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The King's Centre for Integrative Chinese Medicine

伦敦国王学院整合中医药学中心

KING'S College LONDON

Let there be light: Let TCM wisdom inspire modern nephrology & pharmacology.

要有光：让中医智慧启迪现代肾病学与药理学研究

Dr Qihe Xu's PPT for his lecture at the Institute of Integrated Chinese & Western Medicine, Shanghai University of Traditional Chinese Medicine, 13th April 2023.

徐启河博士在上海中医药大学中西医结合研究院演讲幻灯稿 （2023年4月13日 · 中国上海）

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Let There Be Light:

Let TCM Inspire Innovation in Modern Nephrology & Pharmacology

要有光：让传统中医药智慧启发现代肾脏病学与药理学创新

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Discover King's: 发现伦敦国王学院

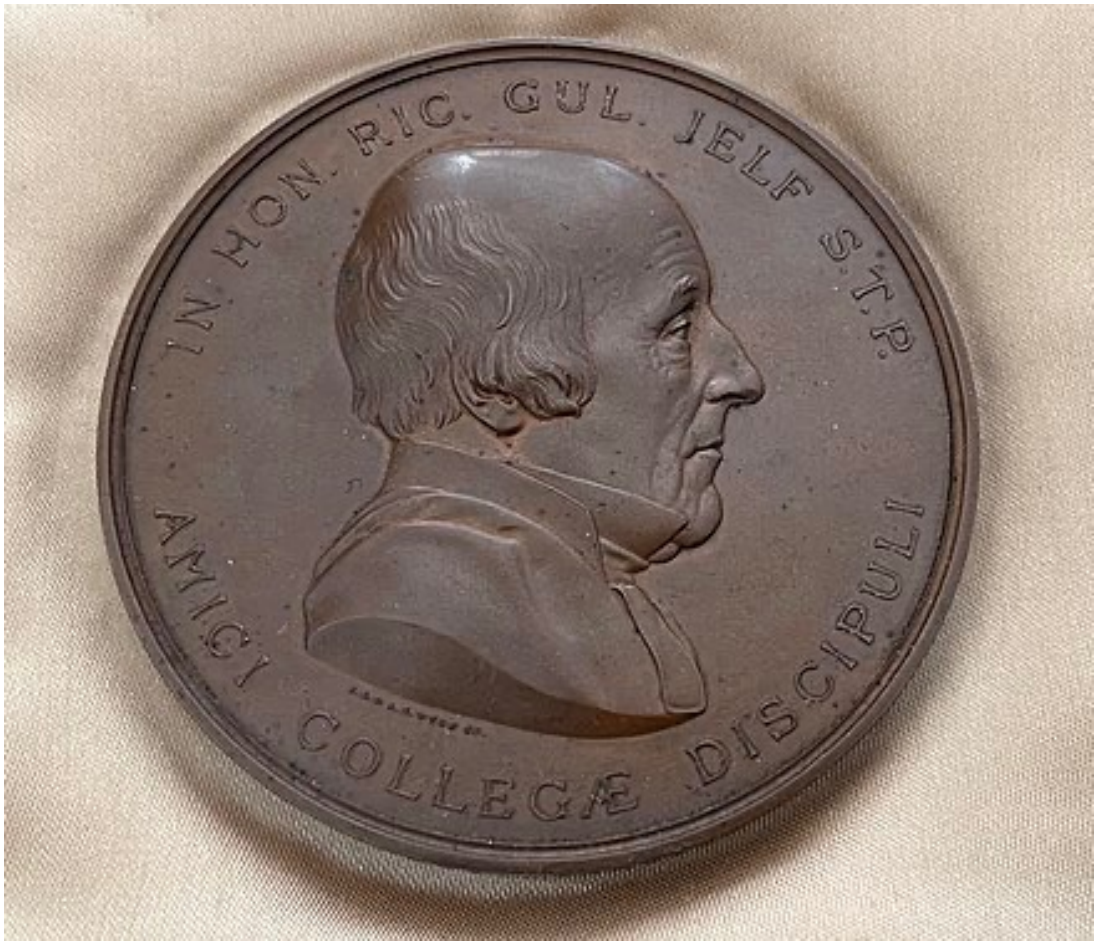
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- Become a LEGEND——成就传奇。
- 2023年最新数字：14位诺奖得主；综合全球QS大学排名第35；THE2023， 健康相关专业QS大学排名均位居世界前20。
  - 护理第2
  - 牙科第5
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  - 药学与药理学第19
  - 心理与精神病学第20


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The Jelf Medal

Professor Richard W. Jelf (1798–1871)
KCL's 4th Principal (1844–1868)

Jelf奖章：以国王学院第四任校长名字命名，是国王学院本科生能获得的最高荣誉。

判断标准： 最与众不同的本科毕业生。

作为国王学院的一员，我追求的“与众不同”是

“整合中医药”——

通过整合中医药智慧与现代医学与科学，催化创新。

Special acknowledgments

特别感谢欧盟第七框架计划GP-TCM协作组的200位同仁们





GP-TCM的总结论：“现代医学可以向传统医学学习”

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Good Practice in Traditional Chinese Medicine Research in the Post-genomic Era

Fact Sheet | Result in Brief | Reporting | News & Multimedia

DE EN ES FR IT PL

Modern medicine can learn from traditional practices

Researchers have finalised a picture of current traditional Chinese medicine (TCM) research practices in the EU and on the use, safety and efficacy of this ancient medical system.

BIOLOGY, MEDICINE



© Thinkstock

TCM is based on an individual and holistic approach to health and disease, with an emphasis on harmony between bodily functions. Although it is generally thought to be at odds with the reductionist approach of western medicine, both systems can learn from one

Project information

GP-TCM

Grant agreement ID: 223154

Status
Closed project

Start date	End date
1 May 2009	31 October 2012

Funded under:
FP7-HEALTH

Overall budget:
€ 1 117 778

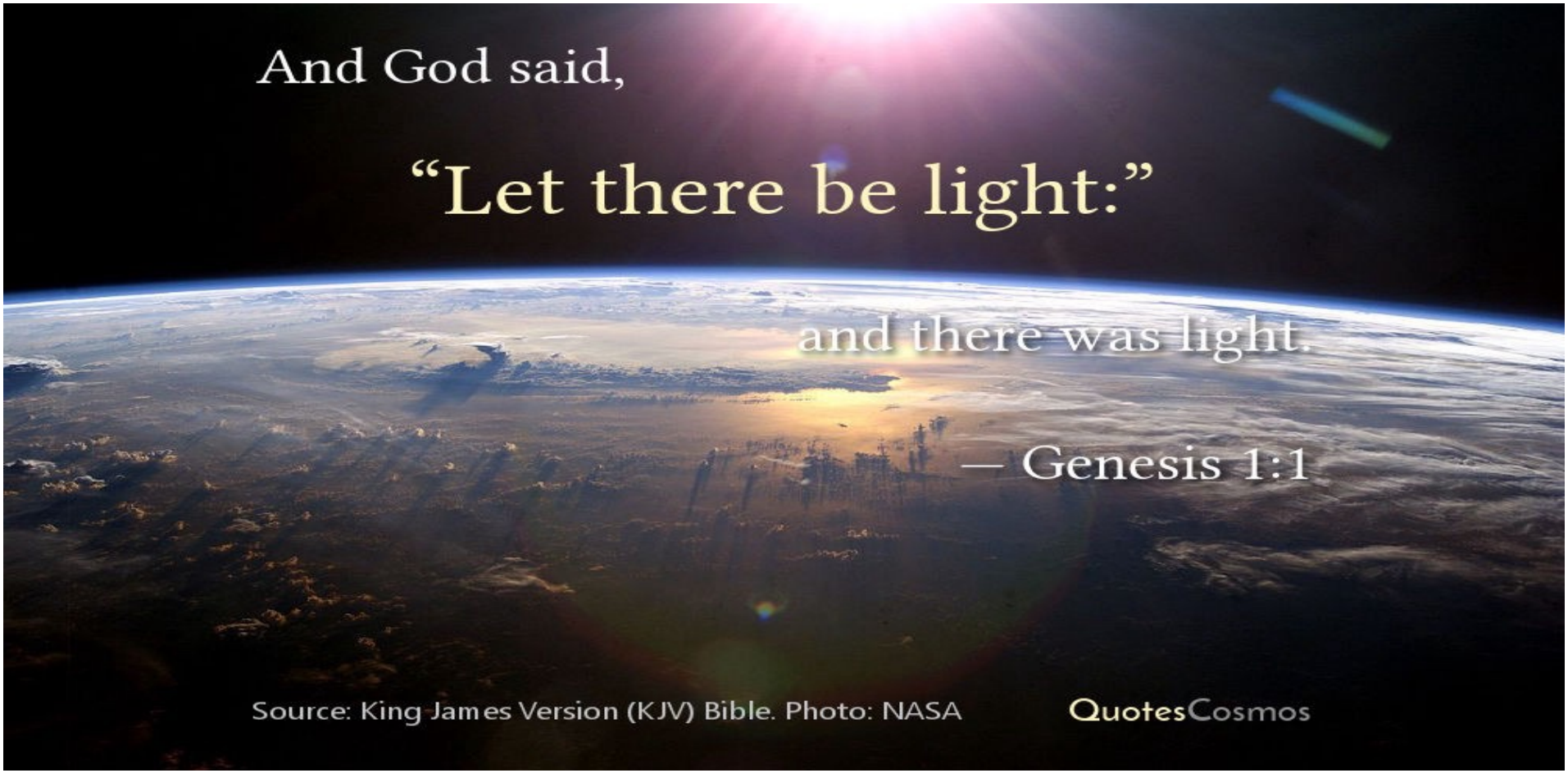
EU contribution
€ 995 100



Coordinated by:
KING'S COLLEGE LONDON

Light is the ultimate inspiration and guide 借圣经《创世纪》中上帝的话

“要有光”：中医药智慧可以成为照亮现代医学、药学创新的启发与指引。



从事肾脏病学研究30余年，从“肾”出发，谈谈为何中医药堪为指引创新之“光”

As a nephrologist for 30 years, I’d like to illustrate these conclusions from a nephrology point of view

- 1989-1992：北大医院肾内科
- 1992-1999：解放军总医院肾科
- 1999-2005：伦敦国王学院肾脏病中心
- 2005-2006：美国卫生研究院肾脏病科
- 2006-2019：伦敦国王学院肾脏病科

整合中医药

(Integrative Chinese Medicine)

- “肾”、“肾精”：科学见证了中西医相向而行，既促进了“肾”功能、“肾精”物质基础的理解，也促进了西医肾功能的认识，以及肾脏病学的药学创新。
- “正气”、“阳气”：中医药智慧与现代科学最新成就相结合，共同指引肾脏病与药学创新。

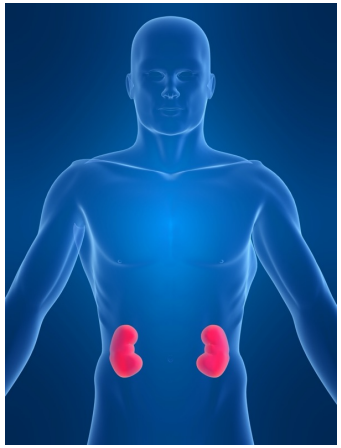
“kidney” and 肾(脏)

- 在西医中，“肾”主要是一个解剖学概念；而在中医中，“肾”更多的是一个功能学概念。

- 二者都认为，“肾”主水盐（“咸入肾”）。

Growing “kidney” functions in keeping with TCM (1)

- 肾主骨: Kidneys govern bone metabolism



- Lieu S H(刘士豪), Chu H I(朱宪彝). Treatment of renal osteodystrophy with dihydrotachysterol (A.T.10) and iron. *Science* 1942;95:388-389
- The first *Science* paper by Chinese authors.
- They even correctly hypothesised the mechanisms – kidneys activate vitamin D!

50 years later…

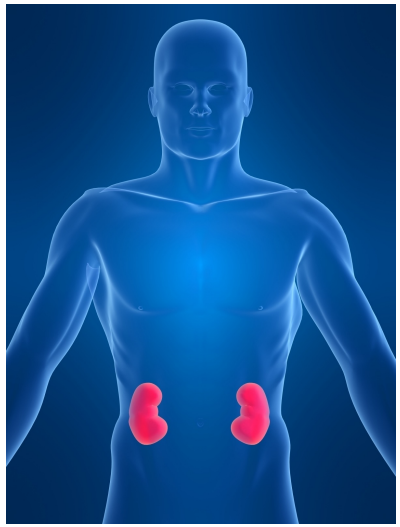
- Xu Q, Liu P, Jiang Y. Non-screen paper cassette radiography and bone mineral density measurement in Diagnosis of **renal bone diseases** of hemodialysis patients. J Dialysis Artificial Organs **1993**; 4:15-17.
- Xu Q, Liu P. **Renal osteodystrophy**. Intermediate Medical Journal. **1993**; 28:10-11.
- Xu Q, Liu P. Use of **Rocaltriol i**n patients with chronic renal failure. J Practical Medicine **1992**; (5): 275-276.
- Xu Q, Liu P, Li J, Jiang Y. Effect of **Shengu Capsule** on calcium and phosphorus metabolism in haemodialysis patients. Acad J PLA Postgrad Med School. **1997**;18:210-212.

Growing “kidney” functions in keeping with TCM (2)

肾主骨,骨生髓，髓造血

- **1960-70s:** Kidney produces erythropoietin (EPO), which controls red blood cell production
- **1980:** Amgen EPO approved by FDA (thanks to Taiwan-born Chinese scientist 林福坤博士)
- **1990:** Advised by Dr Lin, EpoGen was made available to China for free through a donation through the Carter Centre





Growing functions of the kidney

肾为先天之本

- **2014:** Kidneys are the “fountain of youth”, producing 80% of the anti-ageing Klotho.

  Lindberg K . *J Am Soc Nephrol.* 2014;25:2169-75

  Wolf M. *J Am Soc Nephrol.* 2014;25:2143-5



- **2022:** A klotho-derived peptide mimics Klotho function and ameliorates diabetic kidney diseases and renal fibrosis.

  Yuan Q et al. *Nat Commun.* 2022;13:438

  Chen X et al. *Kidney Int.* 2022;102:506-520



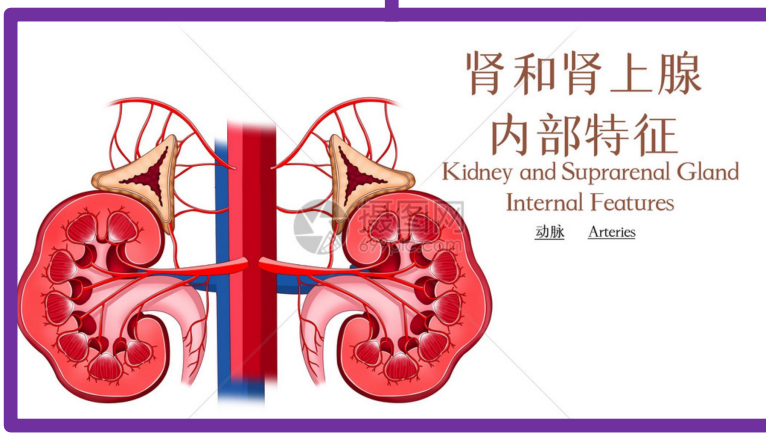
南方医科大学、匹兹堡大学
刘友华教授

“肾藏精”的物质基础

沈自尹教授的研究表明：“肾阳”与下丘脑-垂体-靶腺（肾上腺等）密切相关，强调了中医“肾”的功能不仅限于解剖学的肾脏，还包含肾上腺及其上游神经内分泌腺体，强调了肾脏概念的整体性特征。



- 克洛素 (Klotho)
- 促红细胞生成素 (EPO)
- 骨化三醇 (Calcitriol)
- 犬尿氨酸 (L-kynurenine)：介导孕妇肾与胎盘的对话，防先兆子痫
- 肾素-血管紧张素 (保水、升血压)
- 肾酶 (Renalase)：降解儿茶酚胺，降血压，护心脏
- 糖皮质激素 (Glucocorticoid)
- 盐皮质激素 (mineralocorticoid)
- 肾上腺素 (adrenaline, epinephrine)
- ……



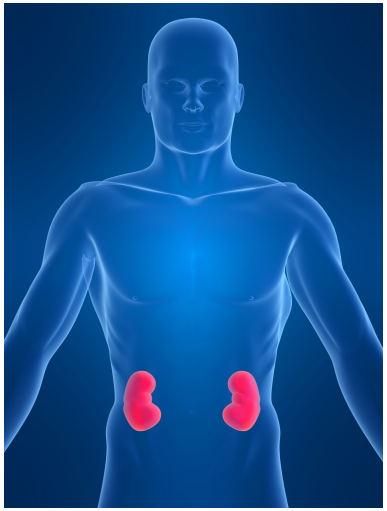
生理和病理状态下肾动脉和肾静脉血浆和亚细胞成分的组学研究有望发现更多“肾藏精”的本质？

Vijayakumar A, Mahapatra NR. *Hypertens Res.* 2022;45:1582-1598.
Enninga, Elizabeth Ann L. et al. *Kidney Int* 2023;103:651–65
Dupont V, Berg AH, Yamashita M, et al. *JCI.* 2022;132:e158346.5

The kidney is not only important,
BUT ALSO vulnerable

- Acute kidney injury (AKI, 急性肾损伤)
- Chronic kidney disease (CKD, 慢性肾脏病)

AKD/CKD are interconnected syndromes



Insults

Normal kidneys

AKI (Up to 7 days)

AKD (8-90 days)

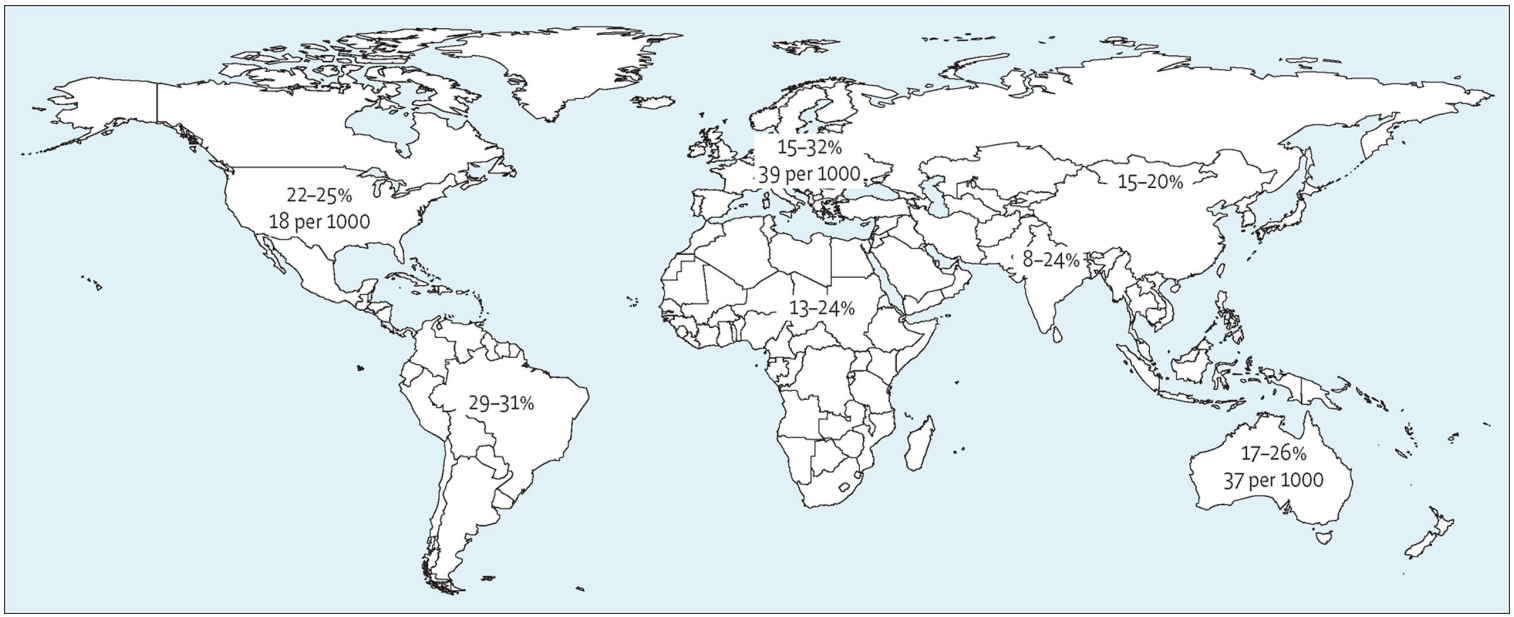
- **Renal Replacement Therapies**
- **Lifespan loss**

CKD (>90 days)

End-stage renal disease (ESRD)

Worldwide, ~20% hospitalised patients suffer from AKI;
community-acquired AKI may double the total incidence

AKI epidemiology per hospital admission (%) and
corresponding incidence by region (per 1000 person)



Lancet. 2019;394:1949-1964.

AKI comes with high mortality:
England as an example

Table 1. Adjusted (males aged 65–74 years) 30 day mortality for patients with an AKI episode by clinical setting in 2017

		Setting of AKI episode		
	All AKI episodes	CA	CAH	HA
Number	441,699	127,767	171,266	142,666
%		28.9	38.8	32.3
% died by 30 days from AKI start	18.0	8.3	20.6	23.6
ADJUSTED MORTALITY (%) BY PEAK AKI STAGE				
1	12.2	6.2	13.5	15.5
2	26.0	20.5	24.5	31.1
3	28.3	21.8	26.4	36.6

CA – community acquired; CAH – community acquired, subsequently hospitalised; HA – hospital acquired

Andrew Lewington and Becky Bonfield, **Global Perspectives in Acute Kidney Injury: England,** Kidney360, Publish Ahead of Print, 2022, 10.34067/KID.0000052022

Doi K, et al. **Impact of AKI on distant organ function: recent findings and potential therapeutic targets.** *Kidney Int* 2016;89:555.

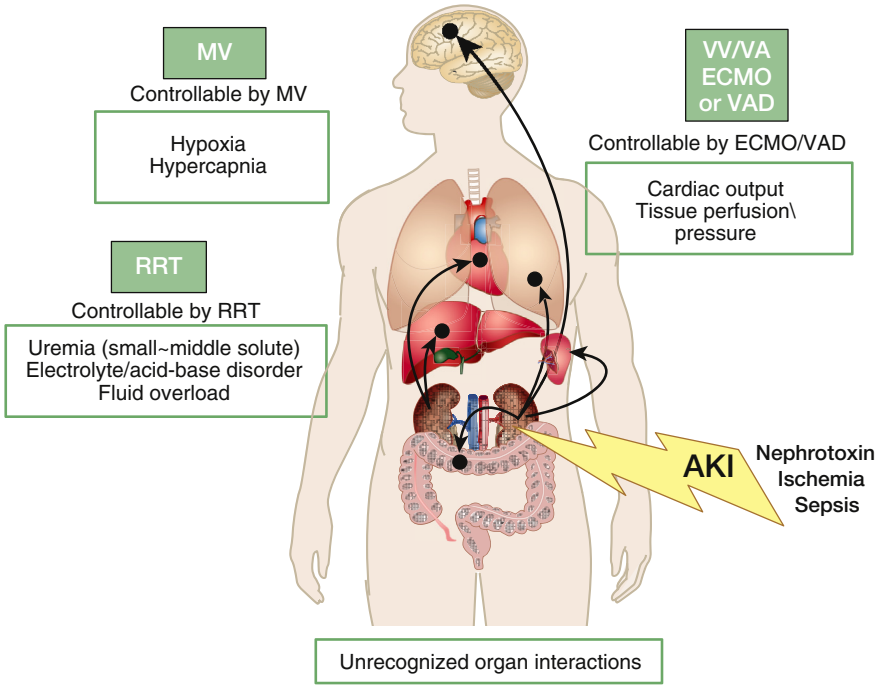


Figure 1 | Unrecognized organ interactions in AKI in the ICU. Mechanical supports including RRT do not sufficiently improve the outcomes of patients with AKI treated in ICU, implicating unrecognized remote organ interactions with the kidney.

RRT, renal replacement therapies; MV, mechanical ventilation; VAD, ventricular assist device; VV/VA-ECMO, venovenous/venoarterial extra- corporeal membrane oxygenation.

Table 1 | Mechanisms of distant organ effects in AKI

Organ	Reference
Lung	
Immune cell infiltration such as neutrophil, T cell, and macrophage	Kramer *et al.*,[33] Awad *et al.*,[35] Ishii *et al.*,[36] Lie *et al.*,[41] Altmann *et al.*[42]
Systemic IL-6 elevation and pulmonary CXCL1 expression	Klein *et al.*,[38] Ahuja *et al.*,[39] Andres-Hernando *et al.*[40]
TLR4 activation by increased plasma HMGB1	Doi *et al.*[50]
Heart	
Cellular apoptosis by cardiac TNF-α expression	Kelly[65]
Mitochondrial fragmentation and apoptosis by dynamin-related protein 1 upregulation	Sumida *et al.*[69]
Macrophage infiltration by osteopontin	Tokuyama *et al.*[68]
Hypertrophy and fibrosis with increased cardiac angiotensin 1 converting enzyme 2 activity	Burchill *et al.*[67]
Spleen	
Supporting protective effect of TLR9 inhibitor chloroquine	Yasuda *et al.*[81]
Secretion of lethal mediator HMGB1	Leelahavanichkul *et al.*[82]
Transient reservoir of mobilized transient endothelial progenitor cells	Patschan *et al.*[86]
Cholinergic anti-inflammatory pathway activation by exposure of the kidney to ultrasound waves	Gigliotti *et al.*[88]
Secretion of protective splenic IL-10 for lung injury	Andres-Hernando *et al.*[40]
Brain	
Increased chemokine expression of keratinocyte-derived chemoattractant and granulocyte-colony stimulating factor in cortex and hippocampus	Liu *et al.*[93]
TLR4 upregulation in hippocampus and striatum	Salama *et al.*[95]
Liver	
Leukocyte infiltration, increased oxidative stress, and hepatocyte apoptosis	Miyazawa *et al.*,[126] Golab *et al.*[127]
Altered cytochrome P450 3A enzyme activity	Lane *et al.*[132]
Gut	
Production of protective short-chain fatty acid for renal injury by microbiota	Jang *et al.*,[135] Andrade-Oliveira *et al.*[139]
Paneth cell activation (IL-17A production)	Park *et al.*[147]

AKI, acute kidney injury; CXCL1, chemokine (C-X-C motif) ligand 1; HMGB1, high-mobility group box protein B1; IL, interleukin; TLR4, Toll-like receptor 4; TLR9, Toll-like receptor 9; TNF-α, tumor necrosis factor-α.

Legrand M, Rossignol P. N Engl J Med 2020;382:2238-47.

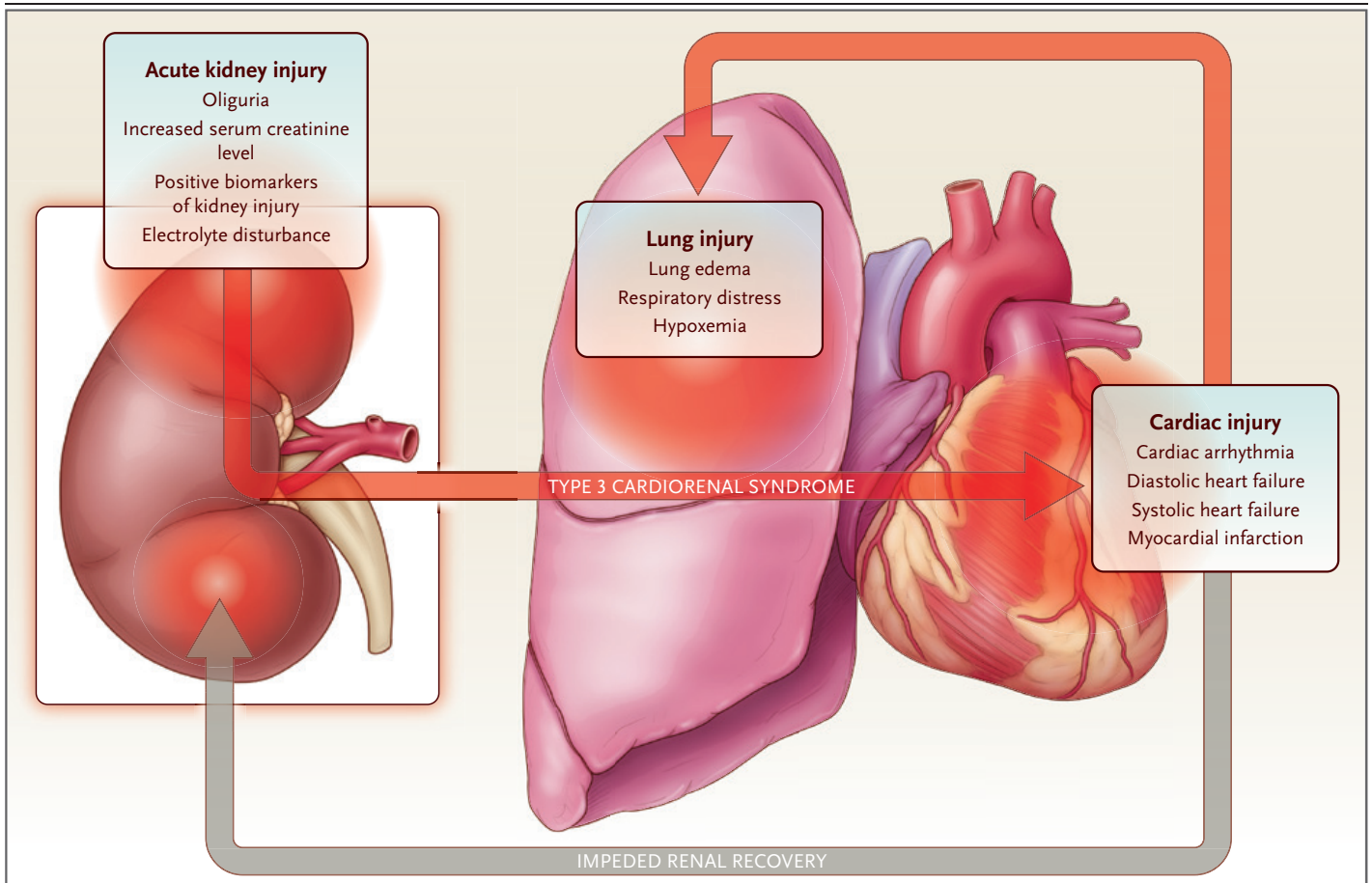


Figure 1. Cardiac and Pulmonary Consequences of Acute Kidney Injury.

Acute kidney injury has been shown to promote cardiac injury and dysfunction, defined as type 3 cardiorenal syndrome. Heart failure, in turn, can impede renal recovery. Lung injury and hypoxemia after acute kidney injury can arise both from increased capillary permeability and from increased hydrostatic capillary pressure due to heart failure.

AKI causes heart injury and increases mortality

Legrand M, Rossignol P. **NEJM** 2020;382:2238-47.

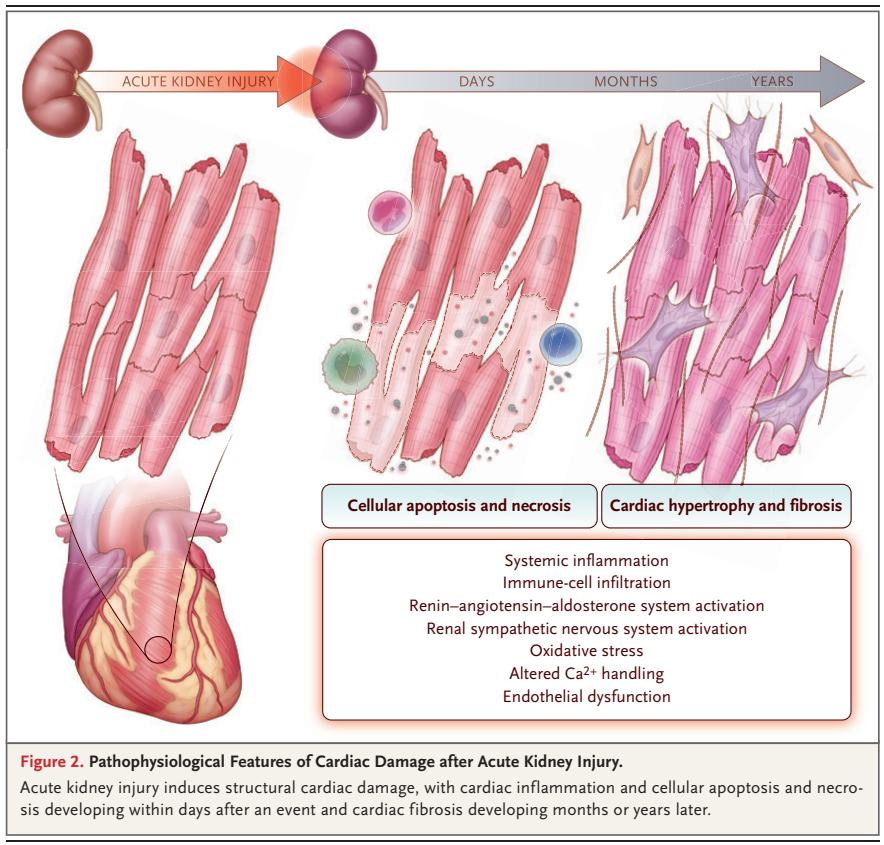


Figure 2. Pathophysiological Features of Cardiac Damage after Acute Kidney Injury.
Acute kidney injury induces structural cardiac damage, with cardiac inflammation and cellular apoptosis and necrosis developing within days after an event and cardiac fibrosis developing months or years later.

- **Cardiac inflammation**
- **Cardiac fibrosis**
- **Neurohormonal activation**
- **Electrolyte disturbances**

AKI is associated with

- 86% increase in death from cardiovascular cause in 1.4 years
- 58% increase in chronic heart failure in 2.9 years of follow-up;
- 40% increase in acute myocardial infarction in 2.3 years of follow-up
- 15% increase in the risk of stroke over a period of 2.7 years

(Odutayo A, et al. AKI and long-term risk for cardiovascular events and mortality. J Am Soc Nephrol 2017;28:377-87)

CKD – An even bigger threat of the AKI/CKD double whammy

- CKD affects ~10% of the world's population—more than diabetes and cancer combine.
- CKD is one of the seven major diseases, death rates of which are increasing worldwide.
- CKD is tipped to become a top-5 cause of mortality worldwide by 2040.

Lancet. 2020;395:179
Lancet. 2015;385:117-71
Lancet 2018;392:2052-2090

An inconvenient truth

As a nephrologist for 30 years, I must acknowledge that we have limited success in:

- preventing AKI;
- stopping AKI transition to CKD; and
- preventing CKD progression.

https://www.thinkkidneys.nhs.uk

GBD 2013 Mortality and Causes of Death Collaborators. Lancet 2015;385:117-71

JAMA Network Open. 2018;1(7):e184412

Action is needed, … and



Prof. Sharon M. Moe
ASN Presidential Address 2014
Moving Past Nephrology's Midlife Crisis

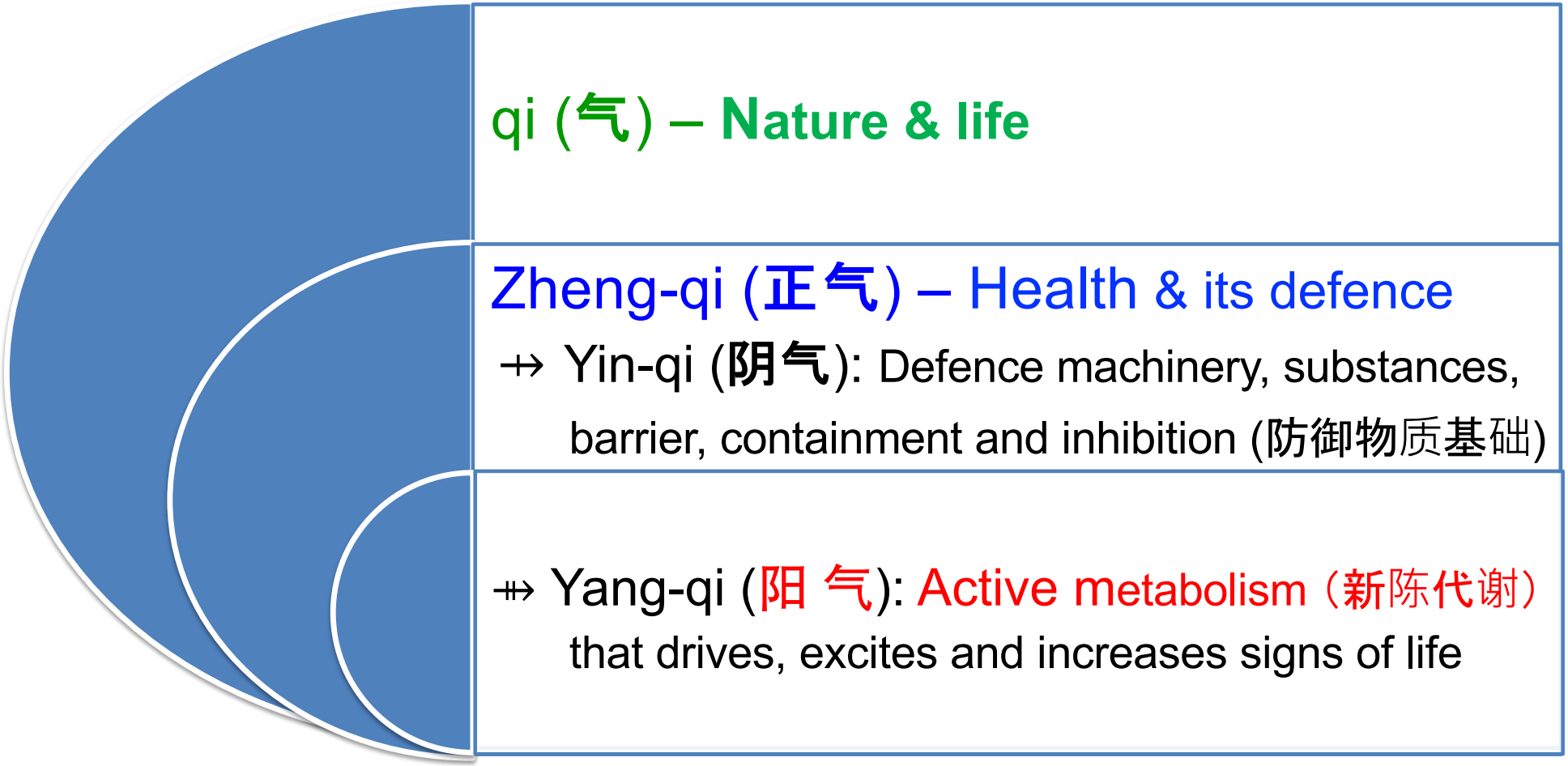
- We need to work together to overcome many of the challenges we face as caregivers, scientists, and educators committed to people with kidney disease.

- **We need to build new paths to kidney health.**
- We need to diagnose early to develop preventive strategies so we can offer hope at screenings, not fear.
- We need to identify those at highest risk for progression to kidney failure so we target the right patients for clinical trials and ensure success of our innovative therapies.
- We need to understand how even mild episodes of AKI can accelerate progression.

The way forward

- To seek inspiration from TCM; and
- To catalyse innovation by integrating TCM wisdom with modern science.

从整合中医药角度审视新陈代谢在健康与疾病中的作用
Role of metabolism *in integrative Chinese medicine*



阳气

李 可：阳气不到的地方就是病

2017-06-24 06:51

导读：“没有阳气就没有生命。从养生治病的经历来看：阳萎则病，阳衰则危，阳亡则死；所以救阳，护阳，温阳，养阳，通阳，一刻不可忘；治病用药切切不可伤阳。所以古人云：万病不治求之于肾。求之于肾就是救阳气。”



李可 原山西灵石县中医院院长

1930-2013年，著名中医。曾任山西灵石县中医院院长，中华全国中医学会山西分会会员，《中医药研究》特邀编委，香港《中华医药报》医事顾问，世界华人交流协会特邀研究员。著有《李可老中医急危重症疑难病经验专集》，又通过四十多年的搜集、整理，校注了清末民初著名医家彭子益的《圆运动的古中医学》。晚年多次到广东带徒传艺，分别在南方医院、广东省中医院开辟传承基地和经典病房，轰动全国。

2005年第 20卷第 11期　　中华中医药杂志 (原中国医药学报)　　· 645 ·

·论著·

中医学的阴气、阳气概念辨析

孙 广 仁

(山东中医药大学中医基础理论教研室，济南 250014)

1. 《黄帝内经》中阴气的涵义　为明确和规范阴气的概念，将《黄帝内经》160篇（除《素问》遗篇）中所有“阴气”二字连读者 98处以及“阴”、“阳”分别确指“阴气”、“阳气”者 5处检出，合为 78条以梳理其涵义。从《黄帝内经》中检出的 78条有关“阴气”的条文中，阴气是指地气，与阳气指代天气相对者 1条，占 1.28%；阴气是指自然界的寒气，与阳气是指风气相对待者 1条，占 1.28%；阴气是指自然界的寒凉之气，与阳气指代温热之气相对待者 9条，占 11.54%；阴气是指人体的在下之气，与阳气指代人体的在上之气相对待者 8条，占 10.26%；阴气指代行于人体的体内之气，与阳气指代行于体表之气相对待者 6条，占 7.69%；阴气是指人体内具有凉润、宁静、抑制等作用的气，与阳气指代具有温煦、推动、兴奋等作用的气相对待者 53条，占 67.95%[1]。因此，《黄帝内经》中阴气的基本涵义是：①指人体内具有凉润、宁静、抑制等作用的气，与阳气指人体内具有温煦、推动、兴奋等作用的气相对待；②有时指人体的在内或在下之气，与阳气指人体的在外或在上之气相对待；③在自然界主要指寒凉之气，与阳气主要指温热之气相对待。

“阳化气，阴成形”与现代医学的代谢观

《中国中医基础医学杂志》2007年 第8期 | 宋清江 白晓莉 刘红燕　河北保定市第一中医院 河北保定071000

摘　要：“阳化气，阴成形”源自《内经》，其本义是论人体阴刚两方面与人的形体和功能之间的关系。笔者在“读经典，做临床”的过程中发现，这一论点与现代医学的新陈代谢理论相比较，不论从过程分析还是从结果判断，都是高度一致的。

纤维化的本质是细胞内代谢紊乱，而抗纤维化效能伴随代谢的改善

Zhou S et al. *Sci Rep* 2020; 10: 19054

heck for up

OPEN

Proteomic landscape of TGF-β1-induced fibrogenesis in renal fibroblasts

Shujun Zhou[1], Xiaoke Yin[2], Manuel Mayr[2], Mazhar Noor[1], Peter J. Hylands[3] & Qihe Xu[1]✉

Zhou S, et al. *Phytomedicine.* 2022;100:154049.

Phytomedicine 100 (2022) 154049

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/phymed

Original Article

Antifibrotic activities of Scutellariae Radix extracts and flavonoids: Comparative proteomics reveals distinct and shared mechanisms

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Fibrosis & metabolism: The state of the art

REVIEWS

Zhao X et al.

Nat Rev Drug Discov. 2020;19:57–75

Targeting metabolic dysregulation for fibrosis therapy

*Xiao Zhao[1,2,7], Jennifer Yin Yee Kwan[2,3,4], Kenneth Yip[5], Peter P. Liu[6] and Fei-Fei Liu[1,2,3,4,5]**

Abstract | Fibrosis is the abnormal deposition of extracellular matrix, which can lead to organ dysfunction, morbidity, and death. The disease burden caused by fibrosis is substantial, and there are currently no therapies that can prevent or reverse fibrosis. Metabolic alterations are increasingly recognized as an important pathogenic process that underlies fibrosis across many organ types. As a result, metabolically targeted therapies could become important strategies for fibrosis reduction. Indeed, some of the pathways targeted by antifibrotic drugs in development — such as the activation of transforming growth factor-β and the deposition of extracellular matrix — have metabolic implications. This Review summarizes the evidence to date and describes novel opportunities for the discovery and development of drugs for metabolic reprogramming, their associated challenges, and their utility in reducing fibrosis. Fibrotic therapies are potentially relevant to numerous common diseases such as cirrhosis, non-alcoholic steatohepatitis, chronic renal disease, heart failure, diabetes, idiopathic pulmonary fibrosis, and scleroderma.

Selvarajah *et al*.

Sci. Signal. 14, eaay1027 (2021)

SCIENCE SIGNALING | REVIEW

FIBROSIS

Fibrometabolism—An emerging therapeutic frontier in pulmonary fibrosis

Brintha Selvarajah[1], Ilan Azuelos[1], Dimitrios Anastasiou[2], Rachel C. Chambers[1]*

Fibrosis is the final pathological outcome and major cause of morbidity and mortality in many common and chronic inflammatory, immune-mediated, and metabolic diseases. Despite the growing incidence of fibrotic diseases and extensive research efforts, there remains a lack of effective therapies that improve survival. The application of omics technologies has revolutionized our approach to identifying previously unknown therapeutic targets and potential disease biomarkers. The application of metabolomics, in particular, has improved our understanding of disease pathomechanisms and garnered a wave of scientific interest in the role of metabolism in the biology of myofibroblasts, the key effector cells of the fibrogenic response. Emerging evidence suggests that alterations in metabolism not only are a feature of but also may play an influential role in the pathogenesis of fibrosis, most notably in idiopathic pulmonary fibrosis (IPF), the most rapidly progressive and fatal of all fibrotic conditions. This review will detail the role of key metabolic pathways, their alterations in myofibroblasts, and the potential this new knowledge offers for the development of antifibrotic therapeutic strategies.

Metabolic mechanisms of other “non-metabolic” disorders

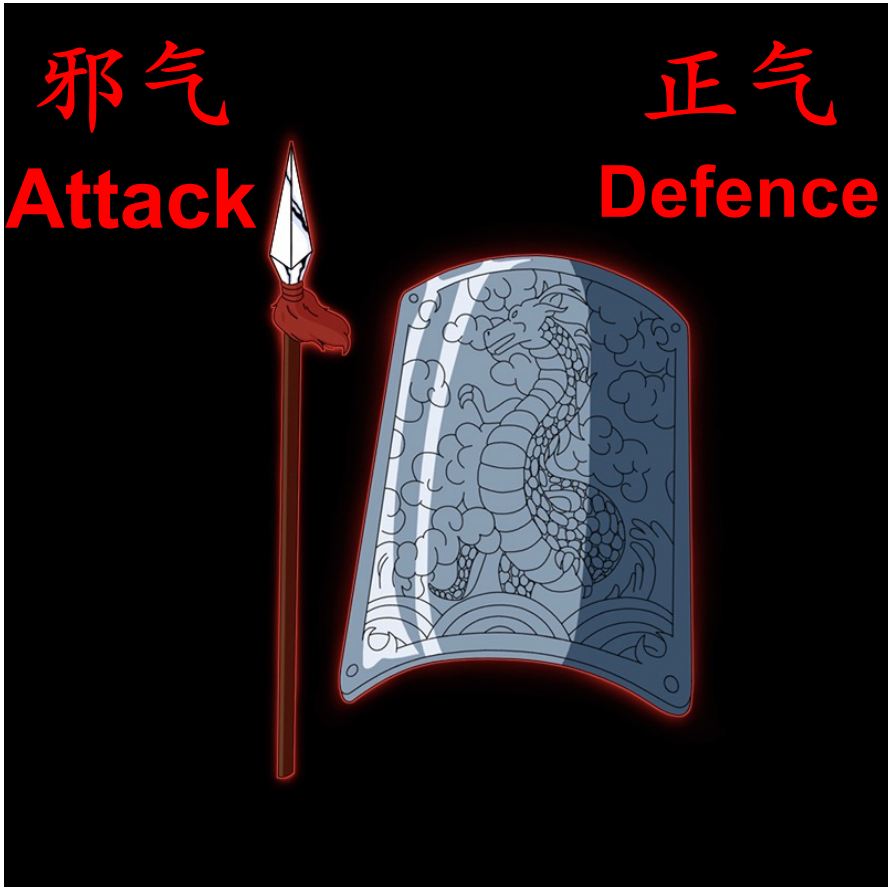
- 炎症（Certo M, et al. Targeting metabolism as a therapeutic approach in **chronic inflammation**. *Br J Pharmacol*. 2021;178:2041-2059）
- 免疫 (Pearce EJ, Pearce EL. Driving **immunity:** all roads lead to metabolism. *Nat Rev Immunol.* 2018;18:81-82).
- 老龄化（Amorim JA, et al. Mitochondrial and metabolic dysfunction in **ageing and age-related diseases**. *Nat Rev Endocrinol.* 2022;18:243-258）。
- 癌症（Gyamfi J, et al. **Cancer as a metabolic disorder.** *Int J Mol Sci.* 2022;23:1155）
- AKI（Li Z, et al. The role of metabolic reprogramming in tubular epithelial cells during the progression of **acute kidney injury**. *Cell Mol Life Sci.* 2021;78:5731-5741）
- AKI-CKD转化 （Zhu Z, et al. **Transition of acute kidney injury to chronic kidney disease**: role of metabolic reprogramming. *Metabolism.* 2022;131:155194）

正气

《黄帝内经》：“正气存内,邪不可干; 邪之所凑,其气必虚”

“When there is **sufficient defence** inside, external pathogenic factors have no way to hurt;”

“when damage does occur, the **defence must be deficient**.”

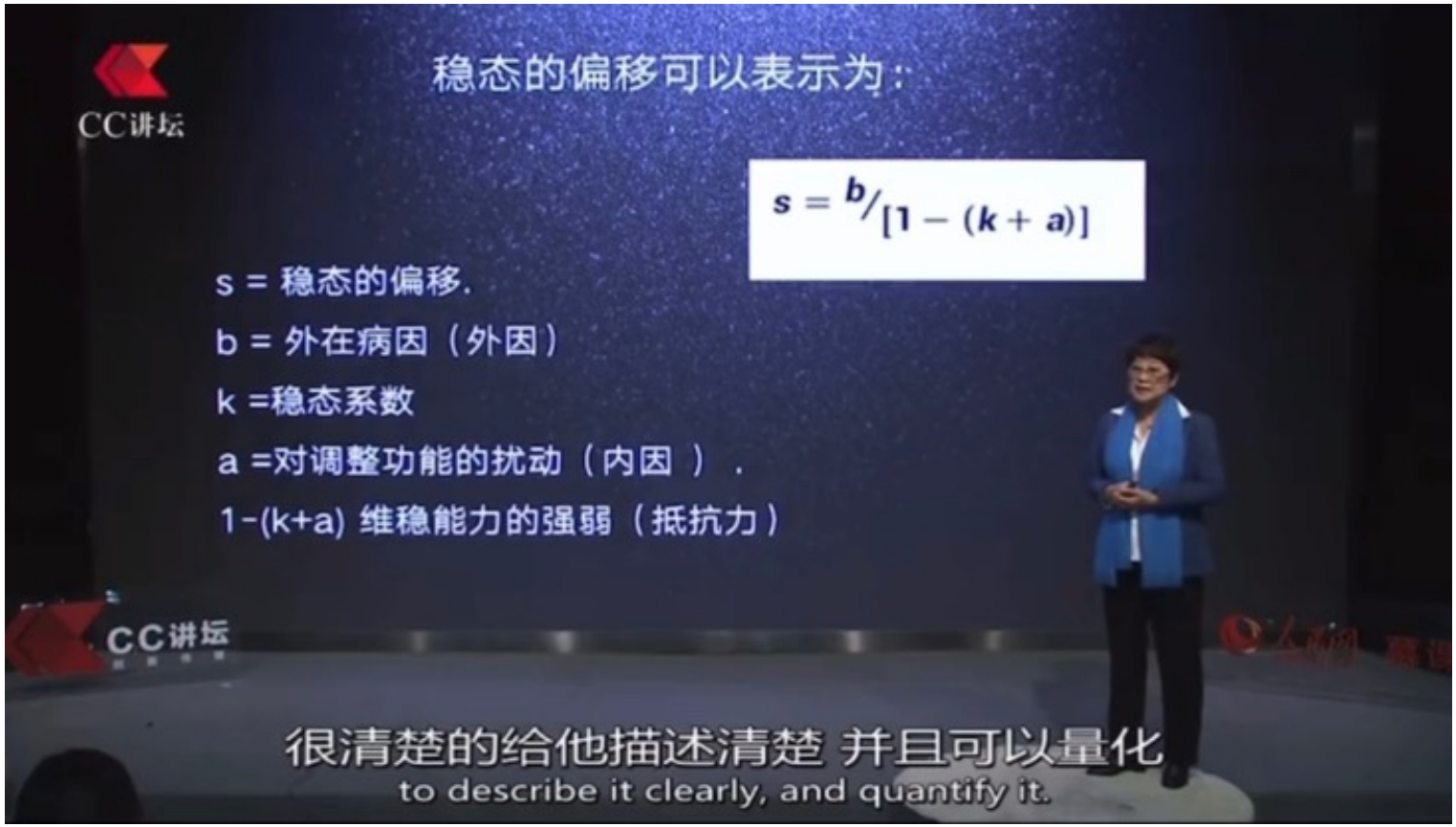


Increasing agreement with the state of the art of science

- “健康的标志”理论：健康需要多维保护机制来捍卫，而对这些保护性防御机制的破坏具有致病性 (López-Otín C, Kroemer G. Hallmarks of Health. *Cell.* 2021;184:33-63).
- “环境致病因子的标志”理论：环境致病因子必须克服机体的防御才能造成伤害 (Peters A, Nawrot TS, Baccarelli AA. Hallmarks of environmental insults. *Cell.* 2021;184:1455-68).
- “铁死亡新理论：”铁死亡是诱导与防御机制失衡的结果 (Dixon SJ, Pratt DA. Ferroptosis: A flexible constellation of related biochemical mechanisms. *Mol Cell.* 2023；83:1030-1042).

什么是机体防御?

In systems medicine, defence=1-(k+a)



https://mp.weixin.qq.com/s/_6eEFzq9buMgMxlZdZa7Og

In AKI/CKD, tubulointerstitial injury plays crucial roles

□ REVIEW ARTICLE □

Mechanisms of Tubulointerstitial Injury in the Kidney: Final Common Pathways to End-stage Renal Failure

Masaomi NANGAKU

Abstract

There are many different glomerular disorders, including glomerulonephritis, diabetic nephropathy, and hypertensive nephrosclerosis. However, once glomerular damage reaches a certain threshold, the progression of renal disease is consistent and irreversible. Recent studies emphasized the crucial role of tubulointerstitial injury as a mediator of progression of kidney disease. One common mechanism that leads to renal failure via tubulointerstitial injury is massive proteinuria. Accumulating evidence suggests critical effects of filtered macromolecules on tubular cells, including lysosomal rupture, energy depletion, and tubular injury directly induced by specific components such as complement components. Another common mechanism is chronic hypoxia in the tubulointerstitium. Tubulointerstitial damage results in the loss of peritubular capillaries, impairing blood flow delivery. Interstitial fibrosis also impairs oxygen diffusion and supply to tubular cells. This induces chronic hypoxia in this compartment, rendering a vicious cycle. Development of novel therapeutic approaches against these final common pathways will enable us to target any types of renal disease.

(Internal Medicine 43: 9–17, 2004)

Careful pathological analysis revealed that the impairment of renal function correlates better with the extent of tubulointerstitial damage than with the degree of glomerular damage (2–6). These pathological findings were supported by clinical observations that urinary markers of tubulointerstitial damage serve as reliable indicators of renal prognosis (7, 8).

Tubulointerstitial damage induces a decrease in GFR via several mechanisms. Tubular atrophy increases fluid delivery to the macula densa and triggers a reduction in GFR via tubuloglomerular feedback (9). Tubular damage also leads to atubular glomeruli and decreases the number of functional nephrons (10). In addition, it results in obliteration of postglomerular capillaries, leading to ischemic renal injury. Thus, it is widely recognized that tubulointerstitial injury serves as an important mediator and a final common pathway of chronic kidney failure (Fig. 1).

One Final Common Pathway, Proteinuria-induced Tubular Damage

One important mechanism that leads to eventual kidney failure via tubulointerstitial injury is massive proteinuria. While proteinuria had been considered merely a marker of glomerular damage, many studies indicate proteinuria as a cause of progression of renal injury (11).

But we know little on
the **defence machinery & mechanisms**
against renal tubulointerstitial injury

What should a defender (bodyguard) look like?



- Be there
- Be resilient
- Well equipped & empowered
- Sense and respond to danger
- Must be tightly controlled
- Cause problems if dysregulated
- Be therapeutic if properly mobilised

2019年首创“集合管中心防御假说”

资深肾脏病学家Mark Dockrell博士:

“真正创新的想法；
以独特的途径阐释一个常见的问题”



英国肾脏基金会主任Elaine Davies:

“有趣的想法；
令人深思的演讲”



2019年首创“集合管中心防御假说”

nephron
Experimental Nephrology and Genetics

Experimental Nephrology and Genetics Special Article

Nephron 2019;143:148–152
DOI: 10.1159/000502452

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Accepted after revision: August 1, 2019
Published online: August 13, 2019

The Renal Collecting Duct Rises to the Defence

Qihe Xu

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地道敏树：受树的启发而知自然规律？

(In 1943)，到李庄后，石声汉将这首词连同《凉州词》写成条幅，又赠以“人道敏政，地道敏树”八个大字。李约瑟把这几个字译成蒲柏式的联句：

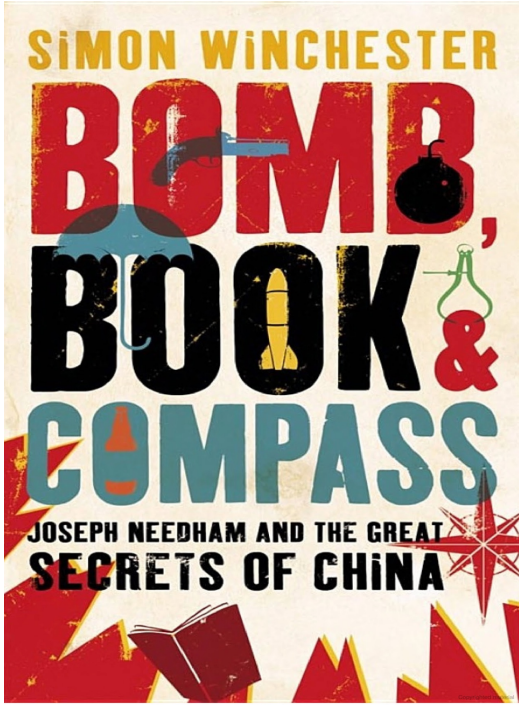
Nature from growing trees we best discern,
And man's estate from social order learn.

节选自《民间影像》第九辑之“1943，李约瑟到访李庄”



刘晓。1943，李约瑟的李庄之行。《民间影像》微信号 2018年11月21日
https://mp.weixin.qq.com/s/s13WdizJ4agm3Tg7Mxt-bQ

Here they said farewell to the remarkable professor, who returned to Loushan by road. He left behind one testament to the pervasive marvels of Chinese culture: it turned out that during the still of the previous night, after his poetry recital, he had prepared two scrolls with the texts of the two poems he had taught his companions, each poem written in a calligraphic style appropriate to its mood. He also left a Chinese couplet of his own composition, which Needham for some reason translated in the style of Alexander Pope: 'Nature from growing trees we best discern,/And man's estate from social order learn.'



Simon Winchester. Bomb, Book and Compass: Joseph Needham and the Great Secrets of China
By VIKING, UK, 2008

The real meanings

“人道敏政，地道敏树。夫政也者，蒲卢也”什么意思?

敏：勉力，用力，致力。蒲卢：即芦苇。芦苇性柔而具有可塑性.
统治百姓的方法就是尽快搞好政事，经营土地的方法就是迅速种植树木。国家政务就像蒲卢的道理一样。

(哀公问政。子曰：“文武之政，布在方策。其人存，则其政举；其人亡，则其政息。人道敏政，地道敏树。夫政也者，蒲卢也。故为政在人，取人以身，修身以道，修道以仁。仁者，人也，亲亲为大 ；义者，宜也，尊贤为大。亲亲之杀，尊贤之等，礼所生也，在下位不获乎上，民不可得而治矣。故君子不可以不修身；思修身，不可以不事亲；思事亲，不可以不知人；思知人，不可以不知天。”
译文：哀公问治理国家的方法。孔子说：“周文王、周武王治理国家的方法，已经在典籍当中记载了。按周礼办事的人存在此办法就能实行；按周礼办事的人不存在此种办法就不复存在。统治百姓的方法就是尽快搞好政事，经营土地的方法就是迅速种植树木。国家政务就像蒲卢的道理一样。所以治理国家在于得到按周礼办事得的人，要得到这样的人，就要修好自身，修养好自身就要实行人道，就要是实行仁。仁就是爱人，爱自己的亲族就是最大的仁；义就是要做事相宜，尊敬贤人是最大的义。爱亲族要有差别，尊敬贤人要分等次，这样就产生了礼。处在臣下的位置，又不能得到君上的信赖，这就不能得到平民而加以治理了。所以君子不能不修身；想要修身，不能不侍奉父母；想侍奉父母，不能不了解贤人，想要了解贤人，不能不知道天命。”)

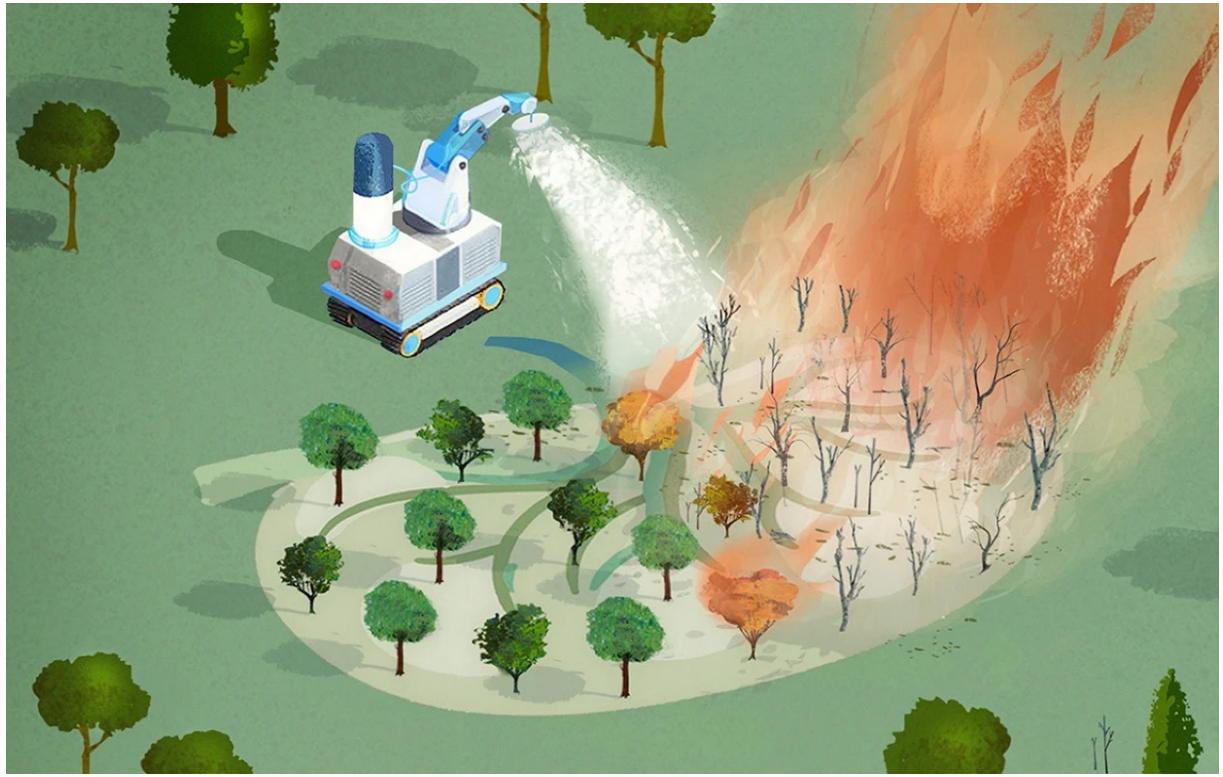
https://zhidao.baidu.com/question/2144469699237040748/answer/2875141508.html

If you were the designer…

Brody H. *Nature* 2023;615:S1



Keener AB. *Nature* 2023;615:S2-S4.



从“树的防御”
到“肾的防御”

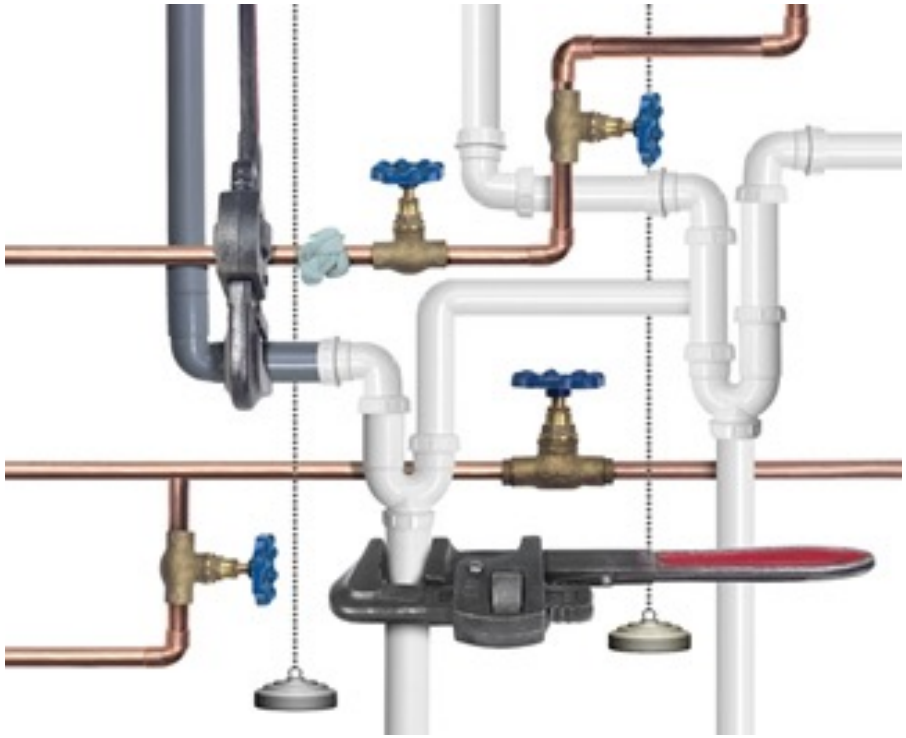
我们认识树的本末倒置

我们对肾的研究是否存在舍本逐末、本末倒置?

CDs: From urinary flow point of view…

- CDs are kidneys' draining pipes that "collect" urine, transporting water, acids, bases, calcium, etc.

…, but some more exciting possibilities exist.

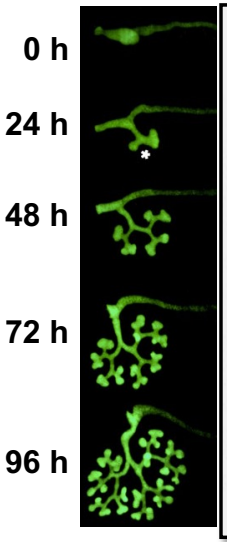


Be the stems…

- CDs are derivatives of ureteric buds (UBs), which direct nephrogenesis during development.

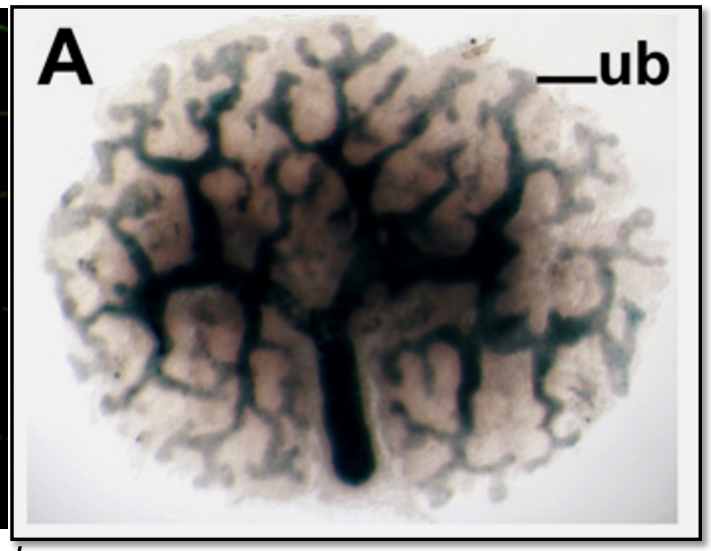
  …suggesting a role for CDs in directing regeneration and repair

Hoxb7/GFP *transgenic* mice



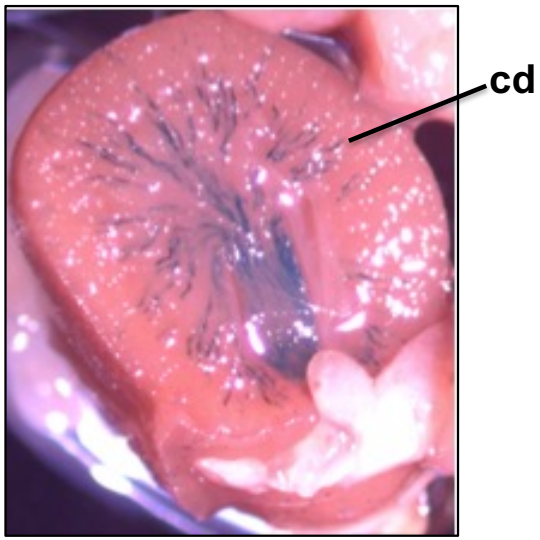
(Michos *et al.*, 2007)

Embryonic kidney



(Rosselot *et al.*, 2010)

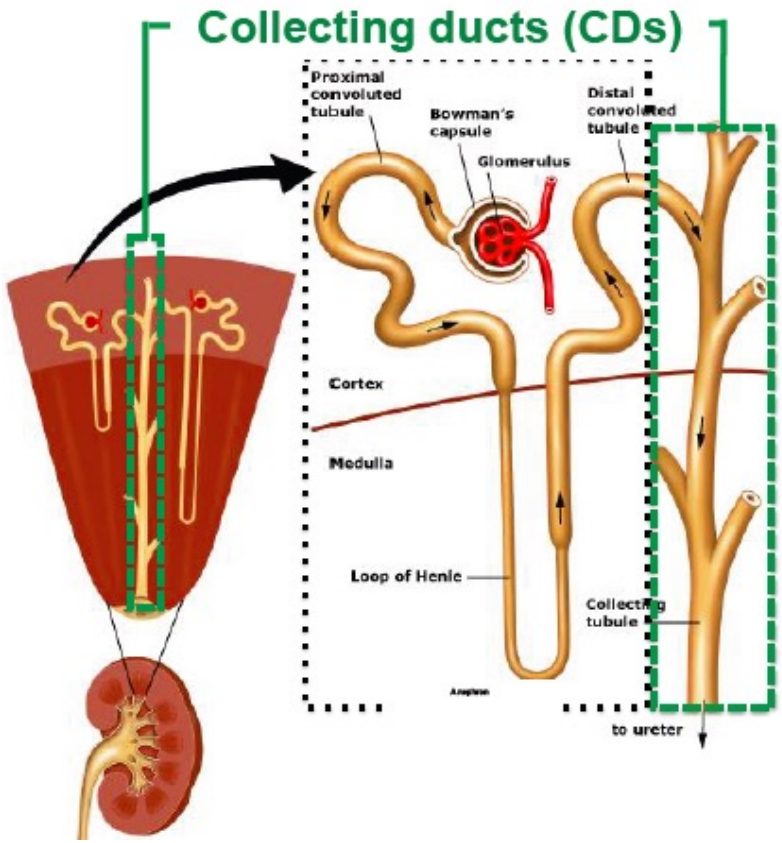
Adult kidney



(Wong YF *et al.*, 2011)

Be there…

- CDs span the whole kidney
  ,…are well positioned to house TI defences



Why CDs?

- Be there
- Be resilient: hi/lo osmotic pressure, pH, hypoxia, I/R, toxins, etc
- Well-equipped to fight
- Sense and respond to danger
- Must be tightly controlled
- Cause problems if dysregulated
- Be therapeutic if properly mobilised

Why CDs?

- Be there
- Be resilient
- Well-equipped and empowered
- Sense and respond to danger
- Must be tightly controlled
- Cause problems if dysregulated
- Be therapeutic if properly mobilised

CDs: Equipped with mesenchymal stem cells



Dr Joan Li
University of Queensland

Li J, et al. J Am Soc Nephrol. 2015;26:81-94.

BASIC RESEARCH www.jasn.org

Collecting Duct-Derived Cells Display Mesenchymal Stem Cell Properties and Retain Selective *In Vitro* and *In Vivo* Epithelial Capacity

Joan Li,* Usukhbayar Ariunbold,* Norseha Suhaimi,* Nana Sunn,† Jinjin Guo,‡ Jill A. McMahon,‡ Andrew P. McMahon,‡ and Melissa Little*

*Institute for Molecular Bioscience, University of Queensland, St. Lucia, Queensland, Australia; †Diamantina Institute, University of Queensland, Woolloongabba, Queensland, Australia; and ‡Department of Stem Cell Biology and Regenerative Medicine, Broad-CIRM Center for Regenerative Medicine and Stem Cell Research, University of Southern California Keck School of Medicine, Los Angeles, California

CDs are stores of antifibrotic microRNAs



Dr Vishal Patel
University of Texas
Southwestern Medical Center

Hajarnis S, et al. J Am Soc Nephrol. 2018;29:518-31

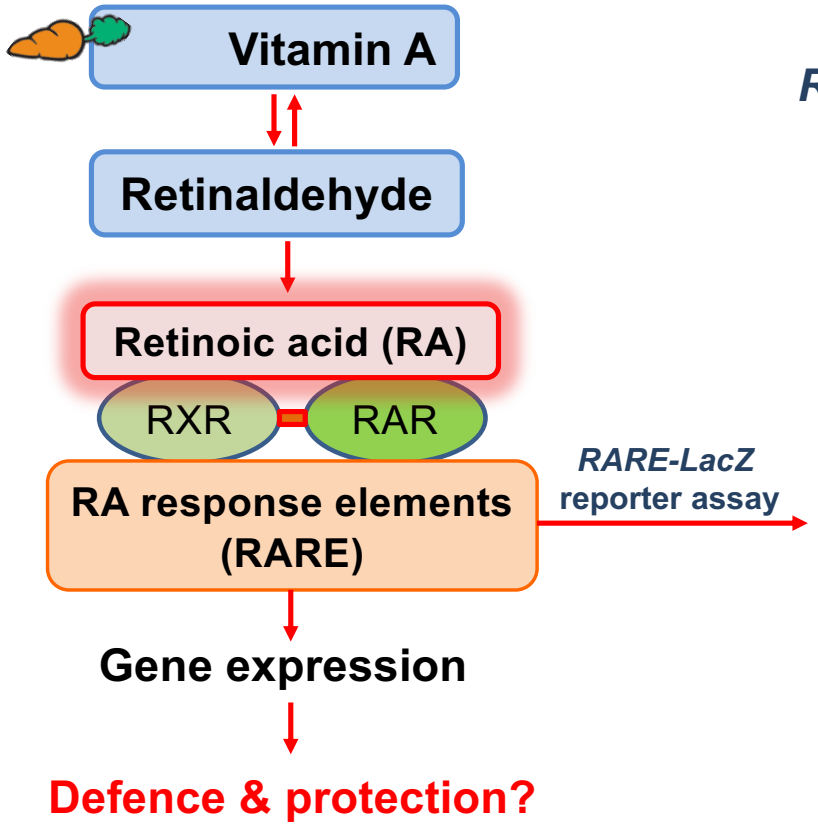
BASIC RESEARCH www.jasn.org

Suppression of microRNA Activity in Kidney Collecting Ducts Induces Partial Loss of Epithelial Phenotype and Renal Fibrosis

Sachin Hajarnis,[1] Matanel Yheskel,[1] Darren Williams,[1] Thomas Brefort,[2] Bob Glaudemans,[3] Huguette Debaix,[3] Michel Baum,[1,4] Olivier Devuyst,[3] and Vishal Patel[1]

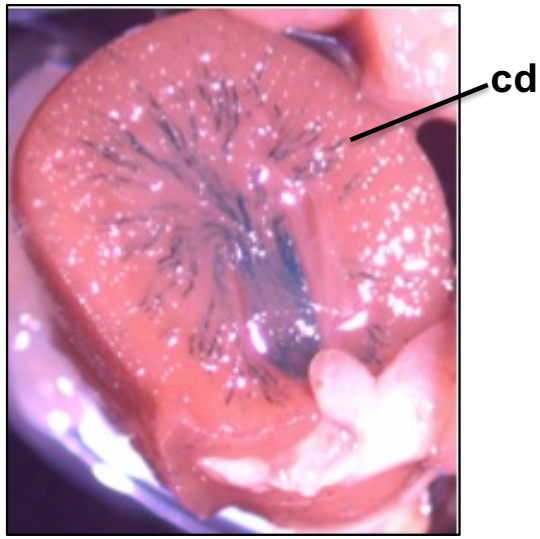
[1]Division of Nephrology, Department of Internal Medicine, and [4]Division of Nephrology, Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas; [2]Comprehensive Biomarker Center, Heidelberg, Germany; and [3]Institute of Physiology, University of Zurich, Zurich, Switzerland

CDs are uniquely equipped with physiological RA/RAR activity!



RARE-lacZ transgenic mice

Adult kidney



RARE-LacZ reporter assay

Funded by

Kidney Research UK
Funding research to save lives

Wong YF, Kopp JB, Roberts C, Scambler PJ, Abe Y, Rankin AC, Dutt N, Hendry BM, **Xu Q**. Endogenous retinoic acid activity in principal cells and intercalated cells of mouse collecting duct system. **PLoS One**. 2011;6:e16770.

RA/RAR-dependent defensive molecules in CD cells

In a mouse inner medullary CD cell line, we catalogued RA/RAR-dependent mRNAs by microarray.

- **At the mRNA level, RA/RAR tightly controls molecular defenders against:**
  - *Bacterial infection* (*Ppbp*, *Lcn2* and *Upk3b*);
  - *Inflammation (Ppbp, Cpm and Muc20);*
  - *Fibrosis (Bmp7)*;

Funded by

Kidney Research UK
Funding research to save lives

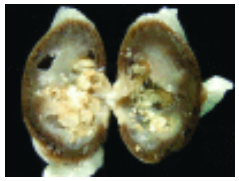
Wong YF, Wilson PD, Unwin RJ, Norman JT, Arno M, Hendry BM, **Xu Q**. Retinoic acid receptor-dependent, cell-autonomous, endogenous retinoic acid signaling and its target genes in mouse collecting duct cells. **PLoS One.** 2012, 7: e45725.

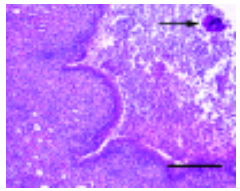
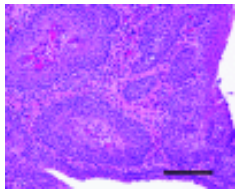
VAD led to renal infection, inflammation and urolithiasis

Munday JS, et al.

Cystitis, pyelonephritis, and urolithiasis in rats accidentally fed a diet deficient in vitamin A.

J Am Assoc Lab Anim Sci. 2009;48:790-4.

Examination of the 44 rats fed a VAD diet that completed the 34-wk experiment revealed

- 100% rats with with squamous metaplasia of the transitional epithelium;
- 68% pyelonephritis in
- 66% cystitis
- 27% urolithiasis, and
- 5% nephrolithiasis.

VAD in adults weakens kidneys

- Polyuria (cows, sheep): *Woelfel* 1965, *Webb* 1968.
- Urolithiasis and calculogenesis; alkaline urine; altered urine calcium excretion (rats, sheep, cows, human): *van Leersum* 1928, *Dutt* 1969, *Kancha* 1992, *Gijbels* 1992, *Grases* 1998.
- Increased susceptibility of the urinary tract/kidney to infection: *Munday* 2009, *Williams* 2009, *Yilmaz* 2007.
- Renal scarring secondary to pyelonephritis: *Kavukçu* 1999, *Dalirani* 2011, *Ayazi* 2011.

From an evolutionary point of view,…

- Given the evidence on pharmaceutical RA,

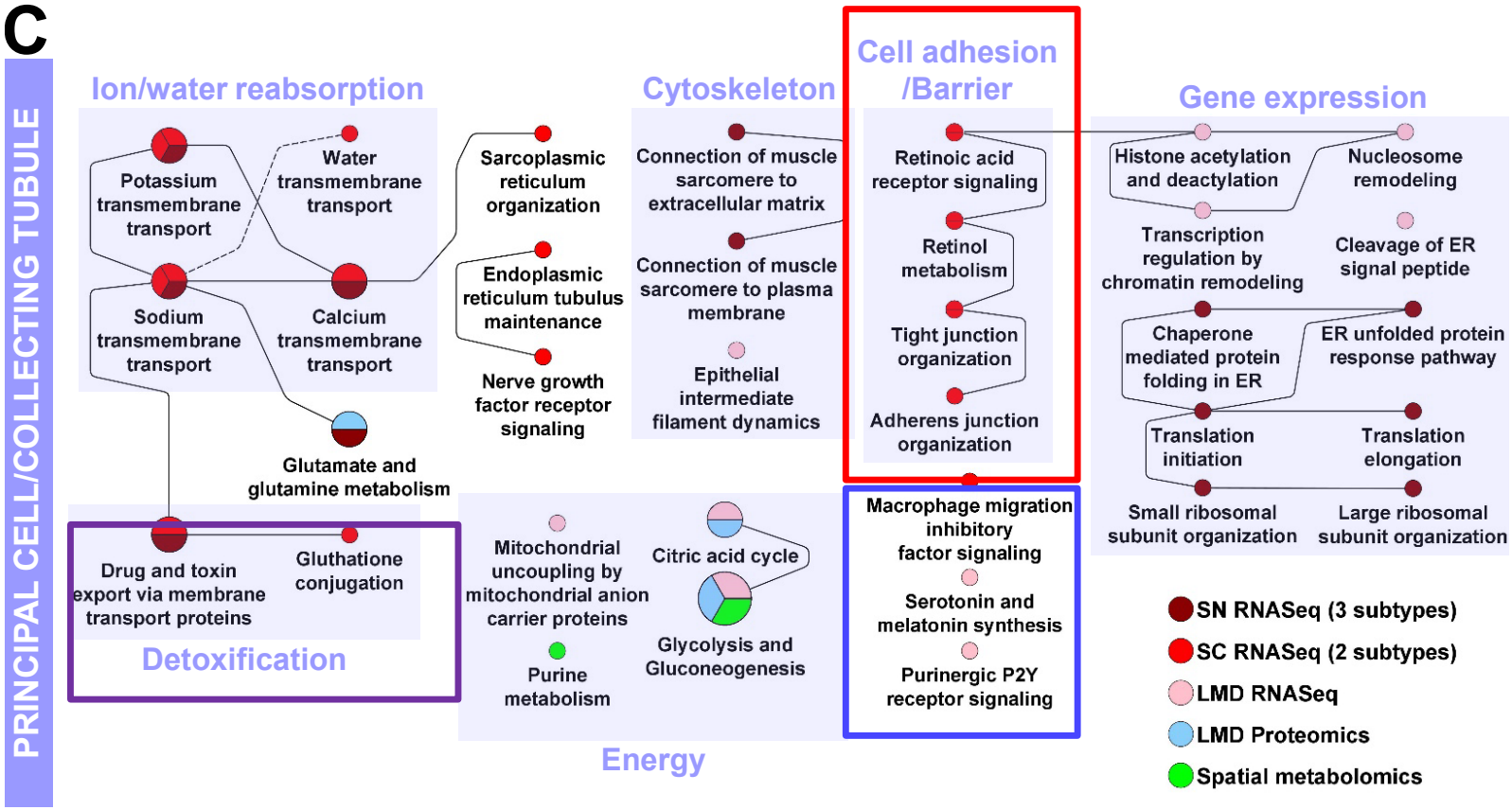
  …is it possible that endogenous RA/RAR in CDs naturally selected defence regulators?

Animal models of kidney diseases: successfully treated by RA

- ✓Acute anti-Thy1 nephritis
- ✓Puromycin aminonucleoside nephrosis
- ✓Lupus nephritis and SLE
- ✓Anti-GBM nephritis
- ✓IL-6 transgenic mice
- ✓Acute allograft rejection
- ✓Intestinal ischemia-reperfusion induced AKI
- ✓Chronic anti-Thy1 nephritis
- ✓Ageing-associated nephropathy
- ✓5/6 nephrectomy
- ✓Diabetic nephropathy
- ✓Adriamycin-induced nephropathy;
- ✓HIV-associated nephropathy
- ✓Unilateral ureteral obstruction

Xu Q, et al. Retinoids in nephrology: promises and pitfalls. **Kidney Int**. 2004; 66: 2119-31.
Xu Q, et al. **Nephron Exp Nephrol**. 2010;114:e127-32.
Rankin AC, Hendry BM, Corcoran JP, **Xu Q**. Br J Pharmacol. 2013;170:1177-89.

snRNA-seq analysis of human kidneys has unveiled the characteristic RA signalling that regulates cell barrier functions and multiple defence-related signalling pathways and detoxification roles of the CD cells.



Suppl. Fig. S12 **Hansen J, et al. Sci Adv. 2022;8(23):eabn4965.** https://www.science.org/doi/10.1126/sciadv.abn4965

Why RA/RAR in CDs?

- Be there
- Be resilient
- Well-equipped to fight
- Sense and respond to danger
- Must be tightly controlled
- Cause problems if dysregulated
- Be therapeutic if properly mobilised

UKKW2109 Poster No. P459: Renal RA/RAR activity changes in AKI

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Funding research to save lives



Dr Alex Papadimitriou

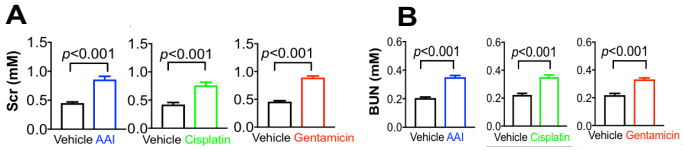


Fig. 3 AAI, cisplatin and gentamicin induced similar increase of Scr (**A**) and BUN (**B**) in *RARE-Luc* mice, n=6.

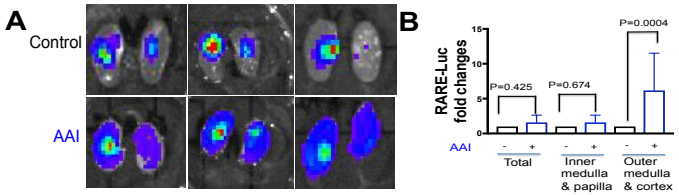


Fig. 4 AAI-induced RA/RAR activity in *RARE-Luc* mice was confined to outer medulla and cortex. **A.** Halved kidneys, n=3; *RARE-Luc* activity decreased from papilla outwards towards cortex; AAI induced an outward expansion of the signal. **B.** AAI-induced rise of *RARE-Luc* signal was confined to outer medulla/cortex, n=6.

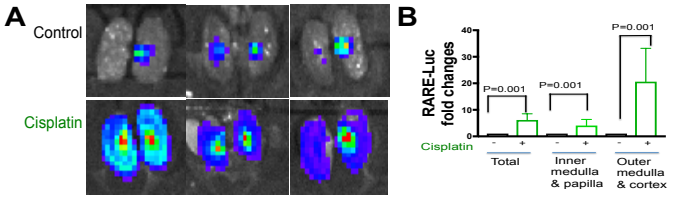


Fig. 5 Cisplatin-induced RA/RAR activity in *RARE-Luc* mice spanned across the entire kidney. **A.** Halved kidneys, n=3; cisplatin induced outward expansion of *RARE-Luc* signal; **B.** Cisplatin-induced rise of *the signal was significant* across the entire kidney, n=6.

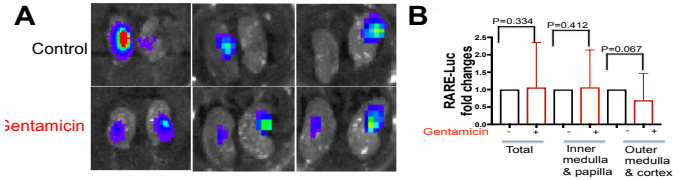


Fig. 6 Gentamicin did not significantly alter renal RA/RAR activity in *RARE-Luc* mice. **A.** Halved kidneys, n=3; **B.** data analysis, n=6.

Summary to findings

at the time of observation

Aristolochic acid I (AA-I)-induced AKI is characterised by increased renal *RARE-Luc* activity in renal cortex only

Cisplatin-induced AKI is characterised by increased renal *RARE-Luc* activity across the whole kidney

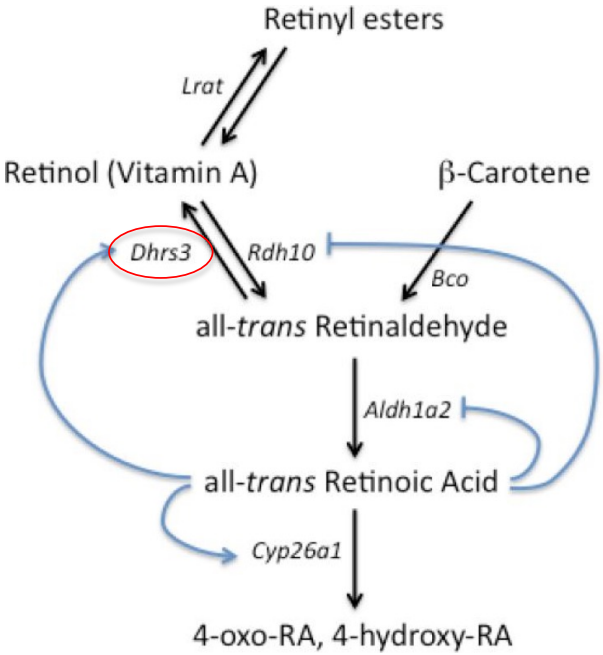
Gentamicin-induced AKI is characterised by *renal RARE-Luc* activity NOT changed significantly

Why RA/RAR in CDs?

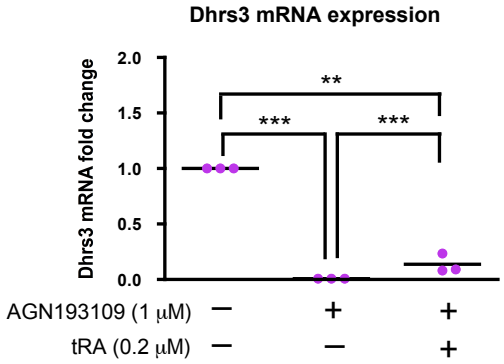
- Be there
- Be resilient
- Well-equipped to fight
- Sense and respond to danger
- Must be tightly controlled
- Cause problems if dysregulated
- Be therapeutic if properly mobilised

RA/RAR signalling in CD cells is controlled by Dhrs3-mediated feedback

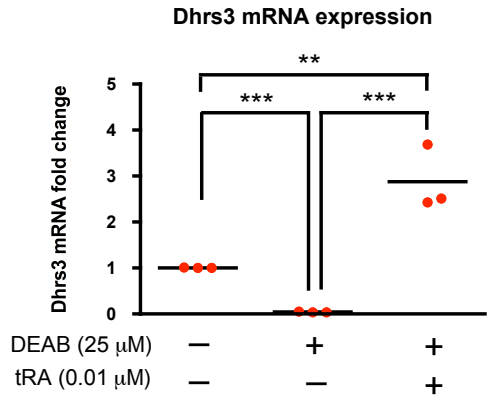
Dhrs3 converts retinaldehyde back into retinol and thus serves as a negative feedback in vitamin A signalling



Dhrs3 is repressed by RAR antagonist AGN193109



Dhrs3 is repressed by RA synthesis inhibitor DEAB



Wong YF, Wilson PD, Unwin RJ, Norman JT, Arno M, Hendry BM, **Xu Q**. Retinoic acid receptor-dependent, cell-autonomous, endogenous retinoic acid signaling and its target genes in mouse collecting duct cells. **PLoS One.** 2012, 7: e45725.

Why CDs?

- Be there
- Be resilient
- Well-equipped to fight
- Sense and respond to danger
- Must be tightly controlled
- Cause problems if dysregulated
- Be therapeutic if properly mobilised

RA/RAR activities in CD cells:
A convergence point of regulation by AKI/CKD mediators

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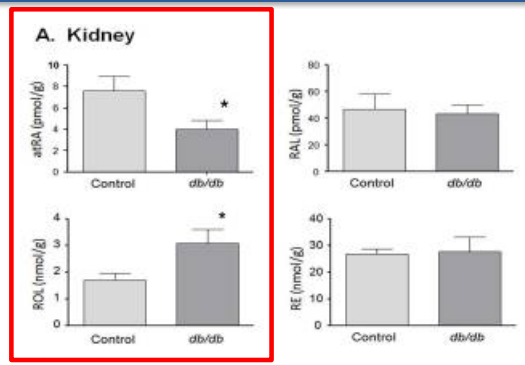

Dr Alex Papadimitriou

- **Repressed by mediators of progressive CKD**, e.g., albuminuria, high glucose, angiotensin II, aldosterone, endotoxin and cisplatin; and
- **Induced by drugs for preventing AKI, e.g., vasopressin and norepinephrine, and mediators of self-limited AKI,** e g., a single exposure to aristolochic acid I, gentamicin, endothelin-1.

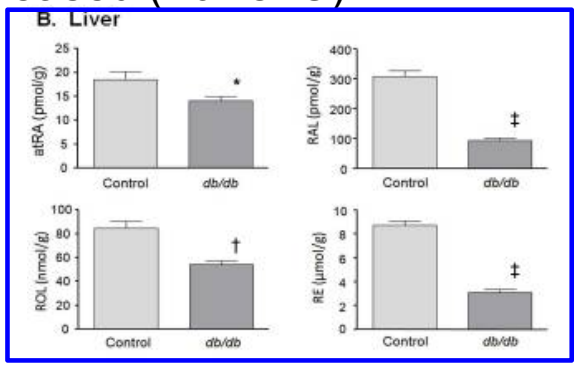
Papadimitriou A, et al. Collecting duct cells show differential retinoic acid responses to acute versus chronic kidney injury stimuli. *Sci Rep* 2020;10:16683.

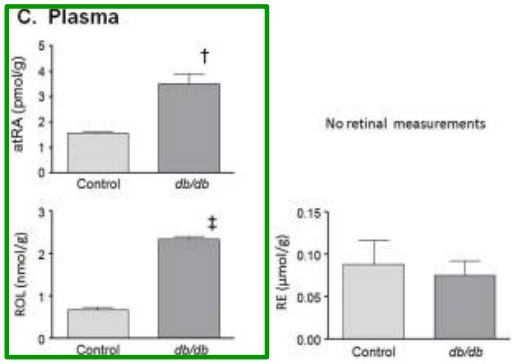
Kidney-specific dysregulation of RA metabolism in type-2 diabetes

- **Failure in vitamin A activation in db/db renal cortex:** tRA decreases despite increased retinol (**Panel A**).



- **Increased retinol systemic recruitment and activation and depletion of vitamin A storage in live in db/db mice:** In liver, all retinoids were lower than control (**Panel B**); in db/db plasma, tRA and retinol were both increased (**Panel C**).

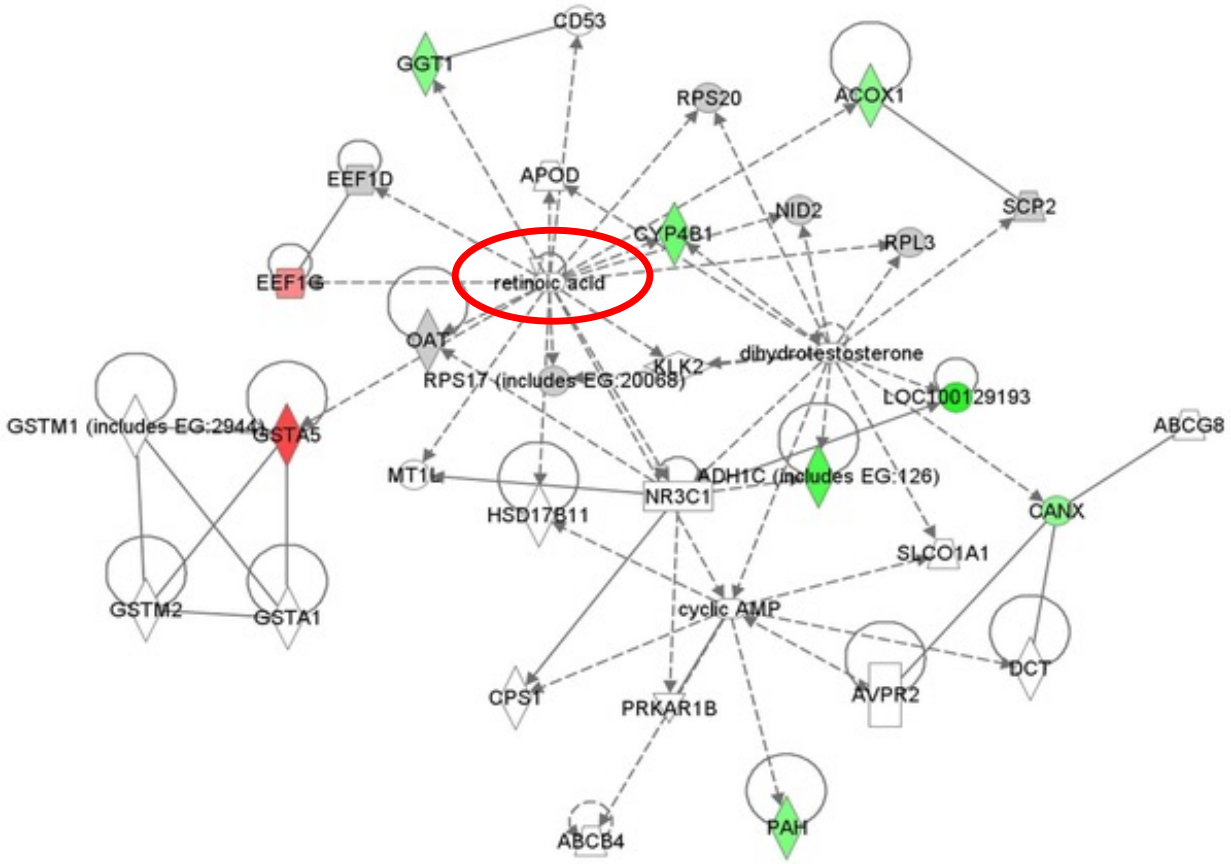




- **Thus, in db/db T2D mice, plasma vitamin A and tRA are poor indicators of vitamin A storage in the liver and activation in the kidney.**

Starkey JM, et al. **PLoS One.** 2010 14;5:e11095.

Renal proteomics: Disturbed RA network a key feature



Starkey JM, et al. PLOS ONE 2010;5:e11095.

What happens to AKI/CKD if RA/RAR in CDs is switched off?

Conditional, CD-specific repression of RA/RAR signalling in transgenic mice: Does it alter AKI/CKD?

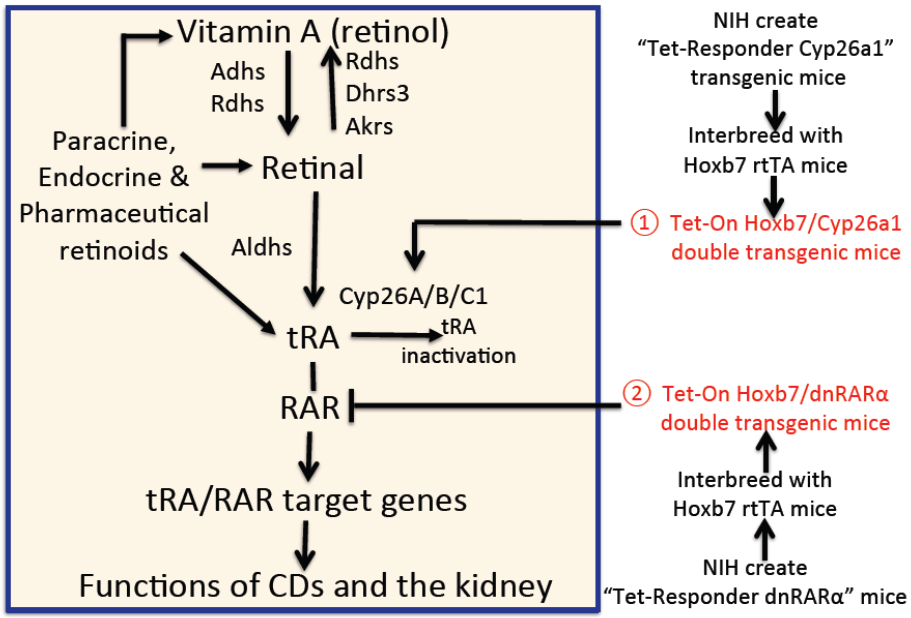


Fig. 5. "Tet-Responder dnRARα" and "Tet-Responder Cyp26a1" mice will be interbred with Hoxb7 rtTA mice to obtain "Tet-On Hoxb7/Cyp26a1" and "Tet-On Hoxb7/dnRARα" mice, in which tRA/RAR signalling is selectively repressed in CDs of adult mice after tetracycline treatment. Tet-On: tetracycline-inducible; rtTA: reverse tetracycline-controlled transactivator; Hoxb7: a UB/CD-specific promoter; dnRARα is a pan-RAR antagonistic dominant negative mutant of RARα.



Dr Jeffrey Kopp
Head, Renal Diseases Section
Senior Investigator
NIDDK, NIH, USA

Why CD?

- Be there
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- Well-equipped to fight
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- Must be tightly controlled
- Cause problems if dysregulated
- Be therapeutic if properly mobilised

RA is protective in AKI & CKD, with ADR noted

Animal models: successfully treated by RA

- ✓Acute anti-Thy1 nephritis
- ✓Puromycin aminonucleoside nephrosis
- ✓Lupus nephritis and SLE
- ✓Anti-GBM nephritis
- ✓IL-6 transgenic mice
- ✓Acute allograft rejection
- ✓Intestinal ischemia-reperfusion induced acute kidney injury in mice.
- ✓Chronic anti-Thy1 nephritis
- ✓Ageing-associated nephropathy
- ✓5/6 nephrectomy
- ✓Diabetic nephropathy
- ✓Adriamycin-induced nephropathy;
- ✓HIV-associated nephropathy
- ✓Unilateral ureteral obstruction

Animal models: Adverse effects reported:

- ✓Aggravates cryoglobulin-associated MPGN in mice;
- ✓Low dose reduced, higher dose increased fibrosis in subtotal Nx rats;
- ✓Higher dose increased fibrosis in TGF-β1 transgenic mice.
- ✓Potentiates radiation nephropathy in animal models;
- ✓Induces acute renal failure in retinoic acid syndrome.

Xu Q, et al. Retinoids in nephrology: promises and pitfalls. **Kidney Int**. 2004; 66: 2119-31.
Xu Q, et al. **Nephron Exp Nephrol**. 2010;114:e127-32.
Rankin AC, Hendry BM, Corcoran JP, **Xu Q**. Br J Pharmacol. 2013;170:1177-89.

Why?

Natural RA activates all RAR isotypes, which have differing roles.

- **e.g. RAR-gamma mediates irritating skin**

✓**Xu Q**, et al. Retinoids in nephrology: promises and pitfalls. *Kidney Int.* 2004; 66: 2119-31.
✓**Xu Q**, et al. *Nephron Exp Nephrol.* 2010;114:e127-32.
✓Konta T, **Xu Q**, et al. *J Biol Chem.* 2001;276:12697-701.
✓**Xu Q**, et al. *J Biol Chem.* 2002;277:41693-700.

All-*trans*-RA → 9-*cis* RA, which activates both RAR and RXR; and

- **RXR is the main mediator of profibrotic effects in fibroblasts**

Rankin AC, Hendry BM, Corcoran JP, **Xu Q**. *Br J Pharmacol.* 2013;170:1177-89.

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RA-568: A potent RARα agonist is an excellent drug lead



Dr Alex Papadimitriou, KCL



Prof. Jonathan Corcoran KCL

- **Natural RA was very poor in rescuing RA/RAR activities in human and mouse CD cells repressed by**
  - Albumin
  - Aldosterone
  - Angiotensin II
  - High glucose; and
  - LPS.
- **Synthetic RARα agonist RA-568 was at least 100-times more potent!**

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Papadimitriou A, et al. Collecting duct cells show differential retinoic acid responses to acute versus chronic kidney injury stimuli. *Sci Rep* 2020;10:16683.

Other questions under investigation

- **Relations between genetic, epigenetic changes and expression levels of key genes of the RA/RAR pathway and susceptibility to kidney injury, clinicopathological phenotypes, TCM diagnosis and prognosis?**

  RA/RAR通路相关基因编码区与非编码区变异、表观遗传学和CD细胞表达水平与肾损伤易感性、临床和病理表型、中医虚实辨证证型与预后的关系?

- **Values of CD-derived urinary exosomes in reporting CD RA/RAR activity and renal defence capacity?**

  尿液中集合管来源外泌体报告RA活性及相关防御生物标志物的价值?

- **Effects of classical and modern TCM therapies, esp. tonifying TCM, on RA/RAR activity and renal defence capacity?**

  补益中药和常用传统与现代治肾名方对肾脏集合管RA通路及其防御功能的影响…

结　论

1. 中西医均认为“肾”调节水盐、骨、造血、老龄化等。深入研究肾脏动、静脉在健康与疾病状态下的亚细胞与分子成分变化与差异，有望进一步理解“肾精”的科学内涵，以及肾与肾上腺的系统功能。

2. 整合中医药学理论提示，加强防御与代谢机制的研究有望科学阐释“正气”的本质，并为肾脏病学、药理学研究提供“新”途径。

   - 受中医正气理论启发，首倡“肾脏集合管中心防御”说。围绕该假说（尤其是肾脏集合管RA通路的内在防御作用）开展研究，有望科学理解肾虚以及肾脏病易感性机理、揭示补法防治肾脏病的科学原理。

   - 在中医阳气理论指导下，我的主要兴趣之一是研究纤维化与抗纤维化药物的代谢原理与干预靶点，并进一步开发新疗法。

3. 以中医药为师，大胆假设，小心求证，整合中医药有望为明日肾脏病学、医药学做出新的、突破性贡献。

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SEVENTH FRAMEWORK PROGRAMME

Kidney Research UK
Funding research to save lives

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  - **Cardiff University:** Donald Fraser.
  - **University of Queensland:** Melissa Little, Joan Li.
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Thank
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