Metabolic Associated Kidney Disease and Inflammation

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Metabolic Syndrome-Related Kidney Injury: A Review and Update

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- MetS called “Syndrome X” at first, it refers to a pathological state of metabolic disorders of proteins, fats, carbohydrates, and other substances in humans.

- It includes hypertension, hyperlipidemia, hyperuricemia, hyperglycemia, central obesity, and insulin resistance.

- A common risk factor for the morbidity and mortality of cardiovascular events.

- An important cause of new-onset CKD and progression of CKD.

Diagnostic criteria of MetS

	WHO,1998	IDF,2005	NCEP ATP III,2004	Modified NCEP ATP III,2010	AHA,2005	CDS,2020
	Presence of impaired glucose tolerance with any 2 of the following criteria	**Presence of central adiposity with 2 or more of the following criteria**	**Presence of 3 or more of the following criteria**			
Serum glucose	plasma glucose at 2h after glucose load ≥7.8 mmol/L	FPG ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.	FPG≥110 mg/dL (6.1 mmol/L)	FPG≥100 mg/dL (5.6 mmol/L)	FPG ≥100 mg/dL (5.6 mmol/L)	FPG≥110mg/dl BG 2h after glucose load ≥140mg/dl
WC	–	M: > 90cm; F: > 80cm	M: >102 cm; F: >88 cm	M: >102 cm; F: >88cm(Asian origin, M: >90 cm and F: >80 cm)	M: >102 cm; F: >88 cm	M: ≥ 90cm; F: ≥ 85cm M≥90cm F≥85 cm
BMI	>30 kg/m2					
WHR	M>0.90 ;F >0.85					
Hyperrension	≥140/≥90 mmHg	≥130/≥85 mmHg	≥130/≥85 mmHg	≥130/≥85 mmHg or current use of antihypertensive drugs	≥130/≥85 mmHg	BP≥ 130/85mmHg
HDL Cholesterol	M: < 35 mg/dL (0.9 mmol/L); F: < 39 mg/dL (1 mmol/L)	M: < 40 mg/L (1.03 mmol/L); F: < 50 mg/L (1.29 mmol/L) or receiving treatment	M: <40 mg/dL (1.03 mmol/ L) ;F: <50 mg/dL (1.29 mmol/L)	M: <40 mg/dL (1.03 mmol/ L) ;F: <50 mg/dL (1.29 mmol/L)	M: <40 mg/dL (1.03 mmol/ L) ;F: <50 mg/dL (1.29mmol/L)	HDL<40mg/dl
Triglycerides	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L) or receiving treatment	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L)	TG≥150mg/dl ≥150 mg/dL (1.7 mmol/L)

- It is estimated that the worldwide **prevalence** of MetS is **20 –25%.**

- This may be due to different **gender**, **age**, **racial**, **eating habits**, **education**, **medical security**, **nature of work**, and **living environments**.

- The **older the age**, the **higher the prevalence** of MetS.

- The prevalence of MetS in **aged ≥60 was 2.33 times** higher than those in **aged 15-39** (32.4% vs. 13.9%).

- MetS is also common in **South Asian** countries, including Afghanistan, Bangladesh, India, Maldives, Nepal, Pakistan, and Sri Lanka.

ASSOCIATION BETWEEN METS AND CKD

- **MetS and CKD** are **causal** and influence each other.

- MetS can lead to changes in **renal structure** and **function**, such as a decreased (**GFR**) and increased **urinary microalbumin**.

- A meta-analysis showed that the risk of **CKD in MetS was 1.34 times higher** than those without MetS (28).

- Another meta-analysis showed that **MetS increased the risk of CKD** by **50%.**

- Many studies found that each component of MetS was associated with CKD.

- The **more components** there were, the **higher the risk** of CKD (odds ratio, 1.96; 95%: 1.71,2.34).

- Similarly, due to impaired renal function, **microenvironment changes** and **disorder of glucose and lipid metabolism in patients with CKD**, the incidence **of MetS patients with CKD** is significantly **higher** than that in the general population.

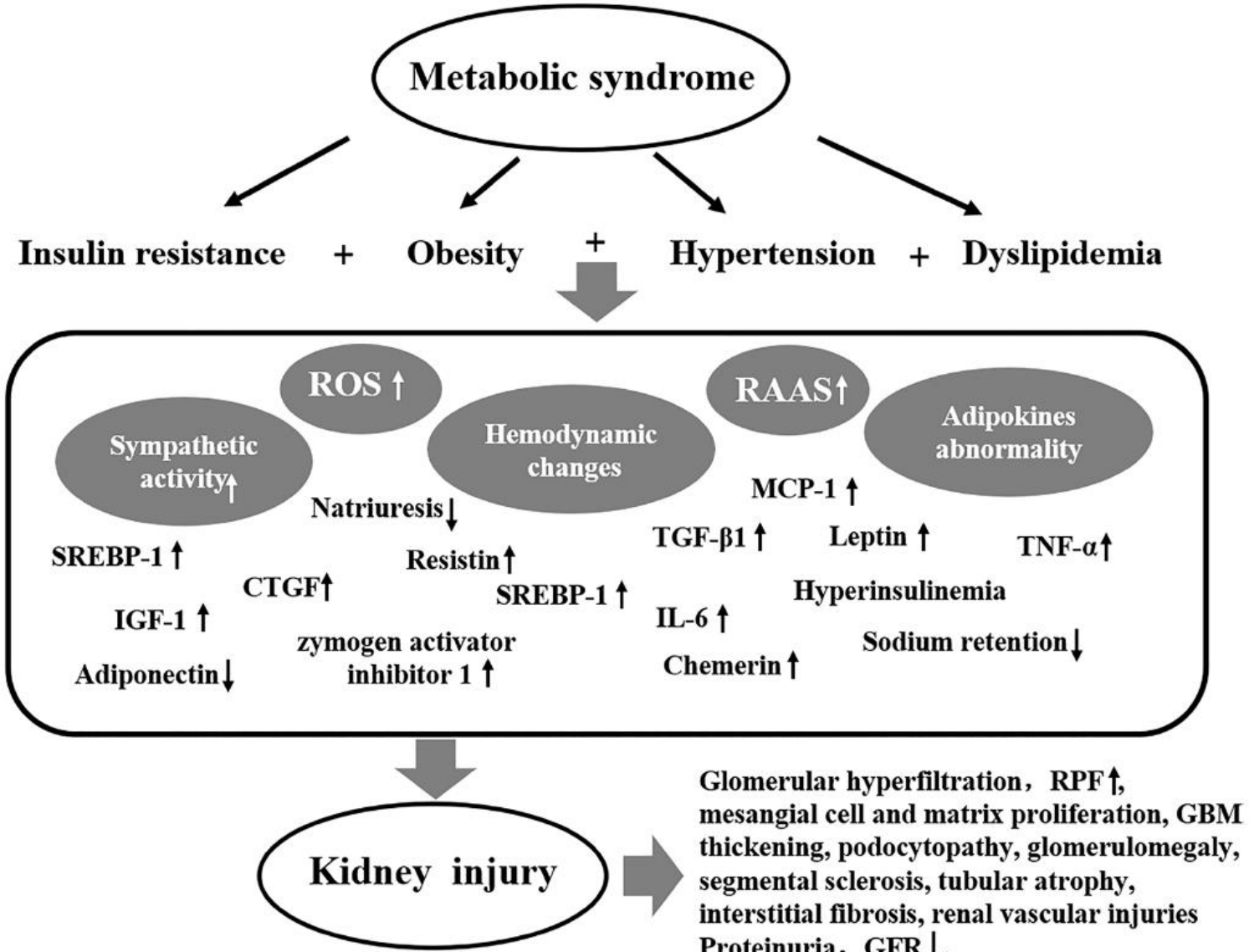
- With the **progress of CKD, the incidence of MetS gradually increases**.
- A study in Thailand found that the prevalence of **MetS in patients with CKD was 71.3%**
- Prevalence of MetS in patients with **ckd3a to 5** was 70.1%, 72.3%, 73.4% and 72.7% respectively.

- Recently, after using the “**MetS score**” and the “**MetS factor**” to refine MetS and its components.

- Regardless of gender and race, the **higher the score of MetS, higher prevalence of CKD**.

THE PATHOGENESIS OF METS RELATED RENAL INJURY

- Insulin resistance
- Obesity
- Hypertension
- Dyslipidemia
- Inflammation
- Oxidative stress
- Endothelial dysfunction.



The pathogenesis of MetS-related kidney injury.

- **Adiponectin**, **leptin**, **chemerin**, **resistin**, **IL-6,** and **TNF-a**,other **adipokines** are abnormally secreted and released, or dysfunctional,
- which induces
- oxidative stress,
- endothelial dysfunction,
- Inflammatory effects,
- increased sympathetic activity

and finally lead to changes in renal function and structure.

- During Mets, **adipose tissue secretion of pro-inflammatory factors** increased, including

(MCP-1), macrophage chemoattractant protein-1

macrophage migration inhibitory factor,

chemokine ligand 5,

macrophage colony-stimulating factor.

- The production of reactive oxygen species **(ROS)** in renal tissue increases due **to inflammatory cell infiltration**.

- ROS can also induce **TGF-b1** and **fibrinolysis** through the activation of the **nuclear factor-k light chain** enhancer and nicotinamide adenine dinucleotide phosphate oxidase (**NADPH)** pathways of activated **B cells**.

- The expression of **pro-fibrotic molecules**, such as **zymogen activator inhibitor 1**, thus aggravates the progress of renal fibrosis.

- **Podocyte foot loss** causes partial shedding of the glomerular filtration barrier (GFB), resulting in macromolecular leakage and proteinuria.

- The **adipose tissue** secretes **all components of the RAAS**.
- During Mets, excessive activation of RAAS will lead to increased **renal volume load** and **hyperfiltration.**

- Thus **damaging the GFB**, including endothelial cells, basement
- membrane, especially the podocytes.

- **In obese patients**, a large number of **lipid droplets** can be found in **renal innate cells**, especially in **podocytes**.

- The deposition of lipid droplets leads to the **depletion of renal cell energy**, and ultimately the **apoptosis of intrinsic renal cells**, resulting in CKD and even ESRD.

Obesity, kidney dysfunction, and inflammation: interactions in hypertension

John E Hall,[1,2,3] Alan J Mouton,[1,2] Alexandre A da Silva,[1,2] Ana C M Omoto,[1,2] Zhen Wang,[1,2] Xuan Li,[1,2] and Jussara M do Carmo[1,2]

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Cardiovasc Res. 2021 Jul 1; 117(8): 1859–1876.

Obesity, inflammation, and insulin resistance

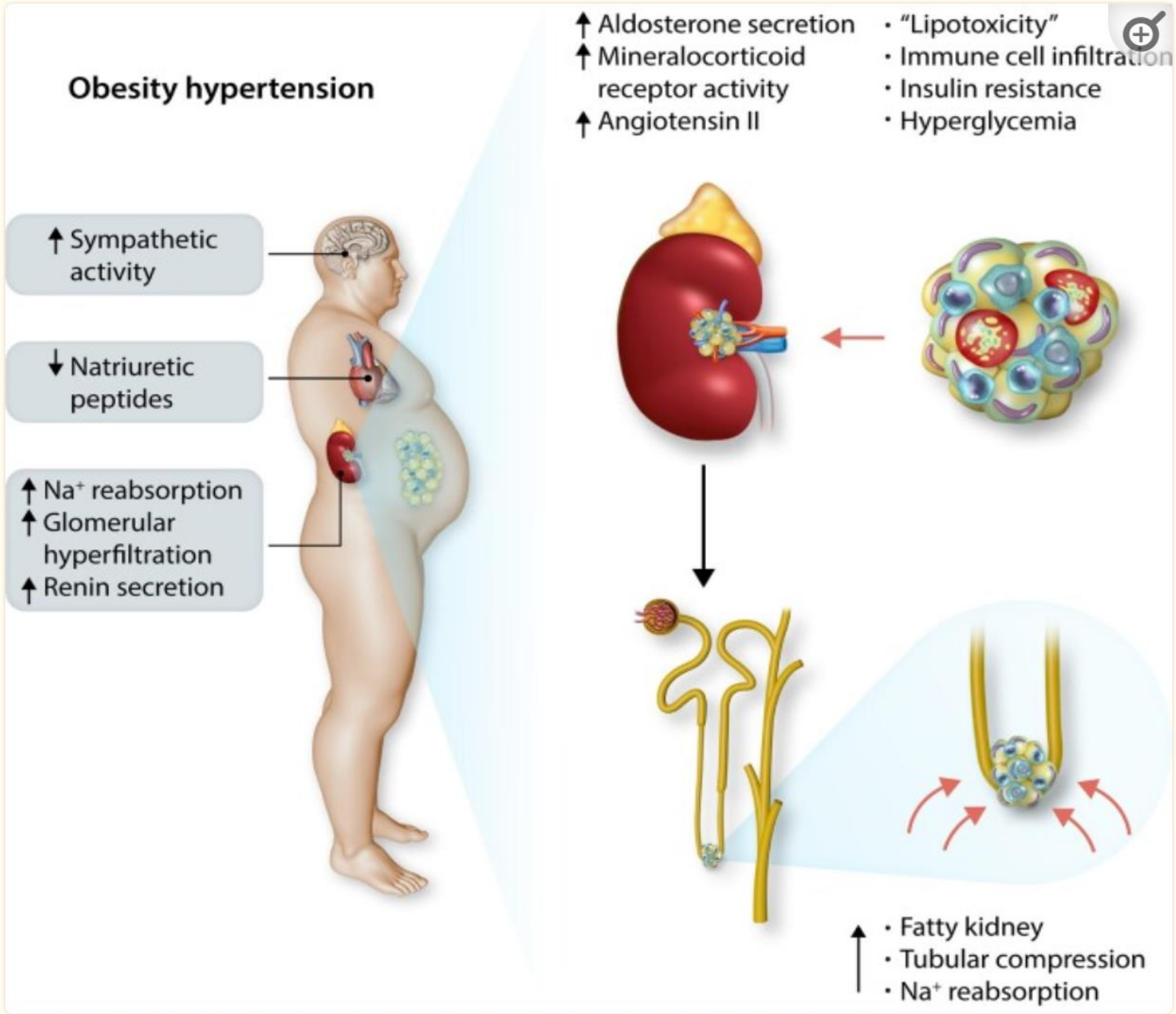
- **Immune cells** also respond to changes in their **nutrient environment** and **energy supply** in various ways, including release of inflammatory cytokines.

- Some of these cytokines circulate in the blood and influence metabolism in other tissues and in tissues that release them.

- **Immunometabolic pathways**, including
- **glycolysis**
- **oxidative phosphorylation**,
- are critical for **phenotypic switching** of various **immune cells**.

- Excess energy is **stored mainly as fat in adipocytes** which undergo hypertrophy and hyperplasia.
- **Visceral adipocytes** have limited hyperplastic potential and undergo **hypertrophy** when storing additional lipids.

- As these cells enlarge, they become **inadequately vascularized** and **hypoxic**, leading to
- **cell stress,**
- **apoptosis,**
- **immune cell infiltration**
- **increased secretion of inflammatory cytokines**


Obesity hypertension
↑ Sympathetic activity
↓ Natriuretic peptides
↑ Na⁺ reabsorption
↑ Glomerular hyperfiltration
↑ Renin secretion
↑ Aldosterone secretion
↑ Mineralocorticoid receptor activity
↑ Angiotensin II
• "Lipotoxicity"
• Immune cell infiltration
• Insulin resistance
• Hyperglycemia
↑
• Fatty kidney
• Tubular compression
• Na⁺ reabsorption

- **Hypertrophied VAT** secretes:

- **pro-inflammatory cytokines** such as **IL-1ß** and **TNF-α**

- **chemokines** that attract **circulating monocytes** into adipose tissue where they become **activated macrophages**.

- The **hypoxic environment** and exposure to other factors, such **hyperglycemia**, impair macrophage and T lymphocyte oxidative metabolism and **promote glycolytic metabolism via hypoxia-inducible factor 1a activation**,

- Thus **polarizing macrophages** to a pro-inflammatory **M1-like phenotype** and T lymphocytes to a **pro-inflammatory Th17 phenotype**, and causing systemic low-grade inflammation.

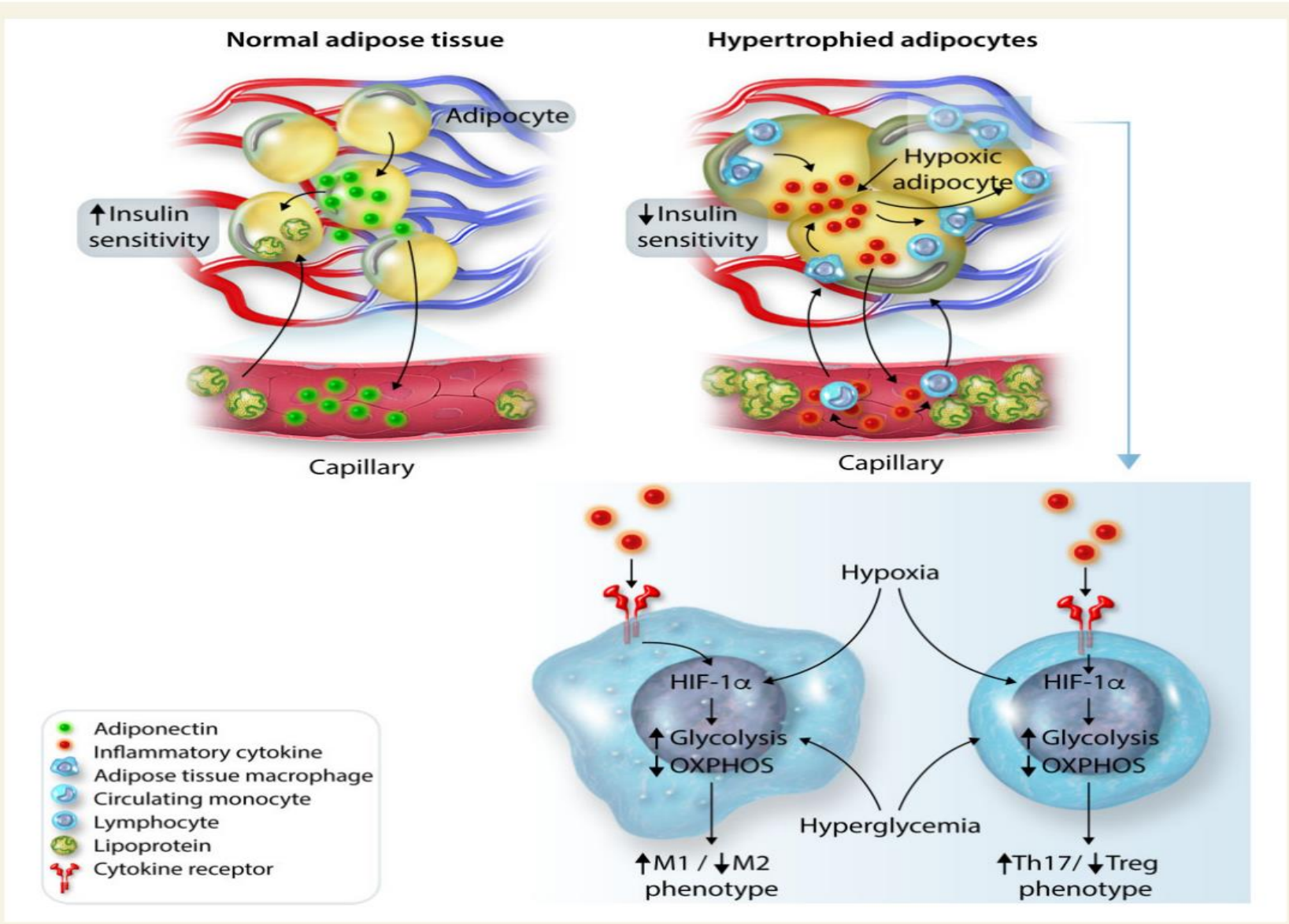


Figure 4 Possible mechanisms of inflammation and insulin resistance associated with excessive adipocyte hypertrophy. Small adipocytes secrete adiponectin locally and into the circulation, promoting insulin sensitivity and lipid storage. Hypertrophied adipocytes become hypoxic, leading to secretion of inflammatory cytokines and recruitment of circulating monocytes/lymphocytes into the tissue, which also secrete inflammatory cytokines. Within the microenvironment of hypertrophied adipocytes, immune cells are also hypoxic, leading to metabolic reprogramming that supports pro-inflammatory phenotypic switching and inflammation. This inflammation decreases insulin sensitivity, leading to hyperglycaemia and hyperlipidaemia. HIF-1α, hypoxia-inducible factor 1-alpha; OXPHOS, oxidative phosphorylation; Th17, T helper subset 17 lymphocyte; Treg, T regulatory lymphocyte.

Cardiovascular Research (2021) 117, 1859–1876

Immunomodulators involved in DN pathogenesis

TABLE 1 Cytokines involved in DN pathogenesis.

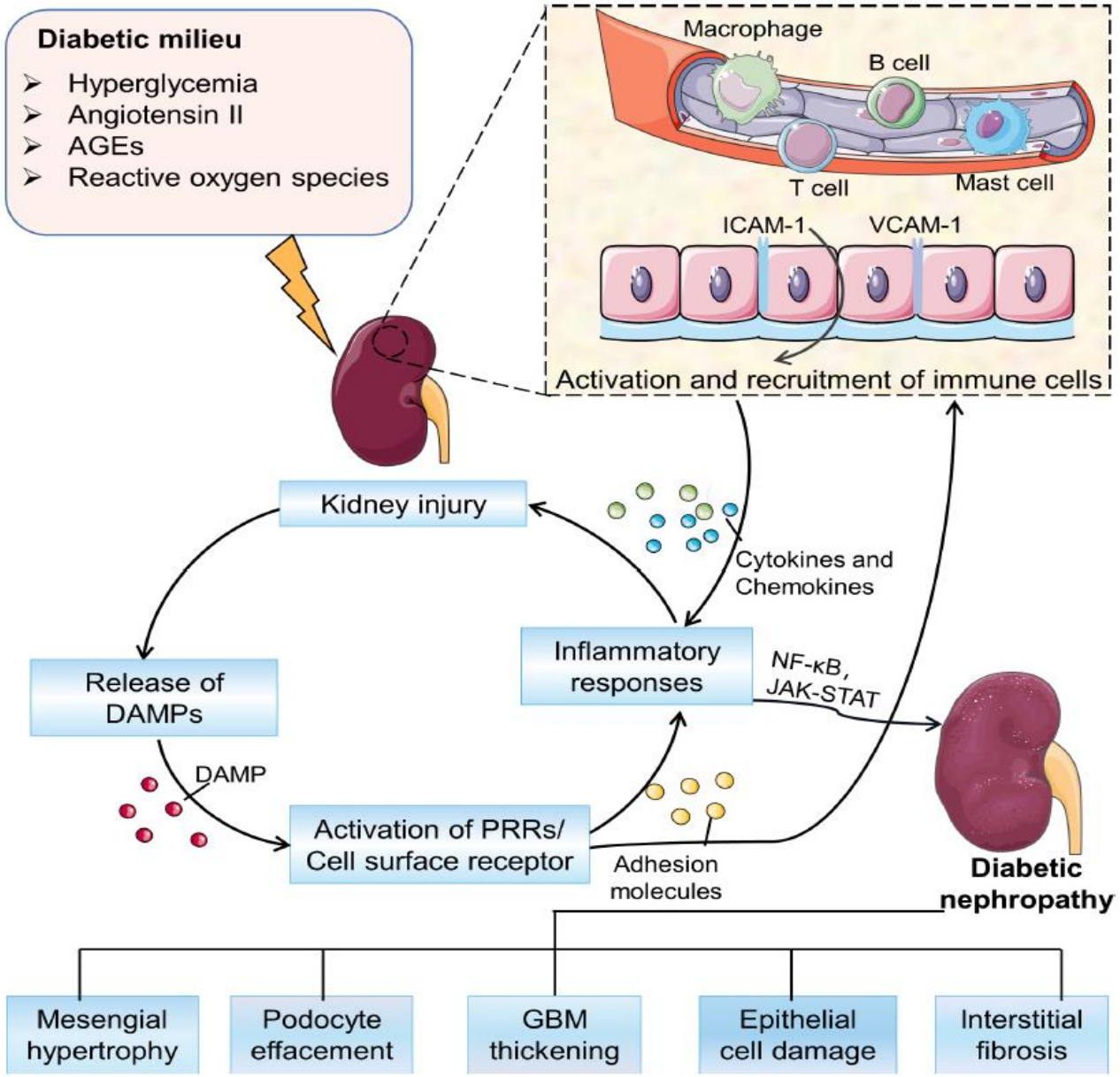
Cytokines	Cell Source	Cell Target	Functions	References
IL-1	Monocytes, macrophages, fibroblasts epithelial cells, endothelial cells, astrocytes	T cells, B cells, endothelial cells	Costimulatory molecule activation, acute phase reactants	(66–68)
IL-2	T cells, NK cells	T cells, B cells, monocytes	Growth and activation	(69)
IL-6	T cells, macrophages, fibroblasts	T cells, B cells	Costimulatory molecule activation, acute phase reactants	(70, 71)
IL-10	T cells	Macrophages, T cells	Inhibits APC activity and cytokine production	(72)
IL-18	Monocytes, macrophages, T cells, proximal tubular cells	T cells, NK cells	Costimulatory molecule activation, acute phase reactants	(73–75)
TNF-α	Macrophages, monocytes, T cells	T cells, B cells, endothelial cells	Costimulatory molecule activation, acute phase reactants	(68, 76–78)
TGF-β	Macrophages, T cells	Macrophages, T cells	Inhibits activation and growth	(79–81)
IFN-γ	T cells, NK cells	Monocytes, macrophages, endothelial cells	Activation increased class I and II MHC	(82)

Adhesion molecules

10.3389/fimmu.2022.958790

TABLE 2 The type and function of adhesion molecules.

Adhesion molecules	Gene Family	Functions	References
ICAM-1	Immunoglobulin superfamily	Adhesion, rolling and crawling of leukocyte	(99–102)
ICAM-2	Immunoglobulin superfamily	Crawling of leukocyte and initiation of diapedesis	(24, 102)
VCAM-1	Immunoglobulin superfamily	Adhesion, rolling and crawling of leukocyte	(29, 103, 104)
ESAM	Immunoglobulin superfamily	Increased endothelial permeability and initiation of diapedesis	(22, 24)



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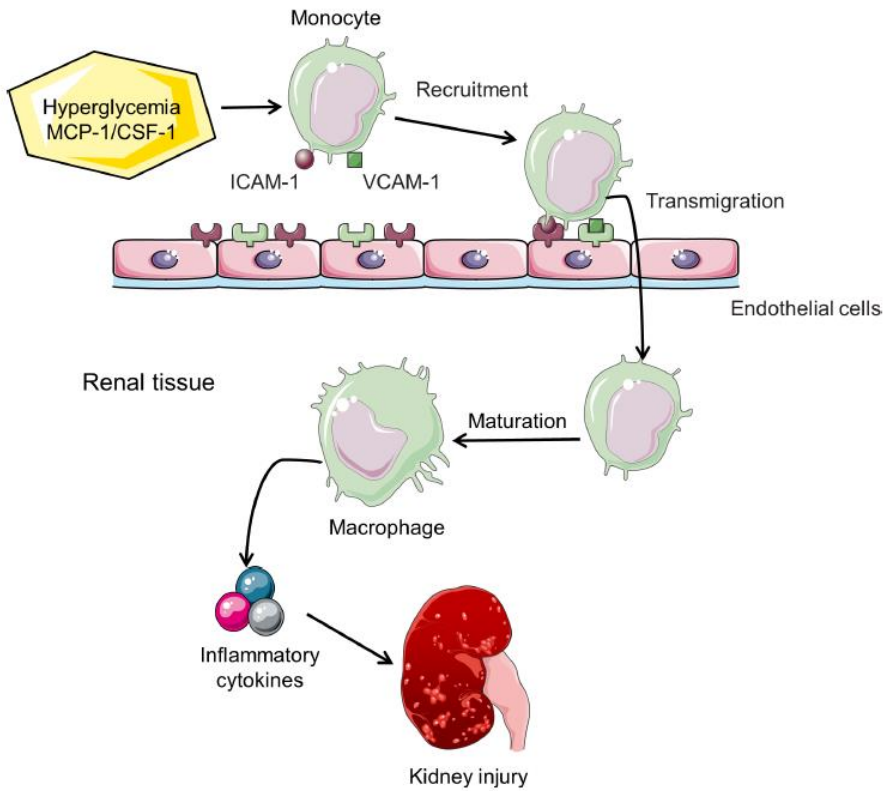

FIGURE 2
Macrophage recruitment and activation in DN. Hyperglycemia induces increased expression of cell adhesion molecules (ICAM-1/VCAM-1) and chemokines (MCP-1/CSF-1), thereby enhancing the recruitment of monocytes to the kidney. Chemokines also promote transendothelial migration. Monocytes mature into macrophages and subsequently release inflammatory cytokines, leading to the progression of DN.

The Complement System in Metabolic-Associated Kidney Diseases

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Hypertensive Kidney Disease

- Clinical trials have shown that **serumC3** is paralleled with **systolic blood pressure** .

- In renal biopsy, studies have found **C3c and C5b-9** activated in **hypertension-associated TMA**, with disordered levels of **factor B, D, P, and H**, while normal C4 level in those patients.

- **kidney-specific enzyme**, **cleaves C3 into C3a and C3b** in a manner identical to the C3 convertase, thus triggering the alternative pathway..

.**Factor H is an important negative regulator of AP and can bind to heparin sulfate (HS).**

- In the **GBM to protect host cells from complement attack.**
- In patients **with hypertensive kidney disease, the GBM** is destroyed and exhibits **lower HS levels**, then the AP would be over activated

.

- More importantly, the kidney is a potential complement source.
- **Tubular epithelial cells can synthesize all complement AP proteins** in vitro.
- Glomerular endothelial cells **(GECs) also synthesize more CFD**.

Diabetic Kidney Disease

- **Proteomic analysis** of laser capture microdissected **glomeruli** confirmed that **C3** and the membrane attack complex (**MAC**, C5b-9) showed an **increase in patients with DKD**.

- I**mmunohistochemical** staining also revealed a high expression of complement **factor B**, **C3d**, **C5aR**, and **MAC** .

- What is more, it is reported that the **urinary excretion of C3b, Bb, and MAC** are increased in DKD patients, and is demonstrated that the presence of complement split products in the urine is associated with accelerated ESRD and death.

Diabetic Kidney Disease

- It is now believed that **increased glycation of proteins**, which activates the lectin pathway, and the **dysfunction of complement regulatory proteins**.

- In vitro experiments have demonstrated that **glycation product fructose lysine**, whose structure is **analogous to mannose**, may **act as a ligand for MBL** and bind to it, **initiating complement activation.**

- In the **streptozotocin-induced type 1 diabetes mellitus (TIDM) models**, mannose-binding lectin (**MBL) levels increase.**

- Elevated MBL in the diabetic models may be due to a combination of
- **increased MBL production** and **decreased catabolism**.

- Compared to controls**, MBL-knockout mice induced by streptozotocin attenuate glomerular hypertrophy**, **urinary albumin excretion**, and **renal fibrosis**.

- In type 2 diabetes mellitus**(T2DM) rats**, **the expression of MASP2**, a key factor to **activate the lectin pathway, is upregulated** in renal tubular cells.

- In several clinical trials involving patients with T1DMor T2DM, it was confirmed **that serum MBL levels were significantly** higher in patients with **DKD** than those DM without DKD.

- **High baseline MBL** along with **CRP levels** could be used as a **predictor** for the development of proteinuria in DM patients.

- **CD59 is a key inhibitor of MAC formation**, which is universally expressed in cells.

- **Hyperglycemia** induces the **dysfunction or inactivation of CD59** after glycation, which proposed the **deposition of MAC** in renal parenchyma.

- A recent study identified **low abundance of urinary CD59** was a significant independent predictor of **faster eGFR decline** as well as higher risk of progression to ESRD.

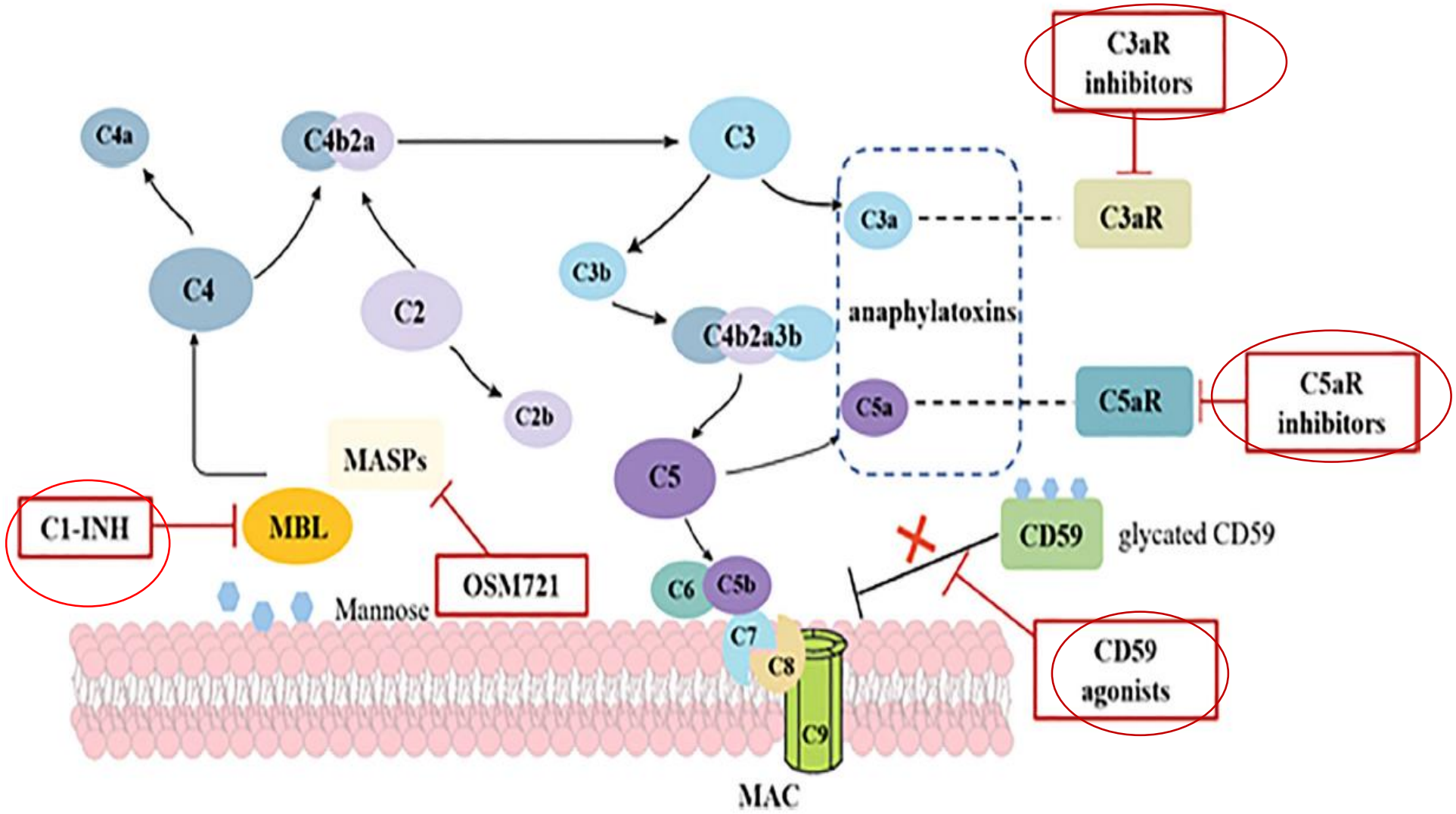
.

- Li et al. showed that the **upregulation** of **C3a/C3aR and C5a/C5aR**
- was associated with endothelial–myofibroblast transition (**EndMT**)

and fibrosis in glomerular endothelial cells of DKD patients and diabetic rats.

- Decay accelarating factor (**DAF/CD55**) is a complement **C3 convertase regulator** **expressed in podocyte**.

- In STZ-induced DKD models, the **DAF-deficient mice** showed more C3b glomerular deposition and exhibit a **more severe disease** phenotype.


C3aR inhibitors
C4a
C4b2a
C3
C3a
C3aR
C3b
C4
C2
C4b2a3b
anaphylatoxins
C2b
C5a
C5aR
C5aR inhibitors
MASPs
C5
C1-INH
MBL
CD59
glycated CD59
OSM721
C6
C5b
Mannose
C7
C8
CD59 agonists
C9
MAC

Obesity-Related Nephropathy

- Lim et al. reported that **targeting the receptors of anaphylatoxin C3a and C5a** can improve visceral adiposity and **inhibit the macrophage signaling**, suggesting that it may be a new strategy for treating metabolic dysfunction in animal models.
- Accumulated evidence indicated that **serum C3 levels** might be a biomarker for **insulin resistance in obesity** and **nonalcoholic fatty liver disease.**

- Furthermore, a **cross-sectional observational study** enrolled **1,191 Chinese** adolescents identified that **serum C1q was positively related to MS,** and may represent a biomarker for **predicting obesity or MS** in adolescents.

Hyperuricemia-Induced Kidney Disease

- In a study including **2,731 non-diabetic adults**, **C3 and C-reactive** protein (CRP) was reported to increase positively related to **stimulation of uric acid.**
-
- Of note, **CRP binds to MSU**, thus recruits and **activates C1 and MASP1**, resulting in the **fixation of MAC**.

- Additionally, a **functional C5 convertase complex assembles at the surface ofMSU** crystals, leading to the **generation of active C5a and C5b**.

- **C5a then activates the NLRP3 inflammasome** in macrophages and promotes the release of IL-1b, which in turn regulates neutrophil recruitment , thereby participates in the **inflammation caused by hyperuricemia.**

TABLE 1 | The role of complement system in the kidney under different metabolic disorders.

Metabolic disorders	Components of complement system	Renal damage
Diabetic kidney disease	The lectin pathway, CD59	Albuminuria, declined eGFR, glomerular hypertrophy, renal fibrosis
Hypertensive kidney disease	The alternative pathway	Glomerular cell proliferation, cell necrosis, glomerulosclerosis, phenotypic transformation of MCs
Obesity-related nephropathy	C3a, C5a, properdin	Albuminuria, MCs proliferation, macrophage accumulation, and polarization
Hyperuricemia-induced kidney disease	The classic pathway The alternative pathway	Albuminuria and renal fibrosis

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DOI: 10.1111/obr.13649

OBESITY Reviews WILEY

REVIEW

Obesity Comorbidities

Association of metabolic syndrome and chronic kidney disease

Florian G. Scurt[1] | Maximilian J. Ganz[1] | Carolin Herzog[1] | Katrin Bose[2] | Peter R. Mertens[1] | Christos Chatzikyrkou[3]

Abdominal obesity, adipose tissue and dyslipoproteinemia

- Renal hemodynamics, podocyte loss, and Proteinuria

- Renal compression
- Direct cytotoxic effects
- The **excessive accumulation of perirenal fat** in the **renal sinus** is directly cytotoxic through the **accumulation of intracellular triglycerides and toxic metabolites**, such as **ceramides.**

ORIGINAL ARTICLE

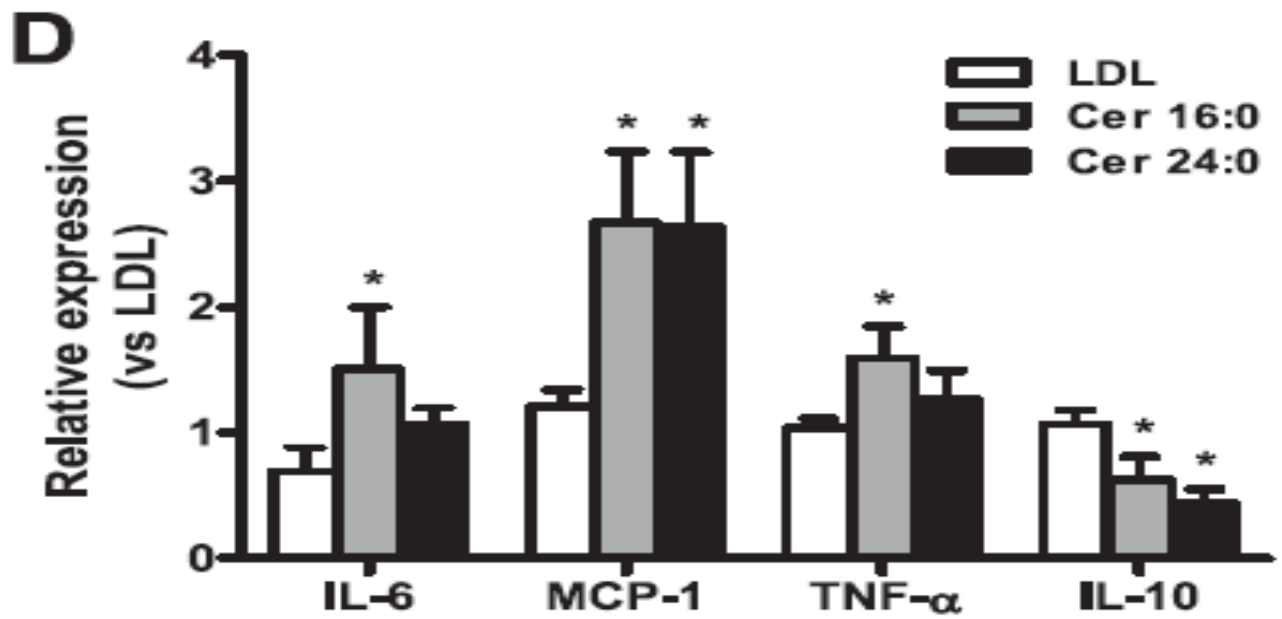
Ceramides Contained in LDL Are Elevated in Type 2 Diabetes and Promote Inflammation and Skeletal Muscle Insulin Resistance

James Boon,[1] Andrew J. Hoy,[1] Romana Stark,[1] Russell D. Brown,[1] Ruth C. Meex,[1] Darren C. Henstridge,[2] Simon Schenk,[3] Peter J. Meikle,[2] Jeffrey F. Horowitz,[4] Bronwyn A. Kingwell,[2] Clinton R. Bruce,[2] and Matthew J. Watt[1]

Diabetes 62:401–410, 2013

- Ceramide causes **NF-kB activation** and **TNF-a, IL-6, IL-1b**,
- and **MCP-1** are controlled by NF-kB.

- Blocking ceramide synthesis or inhibiting Nf-kB reduces TNF-a and IL-6 production, although this is not a universal finding.


D
Relative expression
(vs LDL)
4
3
2
1
0
LDL
Cer 16:0
Cer 24:0
*
*
*
*
*
*
IL-6
MCP-1
TNF-α
IL-10

- **Plasma ceramides** are associated with **pro-inflammatory cytokines** in individuals with cardiovascular disease, type 2 diabetes, and obesity.

- We confirmed the **positive relationship between plasma ceramide and TNF-a in humans** and used

  the LDL-ceramide preparation to determine causality.

- **LDL-ceramide stimulated proinflammatory cytokine production** and secretion via several mechanisms:

first, by promoting the uptake and accumulation of ceramide that is temporally associated with **JNK signaling**,

second, by activation of **NF-kB signalling** that is dependent upon TLR signalling.

- **Circulating ceramides** are elevated in **obese, insulin-resistant** individuals.
- **LDL ceramide can be reduced with diet and exercise.**

- The finding that LDL-ceramide can **accumulate in the plasma membrane of skeletal muscle**, cause insulin resistance, and induce macrophage inflammation.

Diabetes 62:401–410, 2013

Insulin resistance and hyperinsulinemia

- Physiologically, **insulin dependent activation of the Akt signaling**
- pathway in vascular and renal tissues leads to upregulation of the
- endothelial nitric oxide synthase **(eNOS**), resulting in release of endothelial NO and vasorelaxation.

- **Excessive NO products** have detrimental effects on the vascular wall
- by **enhancing recruitment and adhesion** of leucocytes and monocytes
- in the vessel wall, **activating platelet aggregation** and inducing
- **proinflammatory cytokines**.

- **Insulin resistance** induces
- an **increase in sodium retention**
- and **vasoconstriction** of the vascular endothelium via **antidiuretic effects**
- , activation of**(RAAS**) and renal tubular lipid accumulation.

- Accumulation of growth factor (**TGF-β1) from adipocytes** and
- associated proliferation of renal mesangial cells, as well as
- **deposition of lipid droplets** in renal tubular cells (mediated by
- elevation of **sterol regulatory element binding protein-1** [**SREBP-1**]),
- leading to **tubular atrophy and interstitial fibrosis**.

- Inadequate glycemic control leads to the formation **of AGE**, which

are known to activate various proinflammatory signalling pathways and induce **oxidative stress** by interacting with their **membrane-bound receptor (RAGE).**

- In the renal interstitium and mesangium, thereby exacerbating vascular injury.

mini review

http://www.kidney-international.org

Role of adipose tissue renin–angiotensin system in metabolic and inflammatory diseases associated with obesity

Laurent Yvan-Charvet[1] and Annie Quignard-Boulangé[2,3]

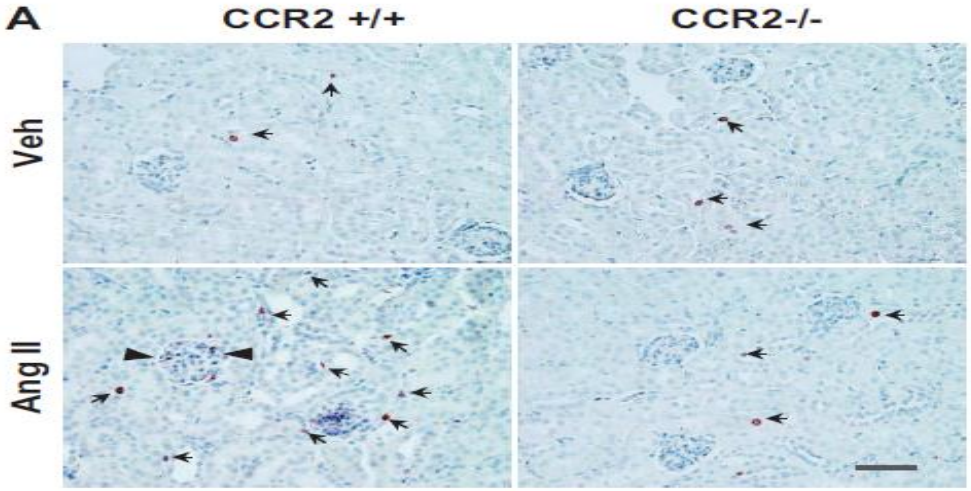
[1]Division of Molecular Medicine, Department of Medicine, Columbia University, New York, New York, USA; [2]INRA, UMR914, Physiologie de la Nutrition et du Comportement Alimentaire, Paris, France and [3]AgroParisTech, UMR914, Physiologie de la Nutrition et du Comportement Alimentaire, Paris, France

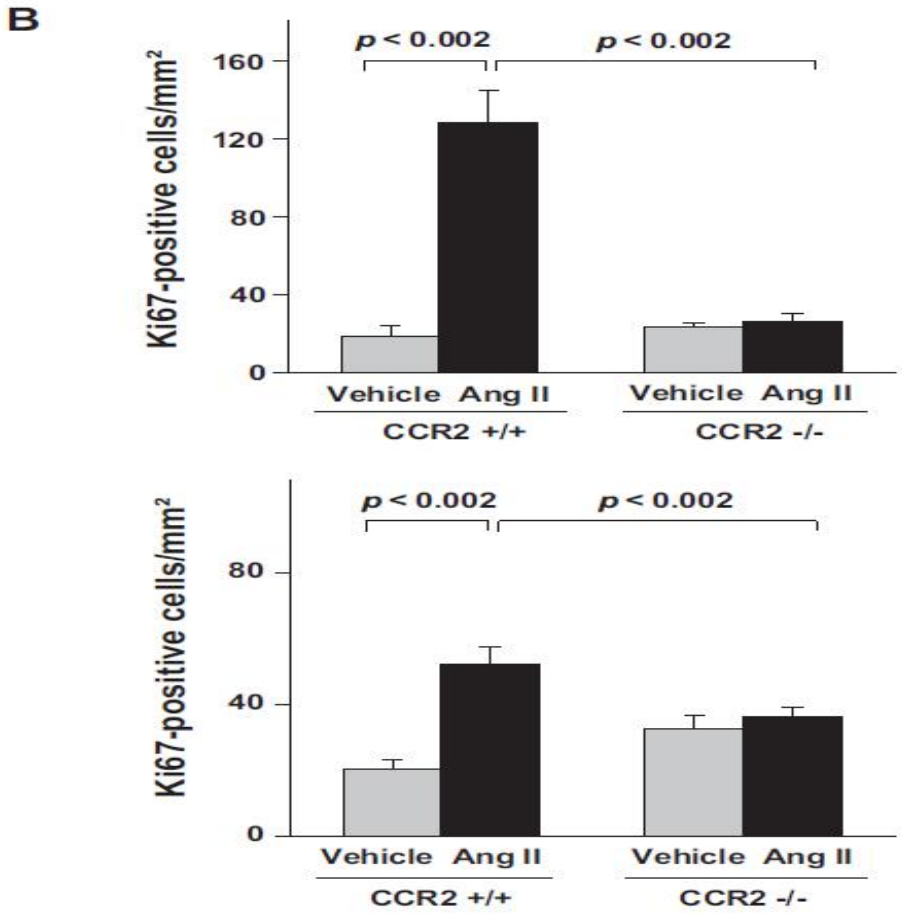
Kidney International (2011) 79, 162–168

- Prolonged exposure to Ang II, as it may occur in the setting of obesity with increased **production of AGT by adipose tissue**, maybe a key event in the development of chronic inflammatory disorders by

Increasing **local inflammation**

promoting the infiltration of **newly produced monocytes**.

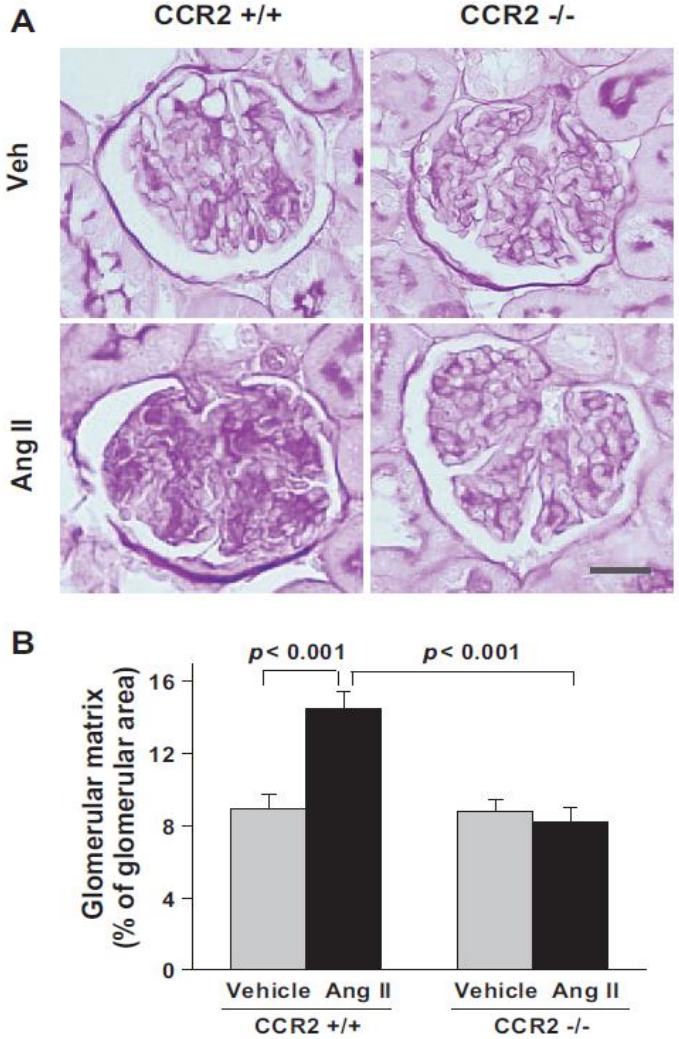


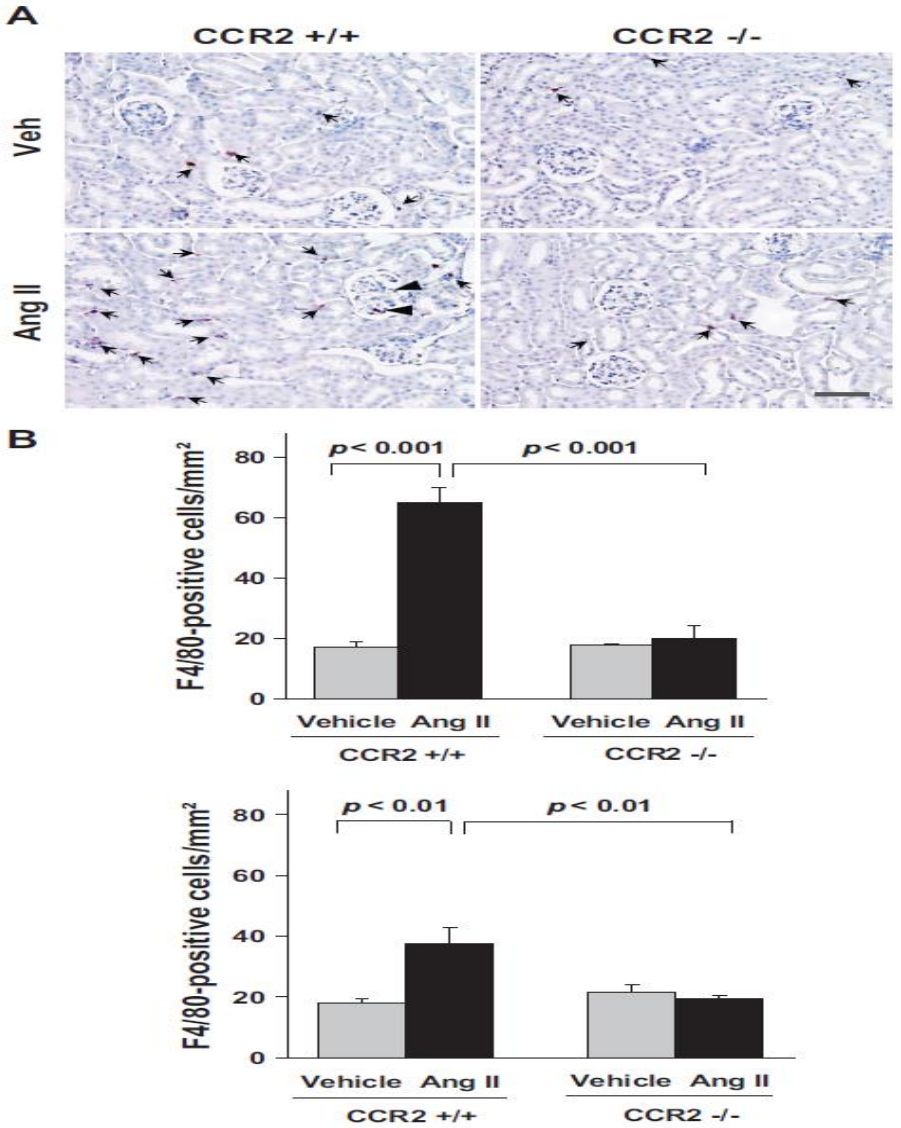


A, Representative immunohistochemical staining for Ki-67–positive cells (an indicator for cell proliferation) in mice infused for 4 weeks with vehicle (Veh) or Ang II. The reddish-brown color in the nucleoli was considered positive.
Positive cells were found in the tubulointerstitial area (arrows) and glomerulus.

Role of Inflammation in the Development of Renal Damage and Dysfunction in Angiotensin II–Induced Hypertension

Tang-Dong Liao, Xiao-Ping Yang, Yun-He Liu, Edward G. Shesely, Maria A. Cavasin, William A. Kuziel, Patrick J. Pagano, Oscar A. Carretero





A, Representative immunohistochemical staining forF4/80-positive cells (macrophages) in mice infused for 2 weeks with either vehicle (Veh) or Ang II.

***Hypertension*. 2008;52:256-263.)**

- Two elegant studies have consecutively shown that Ang II promotes the **differentiation of monocytes from hematopoietic** progenitors and **influences their chemotaxis** potentially through an **upregulation of CCR2**.
- These mechanisms could contribute to an **increased recruitment of immune cells in the site of inflammation** as has been shown in a context of atherosclerosis.

Obesity, Hypertension, and Cardiac Dysfunction: Novel Roles of Immunometabolism in Macrophage Activation and Inflammation

Alan J. Mouton[1,3], **Xuan Li**[1,3], **Michael E. Hall**[1,2,3], **John E. Hall**[1,3]

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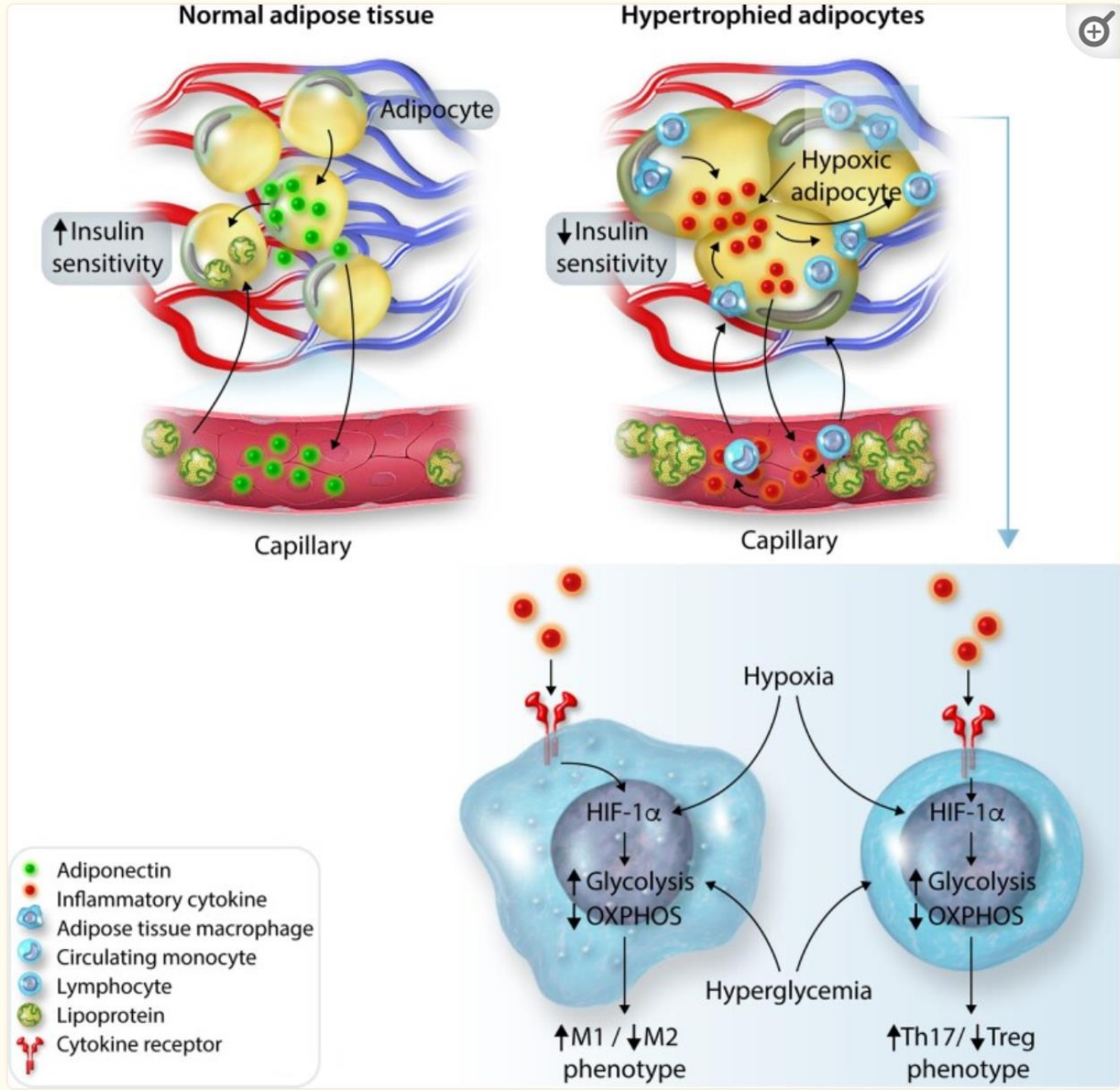
- Peroxisome proliferator activated receptor-gamma (PPAR-γ) is a **nuclear receptor which is activated by fatty acids** and other lipid ligands, and promotes expression of genes for fatty acid (β) oxidation.
- While **adipocytes are the major cell type expressing PPAR-γ**, **macrophages also highly express PPAR-γ** which **regulates fatty acid metabolism and expression of anti-inflammatory/M2 genes.**
- **PPAR-γ stimulates cholesterol efflux and decreases lipotoxicity in macrophages.**
- PPAR-γ is typically **activated by unsaturated fatty acids and omega-3** fatty acid-derived eicosanoids, which are decreased during obesity.

- **PPAR-γ mediates M2 polarization** by interleukin-4 (IL-4), a potent anti-inflammatory cytokine.
- This action is mediated by STAT6, which promotes PPAR-γ activation via expression of the PPAR-γ coactivator-1β (PGC-1β), an inducer of mitochondrial biogenesis.
- Thus, the **IL-4/STAT6/PPAR-γ axis** is critical in promoting the shift towards **oxidative metabolism and an M2 phenotype**.


Normal adipose tissue
Hypertrophied adipocytes
Adipocyte
↑Insulin sensitivity
Hypoxic adipocyte
↓Insulin sensitivity
Capillary
Capillary
Hypoxia
HIF-1α
↑Glycolysis
↓OXPHOS
HIF-1α
↑Glycolysis
↓OXPHOS
Hyperglycemia
↑M1 / ↓M2 phenotype
↑Th17/ ↓Treg phenotype
Adiponectin
Inflammatory cytokine
Adipose tissue macrophage
Circulating monocyte
Lymphocyte
Lipoprotein
Cytokine receptor

- **Activation of the inflammasome complex** enables maturation of pro-inflammatory cytokines **IL-1β and IL-18** and is also an integral part of innate immunity that may contribute to metabolic disorders in obesity.

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Journal Article

Activation of Stimulator of IFN Genes (STING) Causes Proteinuria and Contributes to Glomerular Diseases

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The signaling molecule stimulator of IFN genes (STING) was identified as a crucial regulator of the DNA-sensing cyclic GMP-AMP synthase (cGAS)-STING pathway, and this signaling pathway regulates inflammation and energy homeostasis under conditions of obesity, kidney fibrosis, and AKI. However, the role of STING in causing CKD, including diabetic kidney disease (DKD) and Alport syndrome, is unknown.

Methods

To investigate whether STING activation contributes to the development and progression of glomerular diseases such as DKD and Alport syndrome, immortalized human and murine podocytes were differentiated for 14 days and treated with a STING-specific agonist. We used diabetic *db/db* mice, mice with experimental Alport syndrome, *C57BL/6* mice, and STING knockout mice to assess the role of the STING signaling pathway in kidney failure.

Results

In vitro, murine and human podocytes express all of the components of the cGAS-STING pathway. *In vivo*, activation of STING renders *C57BL/6* mice susceptible to albuminuria and podocyte loss. STING is activated at baseline in mice with experimental DKD and Alport syndrome. STING activation occurs in the glomerular but not the tubulointerstitial compartment in association with autophagic podocyte death in Alport syndrome mice and with apoptotic podocyte death in DKD mouse models. Genetic or pharmacologic inhibition of STING protects from progression of kidney disease in mice with DKD and Alport syndrome and increases lifespan in Alport syndrome mice.

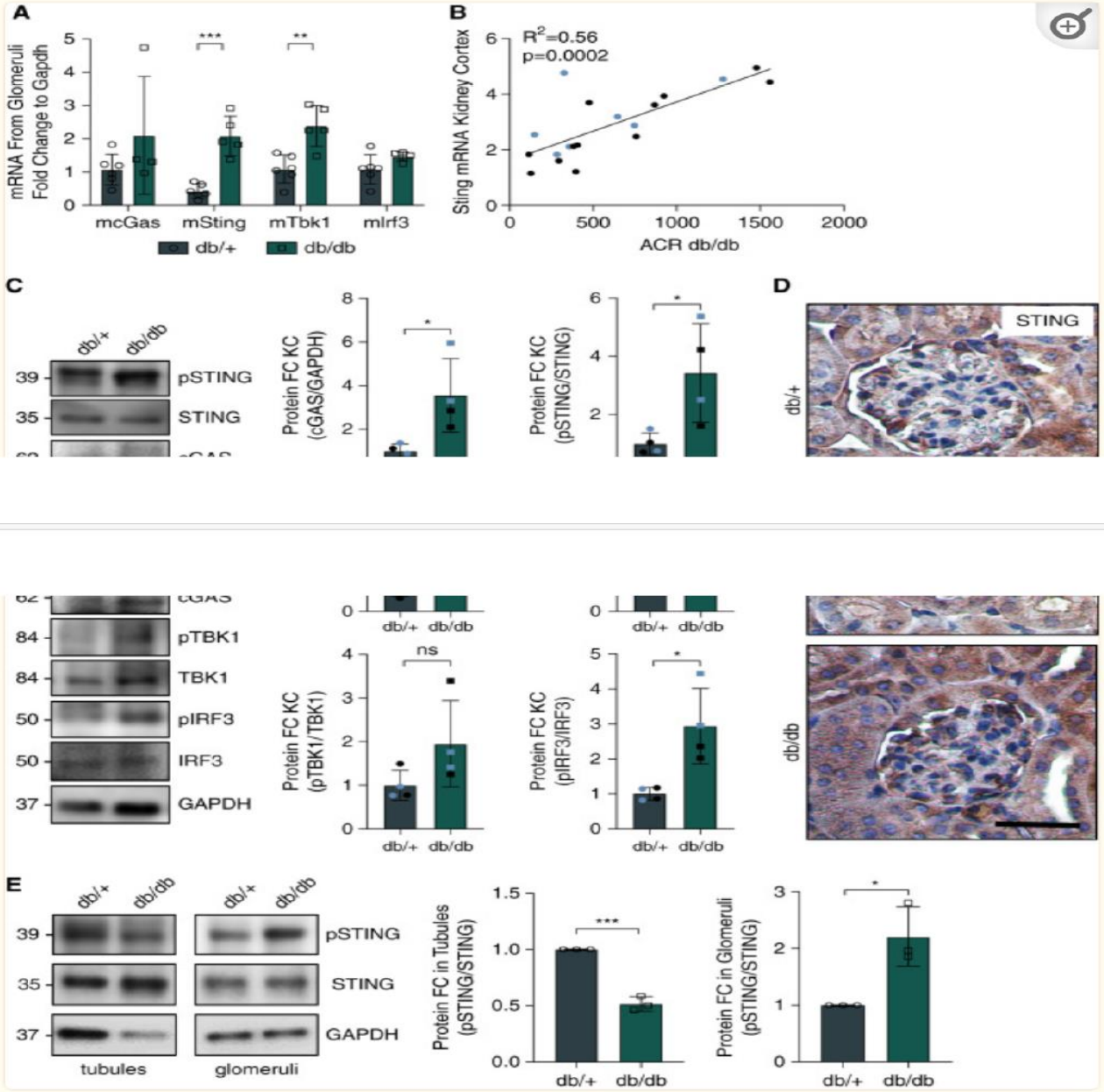

Figure 3.

The cGAS-STING signaling pathway is upregulated in a mouse model of DKD. Sixteen-week-old control (*db/+*)

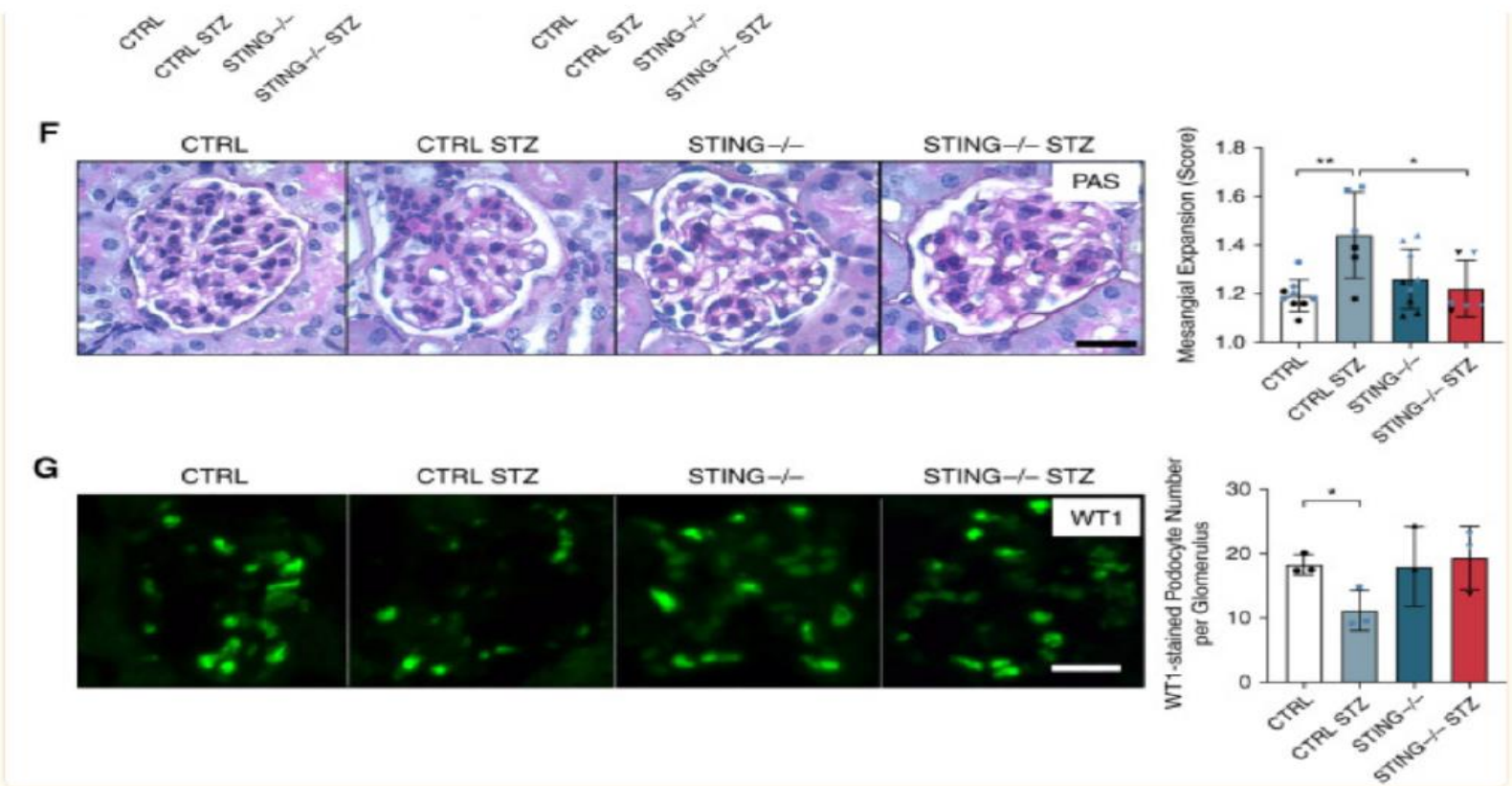

Figure 5.

STING knockout mice are protected from DKD. For STZ-induced diabetes (STZ, 40 mg/kg) four groups of 8-week-

- STZ-treated CTRL mice demonstrated significantly increased ACR levels starting 4 weeks after the establishment of diabetes, whereas in **STZ-treated *STING*$^{-/-}$ mice ACR levels remained unchanged**.
- Functional analysis of the kidney also demonstrated that BUN and serum creatinine levels remained unchanged in STZ-injected *STING*$^{-/-}$ mice compared with *STING*$^{-/-}$ control mice.
- Moreover, the effect of STZ-induced kidney damage was significantly attenuated in *STING*$^{-/-}$ mice compared with CTRL mice based on the histologic analysis of mesangial expansion.

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The Role of the NLRP3 Inflammasome in Mediating Glomerular and Tubular Injury in Diabetic Nephropathy

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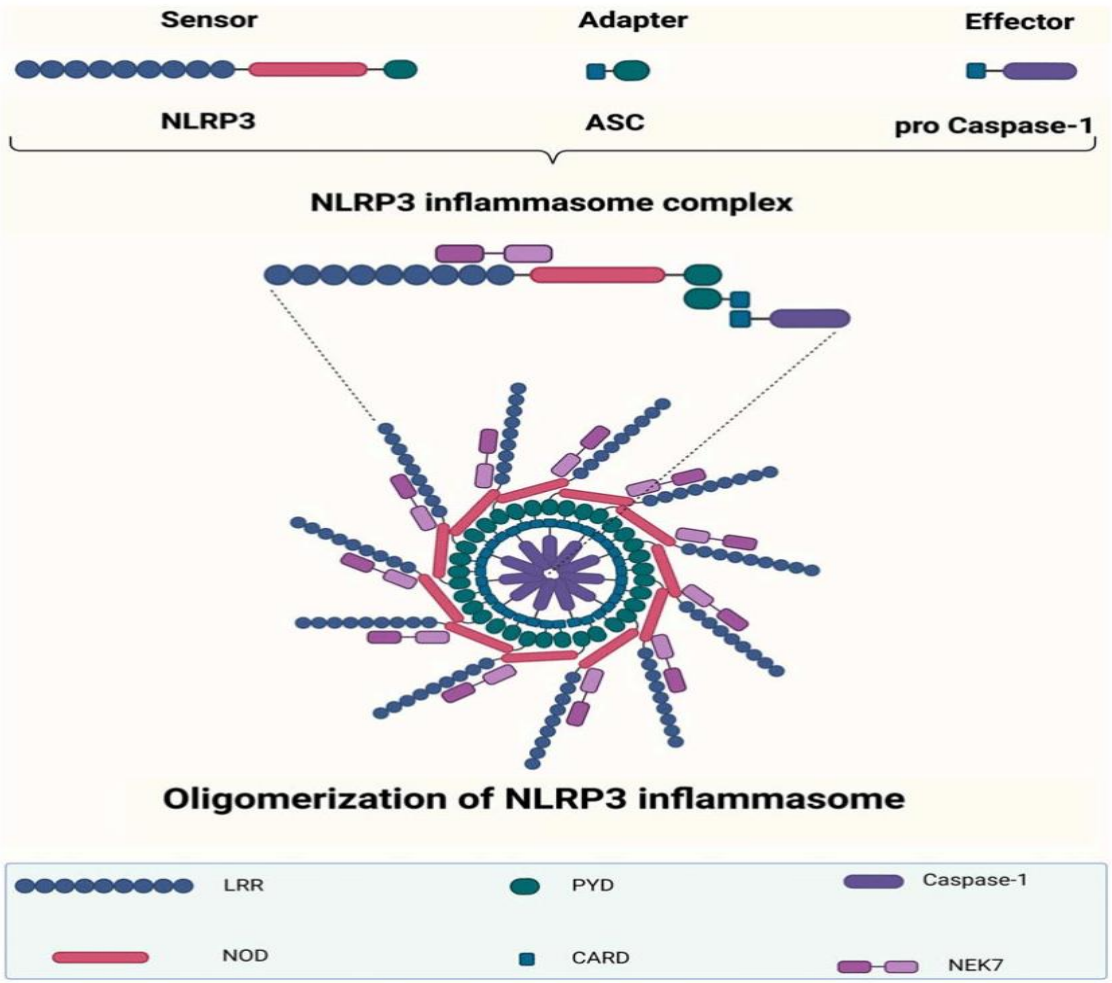

NLRP3 inflammasome structure and oligomerization. The NLRP3 inflammasome complex includes a sensor NLRP3 protein, an adapter ASC protein, and a pro-caspase-1 protein. When the NLRP3 inflammasome is activated, the adaptor protein ASC binds to the sensor NLRP3 protein via PYD-PYD polymerization. NLRP3 oligomerization occurs after this ASC recruits the effector protein pro-caspase-1 via its CARD. The first half of NEK7 binds to the NLRP3 LRR domain, whereas the second half interacts with the NOD. NLRP3, NODlike receptor family-pyrin domain-containing 3; LRR, leucine-rich repeat; NOD, nucleotide-binding oligomerization domain; PYD, pyrin domain; ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase recruitment domain; NEK7, NIMA-related kinase 7. The graph was created using Biorender.com.

From: Inflammasomes as therapeutic targets in human diseases

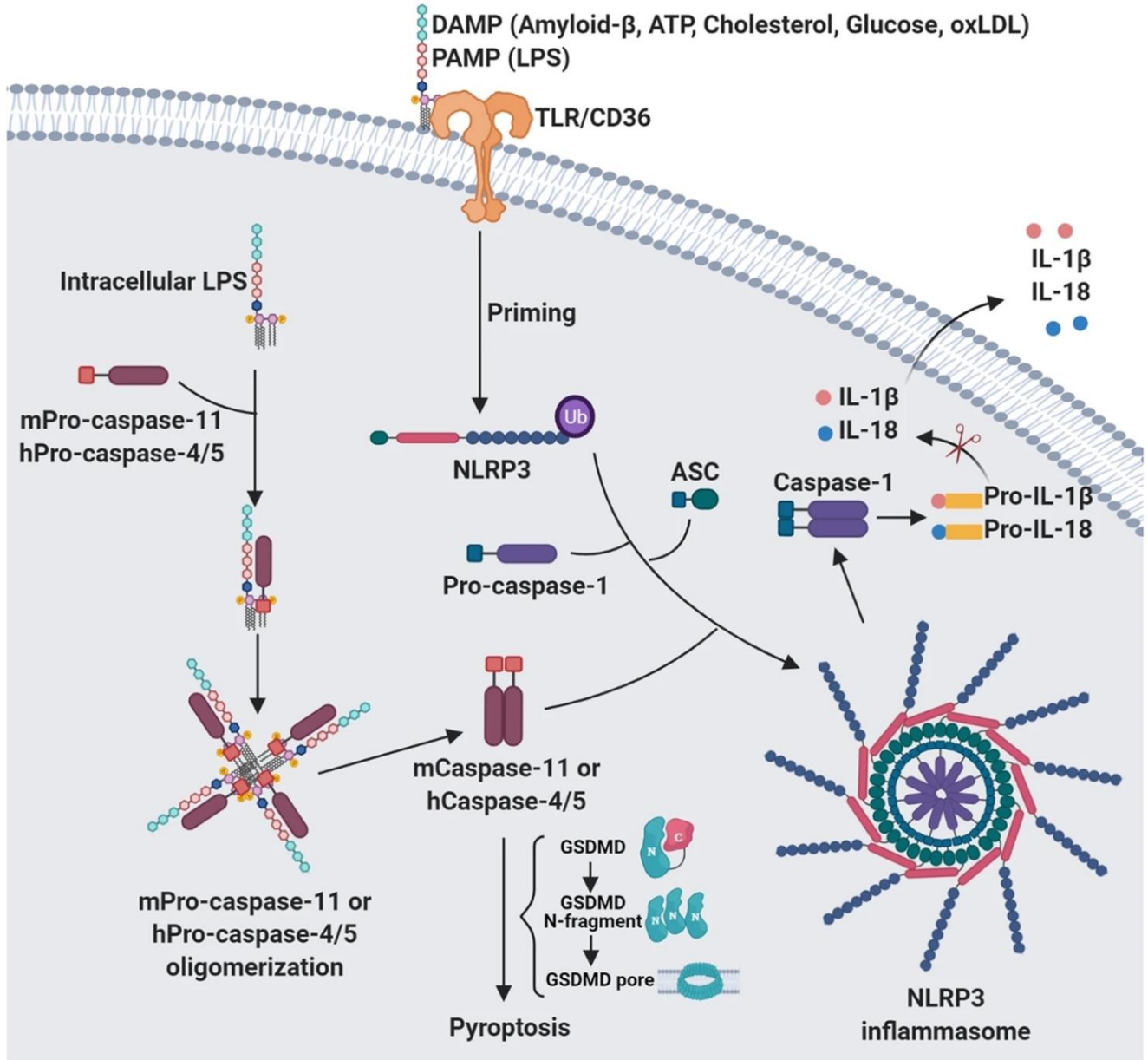

Table 1: Aberrant metabolites activate the NLRP3 inflammasome in kidney-associated cells.

Stimulus	Kidney-related cells	Mechanism	Ref.
Glucose ↑	Monocytes	K^+ outflow, Ca^{2+} inward flow/ROS/NLRP3 inflammasome	[14, 15]
	Glomerular mesangial cells	ROS/p38/FOXO1/TXNIP/NLRP3	[17–19]
		P50(NF-κB)/NLRP3 inflammasome	[20]
	Macrophages	PKM2/NLRP3 inflammasome	[21]
Saturated fatty acids ↑	Macrophages	Lysosomal destabilization/NLRP3 inflammasome	[26]
		AMPK/ROS/NLRP3 inflammasome	[27, 55]
Cholesterol ↑	Macrophages	Lysosomal destabilization/histone B/NLRP3 inflammasome/IL-1β	[34]
		ER to Golgi translocation/SREBP2/NLRP3 inflammasome	[35, 36]
Uric acid ↑	Macrophages	ROS/NLRP3/IL-1β/NF-κB	[40]
	Macrophages	ROS/TXNIP/NLRP3/caspase	[43]
Homocysteine ↑	Vascular endothelial cells	HMGB1/cathepsin V/NLRP3/caspase-1	[47]

ROS: reactive oxygen species; TXNIP: thioredoxin-interacting protein; FOXO1: forkhead box protein O1; NF-κB: nuclear factor kappa B; PKM2: pyruvate kinase M2; AMPK: adenosine 5′-monophosphate-activated protein kinase; ER: endoplasmic reticulum; SREBP2: sterol regulatory element-binding protein 2; HMGB1: high mobility group box-1 protein; HIF1α: hypoxia inducible factor-1α; PDK1: 3-phosphoinositide-dependent kinase-1.

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Diabetology &
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RESEARCH Open Access

TLR9 regulates NLRP3 inflammasome activation via the NF-kB signaling pathway in diabetic nephropathy

Jinfeng Shen, Zaiyou Dai, Yunsheng Li, Huiping Zhu and Lijin Zhao*

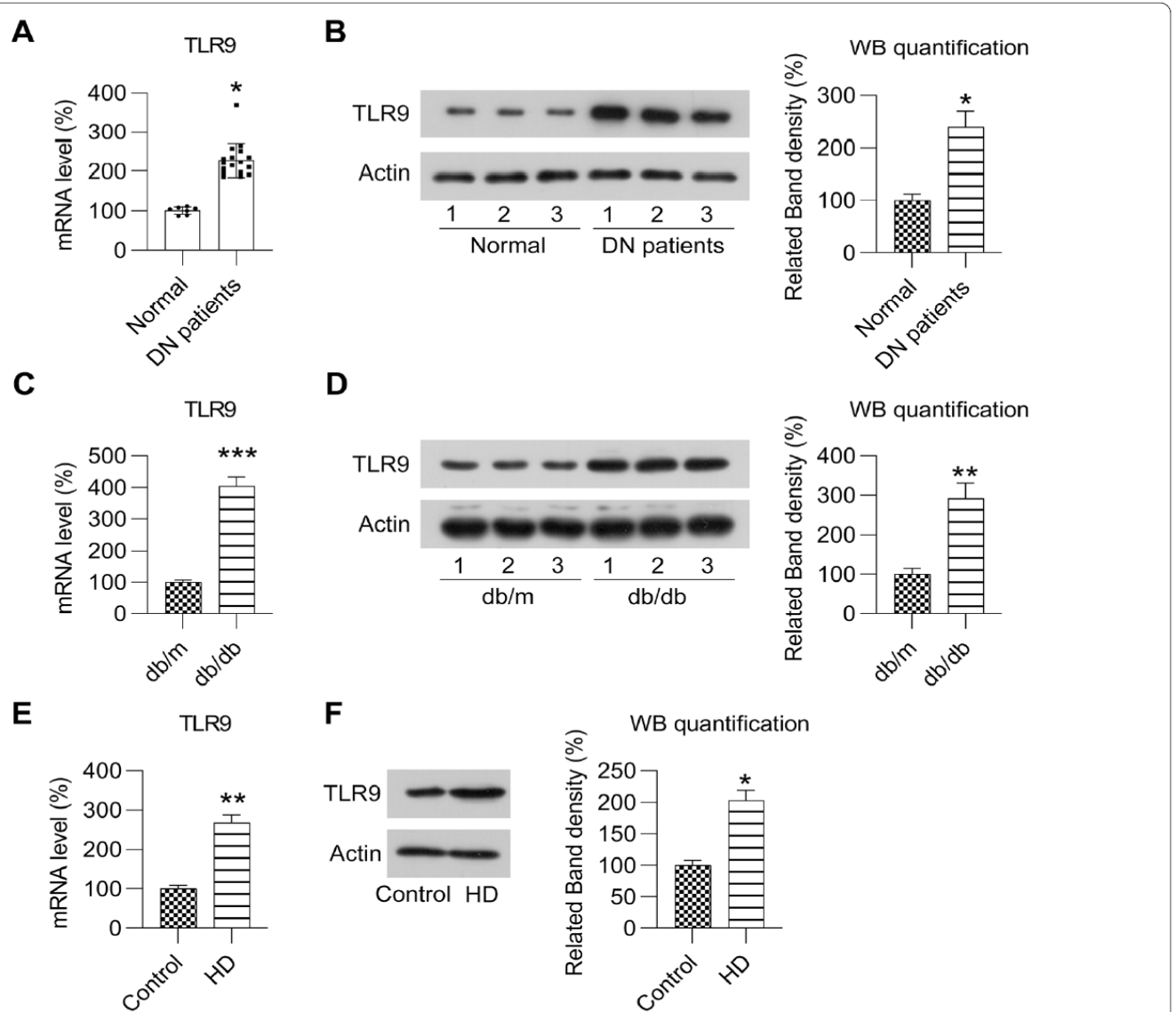

Fig. 1 Expression of TLR9 in DN. **A** Real-time PCR revealed TLR9 expression in PBMCs from patients (healthy = 7 and DN patients = 17). **B** WB revealed protein levels of TLR9 in PBMCs from patients (healthy = 3 and DN patients = 3). **C** Real-time PCR revealed TLR9 mRNA expression in the kidneys of mice (db/db) with DN (n = 6) and mice (db/m) (n = 6) at 12 weeks. **D** WB revealed TLR9 protein levels in the kidneys of mice (db/db) with DN and control mice (db/m) at 12 weeks. **E** MCs were treated with HG for more than 12 h. RT-PCR was used to determine the level of TLR9 mRNA expression in the MCs treated with HG or normal LG. **F** WB was used to determine the protein levels of TLR9 in the MCs treated with HG or normal LG. The data are representative of the results of three independent experiments, and the data are presented as means ± S.E.M (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$)

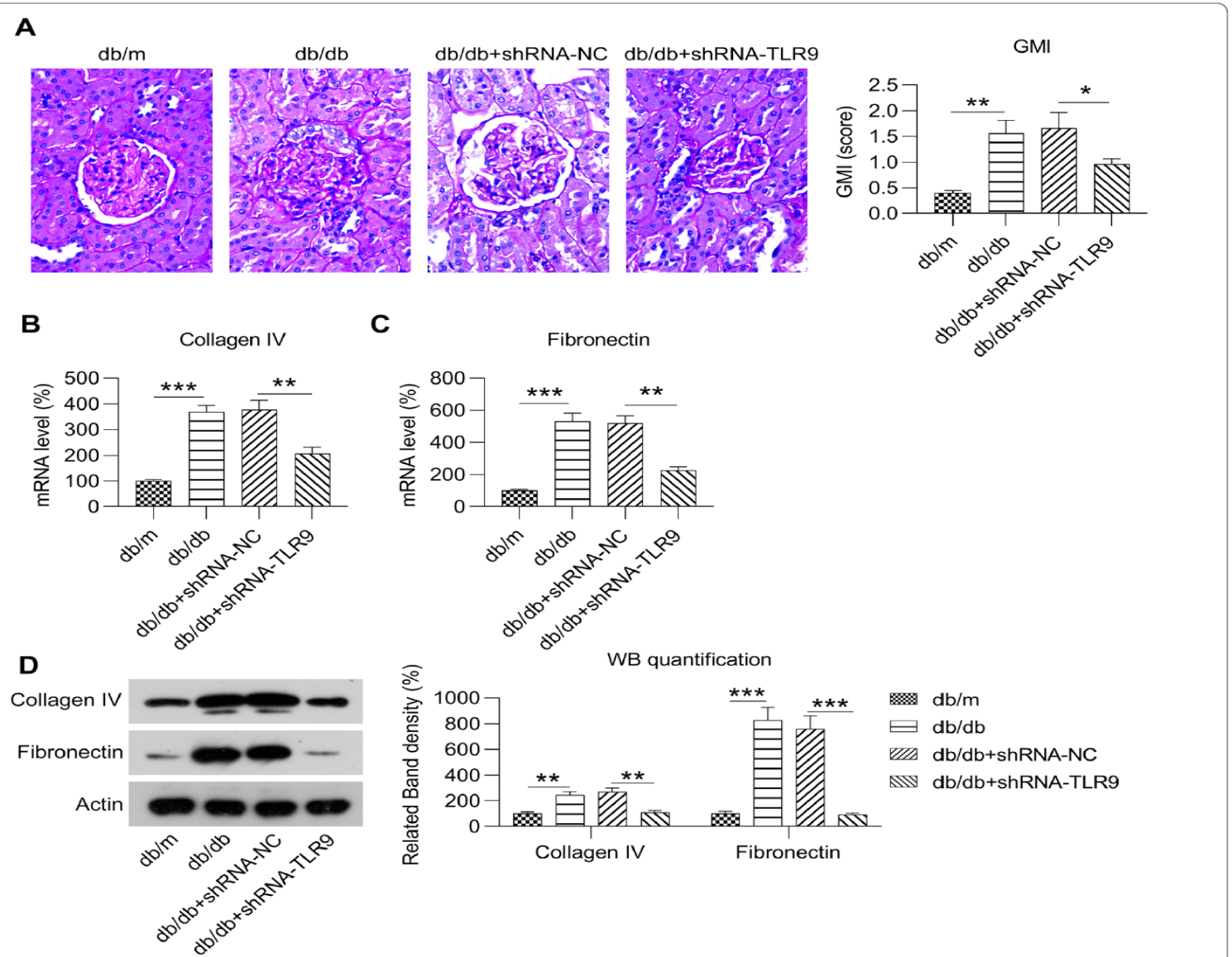

Fig. 3 Effect of TLR9 knockdown on glomerular expansion and the expression levels of fibronectin and collagen IV in renal tissue from experimental mice (db/db). Experimental mice (db/db) were administered lentiviral-shRNA-NC or lentiviral-shRNA-TLR9 via tail vein injection. **A** Representative image of PAS-stained renal cortical slices from mice (db/m), experimental mice (db/db), NC-treated experimental-mice (db/db), and TLR9 knockdown experimental mice (db/db). GMI scores calculated based on the analysis of six glomeruli per mice. **B** RT-PCR was conducted to determine the mRNA expression levels of fibronectin and collagen IV in renal tissues. **C** WB was conducted to determine the protein levels of fibronectin and collagen IV in renal tissues. The data are representative of the results of three independent experiments, and the data are presented as means ± S.E.M (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$)