn Griffith,* Makoto Kuro-o,*§ and Orson W. Moe*†‖

*Charles and Jane Pak Center for Mineral Metabolism and Clinical Research and Departments of †Internal Medicine, §Pathology, ‖Physiology, and ‡Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas

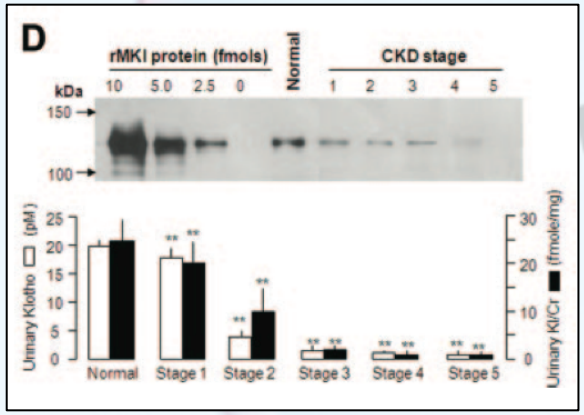
ABSTRACT

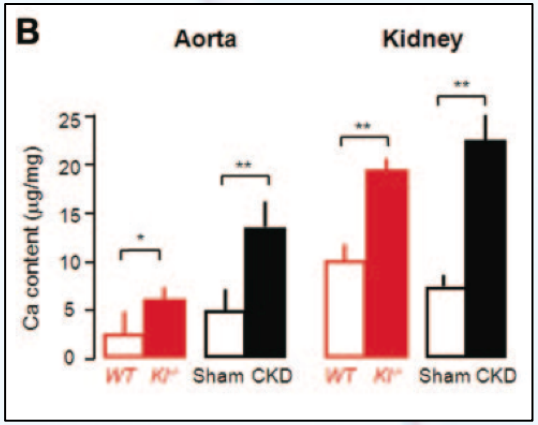
Soft-tissue calcification is a prominent feature in both chronic kidney disease (CKD) and experimental Klotho deficiency, but whether Klotho deficiency is responsible for the calcification in CKD is unknown. Here, wild-type mice with CKD had very low renal, plasma, and urinary levels of Klotho. In humans, we observed a graded reduction in urinary Klotho starting at an early stage of CKD and progressing with loss of renal function. Despite induction of CKD, transgenic mice that overexpressed Klotho had preserved levels of Klotho, enhanced phosphaturia, better renal function, and much less calcification compared with wild-type mice with CKD. Conversely, Klotho-haploinsufficient mice with CKD had undetectable levels of Klotho, worse renal function, and severe calcification. The beneficial effect of Klotho on vascular calcification was a result of more than its effect on renal function and phosphatemia, suggesting a direct effect of Klotho on the vasculature. *In vitro*, Klotho suppressed Na^+-dependent uptake of phosphate and mineralization induced by high phosphate and preserved differentiation in vascular smooth muscle cells. In summary, Klotho is an early biomarker for CKD, and Klotho deficiency contributes to soft-tissue calcification in CKD. Klotho ameliorates vascular calcification by enhancing phosphaturia, preserving glomerular filtration, and directly inhibiting phosphate uptake by vascular smooth muscle. Replacement of Klotho may have therapeutic potential for CKD.

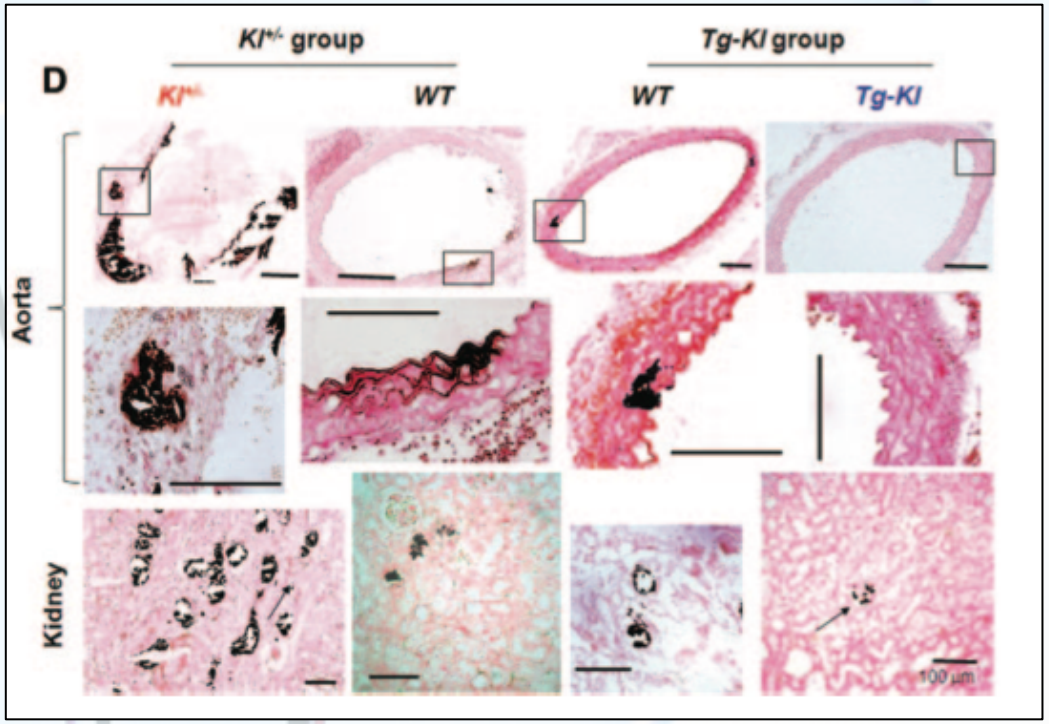
J Am Soc Nephrol 22: 124–136, 2011. doi: 10.1681/ASN.2009121311

Mohsen Agharazii

- La maladie rénale chronique entraîne une hyperphosphatémie, un facteur de risque pour la calcification vasculaire.
- Klotho était connue comme une protéine transmembranaire agissant comme un co-recepteur de FGF-23 permettant d'éliminer l'excès de phosphate.
- Ce papier montre d'abord que Klotho prévient l'insuffisance rénale et la calcification vasculaire.

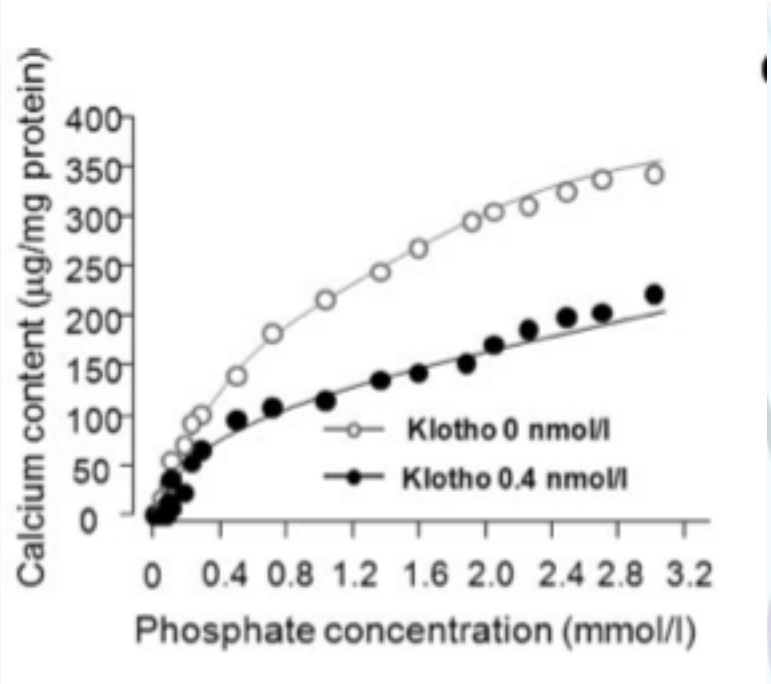


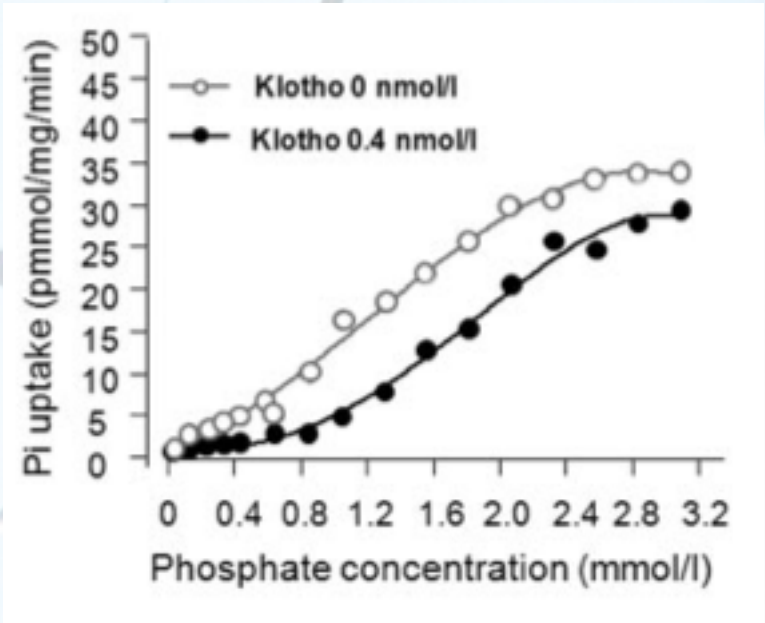




Mohsen Agharazii

- Ensuite, ce papier révèle un rôle pour la forme soluble de Klotho.
- Klotho libre est capable de réguler le taux d'incorporation de phosphate intracellulaire des cellules musculaires lisses (et par conséquence leur transdifférenciation vers des ostéoblast-like)





Mohsen Agharazii

IMPACT

- Ce papier renforce la position de Klotho comme biomarqueur précoce de de maladie rénale chronique et souligne l'importance de cette molécule en tant qu'hormone.
- La restauration de Klotho peut devenir un cible thérapeutique pour préserver la fonction rénale et réduire les complications cardiovasculaires de l'insuffisance rénale.

Anne-Monique Nuyt

Science (2010) **329:72-75**

Genetic Evidence for High-Altitude Adaptation in Tibet

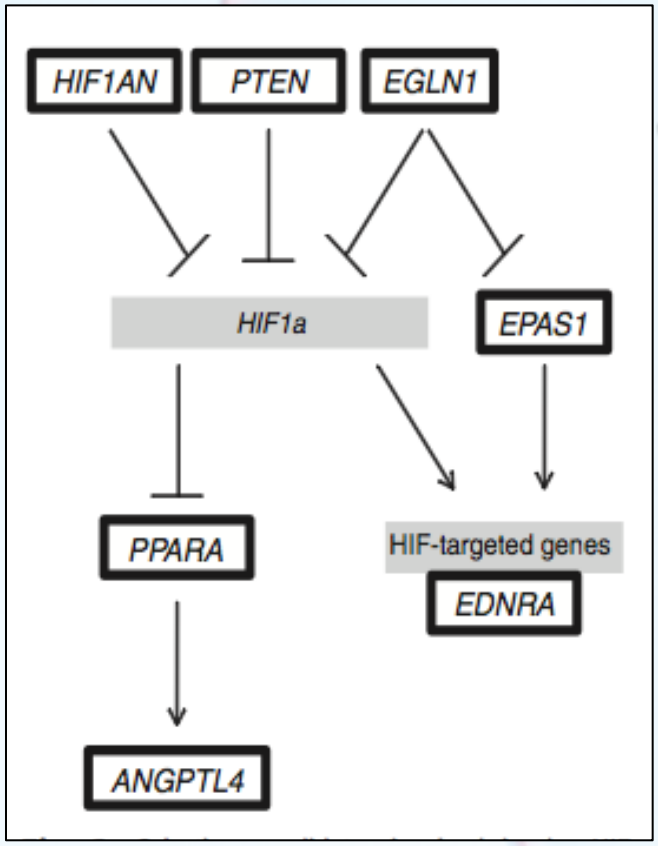
Tatum S. Simonson,[1] Yingzhong Yang,[2*] Chad D. Huff,[1] Haixia Yun,[2*] Ga Qin,[2*] David J. Witherspoon,[1] Zhenzhong Bai,[2*] Felipe R. Lorenzo,[3] Jinchuan Xing,[1] Lynn B. Jorde,[1†] Josef T. Prchal,[1,3†] RiLi Ge[2*†]

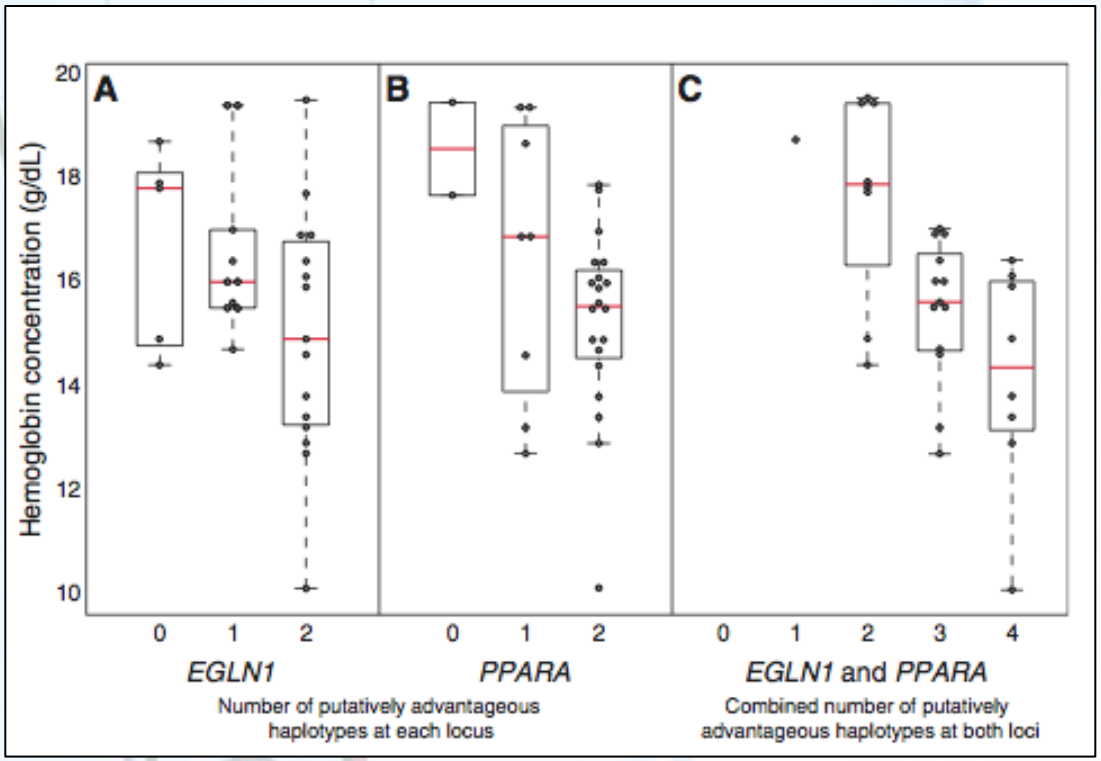
The high life. Tibetans, who have lived at high altitudes for nearly 25,000 years, survive the low-oxygen environment through a low blood hemoglobin concentration.

- Les Tibétains sont les seuls humains pouvant maintenir un taux d'hémoglobine normal à haute altitude (4 000 m). Tous les autres humains (même les habitants des Andes) ont une polycythémie importante à ces altitudes.
- Comment expliquer la résistance à l'hypoxie des Tibétains?

Anne-Monique Nuyt

- *Genome-wide scan*
- Analyse de 1 millions de SNP chez 31 tibétains et comparaison avec carte des haplotypes dans les populations chinoise Han et japonaise.
- Les principaux gènes soumis à une pression de sélection positive pour l'adaptation à la vie en altitude sont dans la voie de HIF et les SNP favorables sont associés à une *baisse* des concentration d'hémoglobine dans le sang.





Anne-Monique Nuyt

IMPACT

- On sait qu'une augmentation de l'hémoglobine dans le sang maternel est associé à une réduction de la croissance de la survie fœtal.
- Ce papier illustre bien que l'hypoxie ne doit pas être considérée seule comme élément délétère au cours de la vie fœtale, mais que d'autres facteurs comme la polycythémie qui existe en réponse à l'hypoxie pourrait être davantage délétère (augmentation de la viscosité et réduction du débit sanguin aux plus petits vaisseaux aux organes).
- Ces gènes peuvent aussi nous indiquer des voies de « résistance » à l'hypoxie qu'il serait importantes à comprendre pour les fœtus et nouveau nés en développement.

Marc Servant

Promotion of CHIP-Mediated p53 Degradation Protects the Heart From Ischemic Injury

Atsuhiko T. Naito, Sho Okada, Tohru Minamino, Koji Iwanaga, Mei-Lan Liu, Tomokazu Sumida, Seitaro Nomura, Naruhiko Sahara, Tatsuya Mizoroki, Akihiko Takashima, Hiroshi Akazawa, Toshio Nagai, Ichiro Shiojima, Issei Komuro

Rationale: The number of patients with coronary heart disease, including myocardial infarction, is increasing and novel therapeutic strategy is awaited. Tumor suppressor protein p53 accumulates in the myocardium after myocardial infarction, causes apoptosis of cardiomyocytes, and plays an important role in the progression into heart failure.

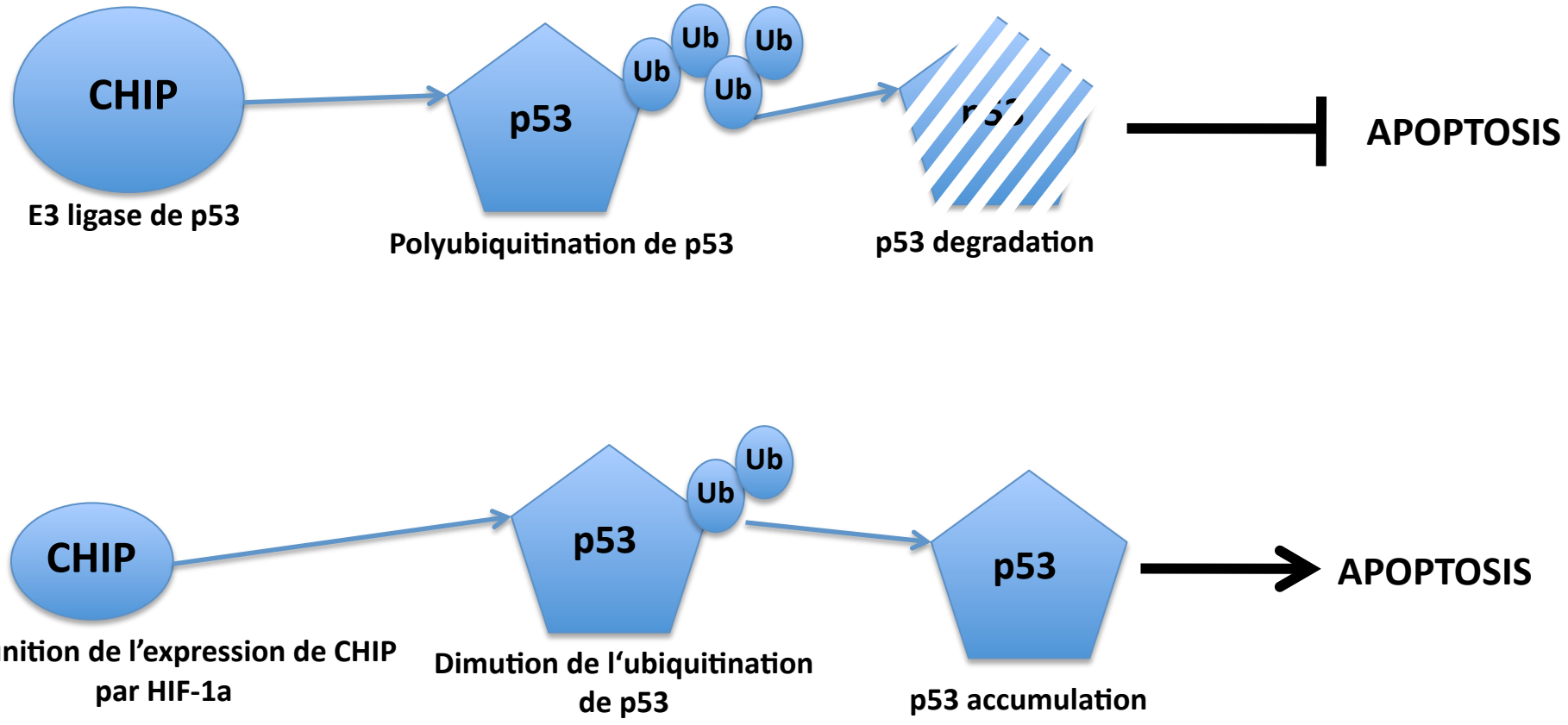
Objectives: We investigated the molecular mechanisms of p53 accumulation in the heart after myocardial infarction and tested whether anti-p53 approach would be effective against myocardial infarction.

Methods and Results: Through expression screening, we found that CHIP (carboxyl terminus of Hsp70-interacting protein) is an endogenous p53 antagonist in the heart. CHIP suppressed p53 level by ubiquitinating and inducing proteasomal degradation. CHIP transcription was downregulated after hypoxic stress and restoration of CHIP protein level prevented p53 accumulation after hypoxic stress. CHIP overexpression in vivo prevented p53 accumulation and cardiomyocyte apoptosis after myocardial infarction. Promotion of CHIP function by heat shock protein (Hsp)90 inhibitor, 17-allylamino-17-demethoxy geldanamycin (17-AAG), also prevented p53 accumulation and cardiomyocyte apoptosis both in vitro and in vivo. CHIP-mediated p53 degradation was at least one of the cardioprotective effects of 17-AAG.

Conclusions: We found that downregulation of CHIP level by hypoxia was responsible for p53 accumulation in the heart after myocardial infarction. Decreasing the amount of p53 prevented myocardial apoptosis and ameliorated ventricular remodeling after myocardial infarction. We conclude that anti-p53 approach would be effective to treat myocardial infarction. (*Circ Res.* 2010;106:1692-1702.)

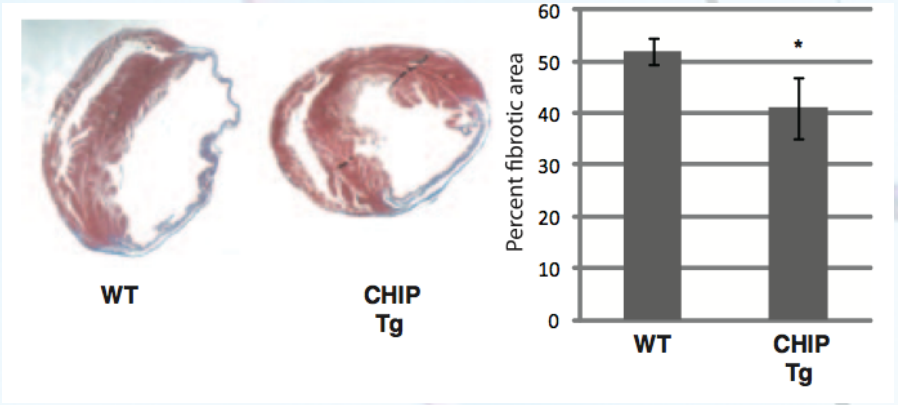
Key Words: myocardial infarction ■ CHIP ■ p53 ■ hypoxia

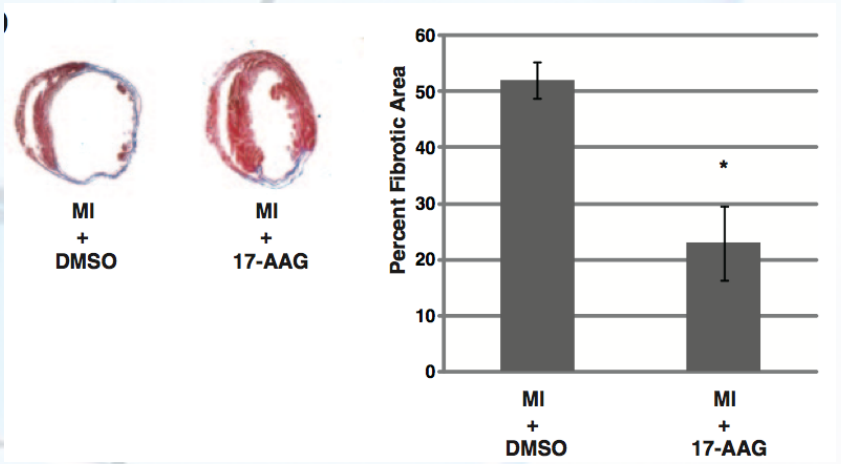
Marc Servant



Marc Servant

- La surexpression de p53 en post-infarctus cause une augmentation de l'apoptose des cardiomyocytes.
- La protéine CHIP (carboxyl terminus of Hsp70-interacting protein) est un inhibiteur naturel de p53 dans le cœur.
- CHIP est diminué par l'hypoxie.
- Empêcher la suppression de CHIP dans le cœur augmente la survie cardiaque post-ischémie.





Marc Servant

IMPACT

- Une étude qui identifie un nouveau régulateur important de p53 dans le cœur.
- La stimulation de la dégradation de p53 par CHIP représente une nouvelles stratégie dans le traitement des maladies cardiaques.

Guy Rousseau

Molecular Cardiology

Myocardial Ischemia/Reperfusion Injury Is Mediated by Leukocytic Toll-Like Receptor-2 and Reduced by Systemic Administration of a Novel Anti–Toll-Like Receptor-2 Antibody

Fatih Arslan, MD; Mirjam B. Smeets, PhD; Luke A.J. O'Neill, PhD; Brian Keogh, PhD; Peter McGuirk, PhD; Leo Timmers, MD, PhD; Claudia Tersteeg, MSc; Imo E. Hoefer, MD, PhD; Pieter A. Doevendans, MD, PhD; Gerard Pasterkamp, MD, MSc, PhD; Dominique P.V. de Kleijn, PhD

Background—Reperfusion therapy for myocardial infarction is hampered by detrimental inflammatory responses partly via Toll-like receptor (TLR) activation. Targeting TLR signaling may optimize reperfusion therapy and enhance cell survival and heart function after myocardial infarction. Here, we evaluated the role of TLR2 as a therapeutic target using a novel monoclonal anti-TLR2 antibody.

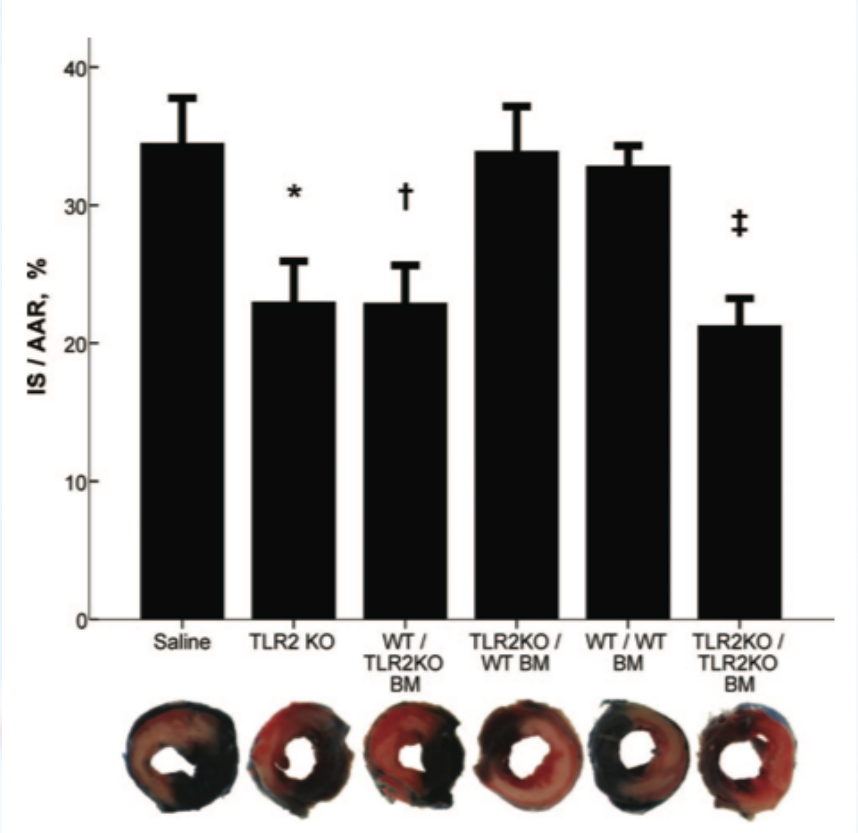
Method and Results—Mice underwent 30 minutes of ischemia followed by reperfusion. Compounds were administered 5 minutes before reperfusion. Cardiac function and dimensions were assessed at baseline and 28 days after infarction with 9.4-T mouse magnetic resonance imaging. Saline and IgG isotype treatment resulted in 34.5±3.3% and 31.4±2.7% infarction, respectively. Bone marrow transplantation experiments between wild-type and TLR2-null mice revealed that final infarct size is determined by circulating TLR2 expression. A single intravenous bolus injection of anti-TLR2 antibody reduced infarct size to 18.9±2.2% (P=0.001). Compared with saline-treated mice, anti-TLR2–treated mice exhibited less expansive remodeling (end-diastolic volume 68.2±2.5 versus 76.8±3.5 μL; P=0.046) and preserved systolic performance (ejection fraction 51.0±2.1% versus 39.9±2.2%, P=0.009; systolic wall thickening 3.3±6.0% versus 22.0±4.4%, P=0.038). Anti-TLR2 treatment significantly reduced neutrophil, macrophage, and T-lymphocyte infiltration. Furthermore, tumor necrosis factor-α, interleukin-1α, granulocyte macrophage colony-stimulating factor, and interleukin-10 were significantly reduced, as were phosphorylated c-jun N-terminal kinase, phosphorylated p38 mitogen-activated protein kinase, and caspase 3/7 activity levels.

Conclusions—Circulating TLR2 expression mediates myocardial ischemia/reperfusion injury. Antagonizing TLR2 just 5 minutes before reperfusion reduces infarct size and preserves cardiac function and geometry. Anti-TLR2 therapy exerts its action by reducing leukocyte influx, cytokine production, and proapoptotic signaling. Hence, monoclonal anti-TLR2 antibody is a potential candidate as an adjunctive for reperfusion therapy in patients with myocardial infarction. (***Circulation.*** **2010;121:80-90.)**

Key Words: immune system ■ inflammation ■ myocardial infarction ■ reperfusion ■ Toll-like receptors

Guy Rousseau

- Enfin une nouvelle voie de signalisation dans les lésions de réperfusion.
- Pour ma part c'est très intéressant car nous avons observé que la barrière intestinale est affectée après un infarctus et que les TLR pourraient avoir un rôle à jouer dans la dépression.
- Je pense que la figure sur la taille de l'infarctus dit tout…



Darren Richard

nature medicine

Nat. Med (2010) 16:183-191

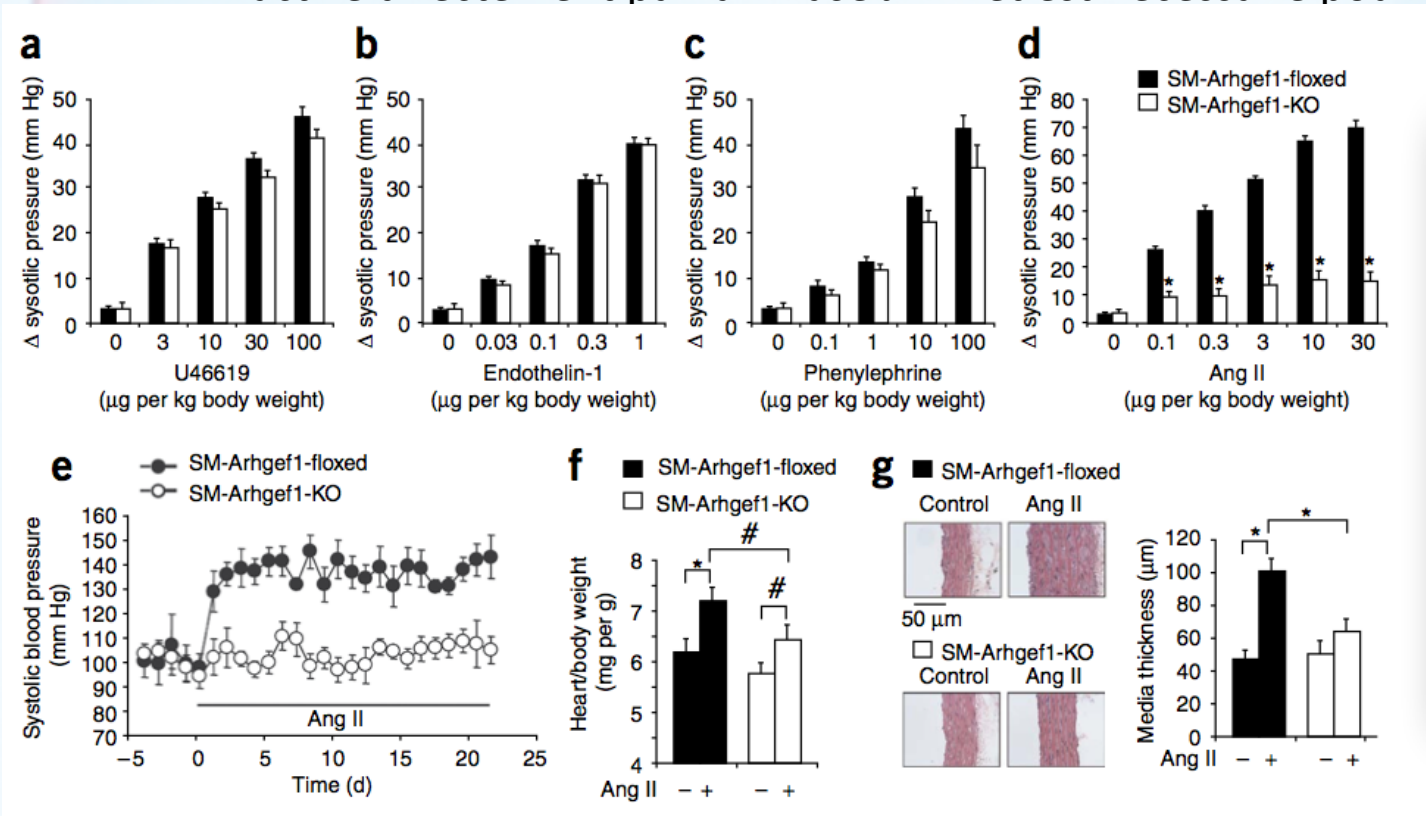
The Rho exchange factor Arhgef1 mediates the effects of angiotensin II on vascular tone and blood pressure

Christophe Guilluy[1,2,8], Jérémy Brégeon[1,2,8], Gilles Toumaniantz[1,2], Malvyne Rolli-Derkinderen[1,2], Kevin Retailleau[3], Laurent Loufrani[3], Daniel Henrion[3], Elizabeth Scalbert[4], Antoine Bril[4], Raul M Torres[5], Stephan Offermanns[6], Pierre Pacaud[1,2] & Gervaise Loirand[1,2,7]

Hypertension is one of the most frequent pathologies in the industrialized world. Although recognized to be dependent on a combination of genetic and environmental factors, its molecular basis remains elusive. Increased activity of the monomeric G protein RhoA in arteries is a common feature of hypertension. However, how RhoA is activated and whether it has a causative role in hypertension remains unclear. Here we provide evidence that Arhgef1 is the RhoA guanine exchange factor specifically responsible for angiotensin II–induced activation of RhoA signaling in arterial smooth muscle cells. We found that angiotensin II activates Arhgef1 through a previously undescribed mechanism in which Jak2 phosphorylates Tyr738 of Arhgef1. Arhgef1 inactivation in smooth muscle induced resistance to angiotensin II–dependent hypertension in mice, but did not affect normal blood pressure regulation. Our results show that control of RhoA signaling through Arhgef1 is central to the development of angiotensin II–dependent hypertension and identify Arhgef1 as a potential target for the treatment of hypertension.

Darren Richard

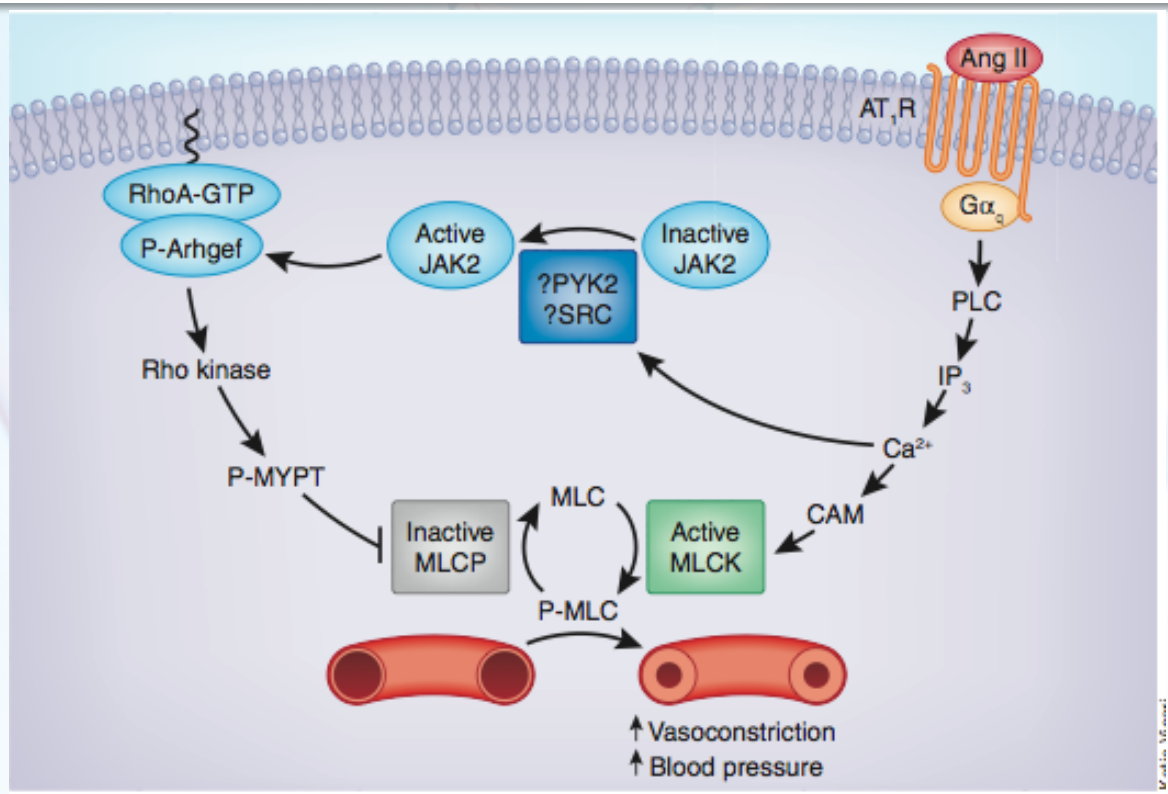
- Cette étude identifie Arhgef1, un facteur d'échange de guano-nucléotides (GEF), comme intermédiaire essentielle dans l'augmentation de la pression sanguine par l'angiotensine II et son récepteur AT1.
- Les auteurs démontrent que Arhgef1 est un partenaire de RhoA, est activé directement par la kinase JAK2 et est nécessaire pour la voie de u muscle



Darren Richard

IMPACT

L'implication de JAK2 – Arhgef1 dans l'activation de RhoA représente une découverte importante permettant de mieux comprendre les effets vasoconstricteurs et hypertenseurs spécifiques à l'angiotensine II.



Denis deBlois

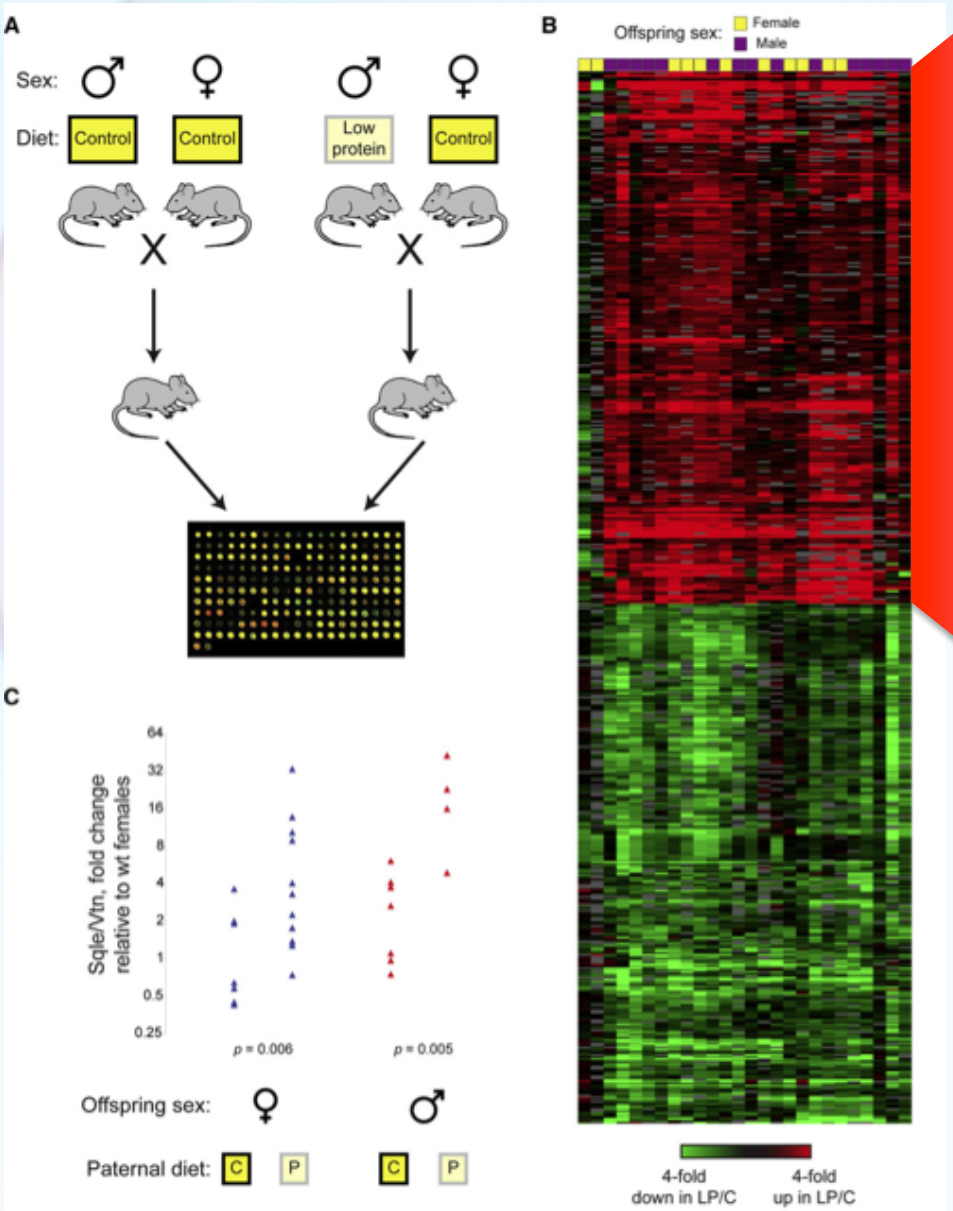
Cell

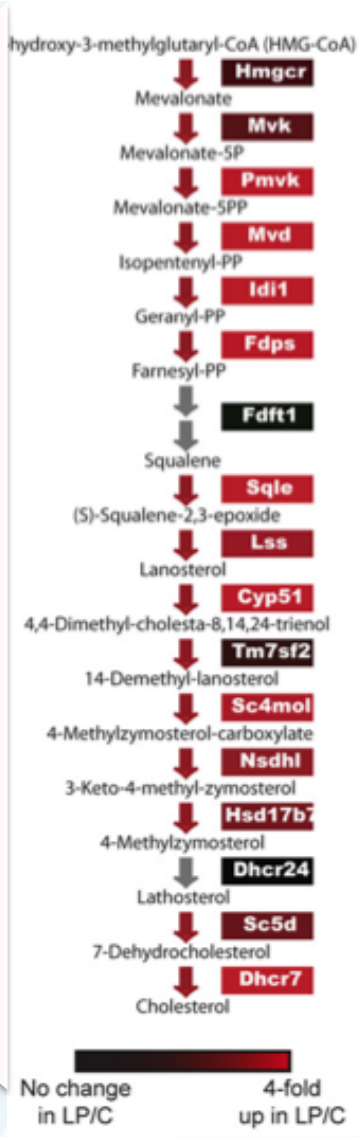
Cell 143, 1084–1096, December 23, 2010

Paternally Induced Transgenerational Environmental Reprogramming of Metabolic Gene Expression in Mammals

Benjamin R. Carone,[1,10] Lucas Fauquier,[1,10] Naomi Habib,[4,5,10] Jeremy M. Shea,[1,10] Caroline E. Hart,[1] Ruowang Li,[2] Christoph Bock,[6,7] Chengjian Li,[1] Hongcang Gu,[6] Phillip D. Zamore,[1,3] Alexander Meissner,[6,7] Zhiping Weng,[2] Hans A. Hofmann,[8] Nir Friedman,[4,9] and Oliver J. Rando[1,*]

- Souris mâles élevés ± diète pauvre en protéines (11% vs 20%)
- Accouplés à des femelles élevées sous diète régulière
- Temps de vie commune: *one night stand*
- Profil hépatique d'expression génique chez la progéniture (âgée de 3 mois)
- Surexpression des enzymes impliquées dans la synthèse du cholestérol.


A
Sex:
Diet:
Control
Control
Low protein
Control
B
Offspring sex:
Female
Male
4-fold down in LP/C
4-fold up in LP/C
C
Sqle/Vtn, fold change relative to wt females
64
32
16
8
4
2
1
0.5
0.25
p = 0.006
p = 0.005
Offspring sex:
Paternal diet:
C
P
C
P


hydroxy-3-methylglutaryl-CoA (HMG-CoA)
Hmgcr
Mevalonate
Mvk
Mevalonate-5P
Pmvk
Mevalonate-5PP
Mvd
Isopentenyl-PP
Idi1
Geranyl-PP
Fdps
Farnesyl-PP
Fdft1
Squalene
Sqle
(S)-Squalene-2,3-epoxide
Lss
Lanosterol
Cyp51
4,4-Dimethyl-cholesta-8,14,24-trienol
Tm7sf2
14-Demethyl-lanosterol
Sc4mol
4-Methylzymosterol-carboxylate
Nsdhl
3-Keto-4-methyl-zymosterol
Hsd17b7
4-Methylzymosterol
Dhcr24
Lathosterol
Sc5d
7-Dehydrocholesterol
Dhcr7
Cholesterol
No change in LP/C
4-fold up in LP/C

Denis deBlois

IMPACT

L'environnement fœtal peut avoir un impact la vie durant (programmation maternelle).
Ce papier utilise une approche très originale qui permettra de mieux comprendre comment l'environnement *avant la conception* peut influencer le développement des générations suivantes.