IV REUNIÓN ANUAL DEL ÁREA DE ENFERMEDADES RENALES, METABÓLICAS Y CARDIOVASCULARES DEL IIS-FJD

“Mecanismos de la inmunidad innata en el daño renal”

Adrián M. Ramos
Grupo: Nefrología e Hipertensión, Patología Vascular y Diabetes
Laboratorio de Nefrología e Hipertensión

INNATE IMMUNITY IN KIDNEY DISEASE

INNATE IMMUNITY

PAMPs
DAMPs(alarminas)

- Lipopolisacáridos bacterianos
- Cyclic dinucleotides (CDNs)
- dsDNA/RNA
- Prots cromatina, ME, mit

- Receptors (TLRs, Inflammasome, nucleic acid sensors)

1.IMMUNE CELLS: DCs, Mφs, Neutophils, NK, Mast cells

2. Epithelial cells → Tubular cells

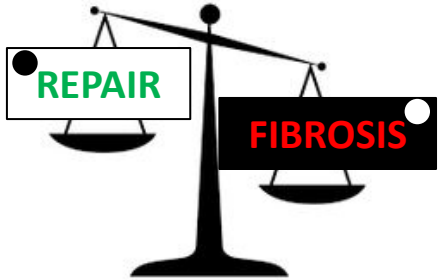
3. Endothelial cells → Renal endothelium

4.CYTOKINE sinthesis

5. Complement activation

Adaptive inflammation

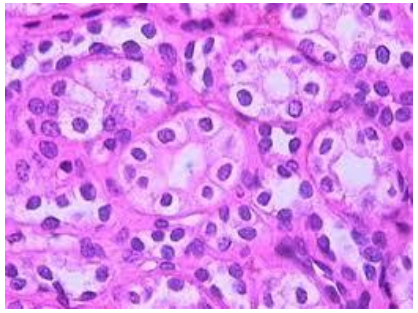
Repair/Resolution



Maladaptive inflammation

Chronic kidney injury/Fibrosis

Tubular cell



Immunomodulation

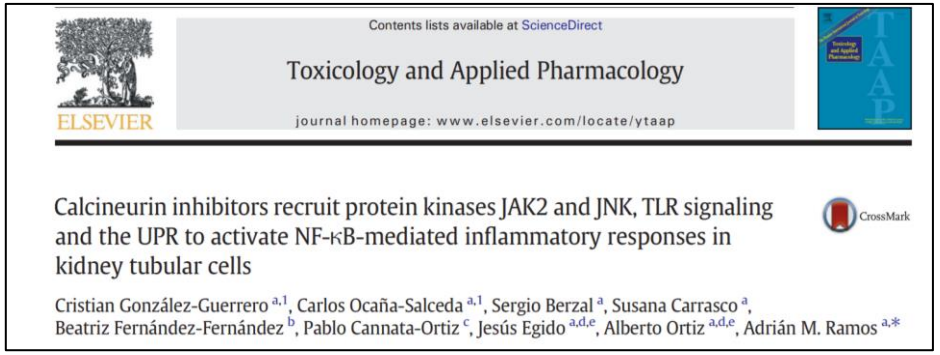
Cytokines

DAMPs (stressed/damaged, aged/senescent cells)

Ag present. (HMCII=Th1 resp)

INNATE IMMUNITY IN KIDNEY DISEASE

Previous works



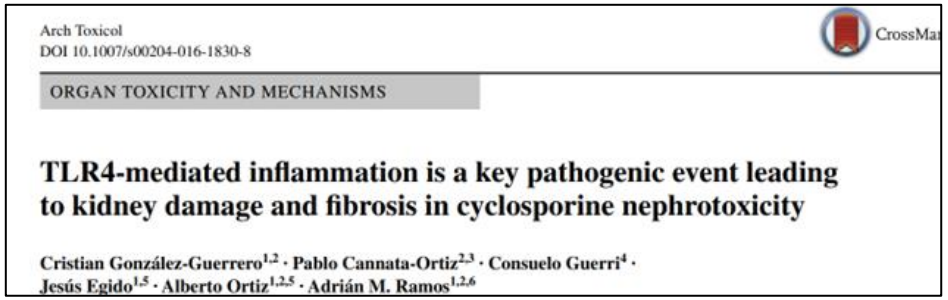
Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

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

Calcineurin inhibitors recruit protein kinases JAK2 and JNK, TLR signaling and the UPR to activate NF-κB-mediated inflammatory responses in kidney tubular cells

Cristian González-Guerrero [a,1], Carlos Ocaña-Salceda [a,1], Sergio Berzal [a], Susana Carrasco [a], Beatriz Fernández-Fernández [b], Pablo Cannata-Ortiz [c], Jesús Egido [a,d,e], Alberto Ortiz [a,d,e], Adrián M. Ramos [a,*]

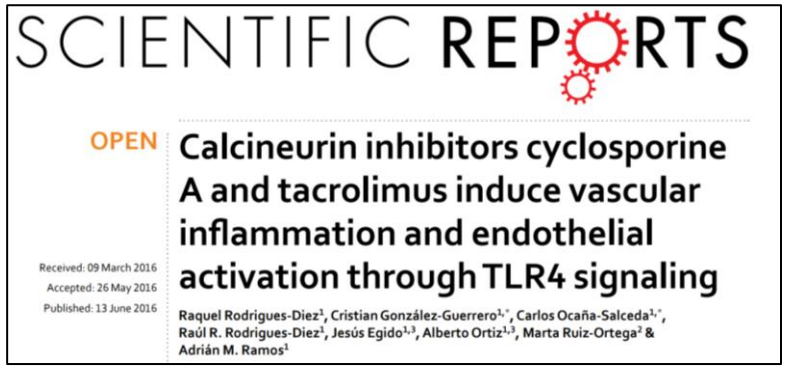


Arch Toxicol
DOI 10.1007/s00204-016-1830-8

ORGAN TOXICITY AND MECHANISMS

TLR4-mediated inflammation is a key pathogenic event leading to kidney damage and fibrosis in cyclosporine nephrotoxicity

Cristian González-Guerrero[1,2] · Pablo Cannata-Ortiz[2,3] · Consuelo Guerri[4] · Jesús Egido[1,5] · Alberto Ortiz[1,2,5] · Adrián M. Ramos[1,2,6]



SCIENTIFIC REPORTS

OPEN

Calcineurin inhibitors cyclosporine A and tacrolimus induce vascular inflammation and endothelial activation through TLR4 signaling

Received: 09 March 2016
Accepted: 26 May 2016
Published: 13 June 2016

Raquel Rodrigues-Diez[1], Cristian González-Guerrero[1,*], Carlos Ocaña-Salceda[1,*], Raúl R. Rodrigues-Diez[1], Jesús Egido[1,3], Alberto Ortiz[1,3], Marta Ruiz-Ortega[2] & Adrián M. Ramos[1]

INNATE IMMUNITY and KIDNEY INJURY

Pre published and ongoing research

Signaling by the **TBK1/IKKε** node and the **T1-INF pathway** in kidney injury (PI18/01133)

Participation of the **Sting** pathway in acute and chronic kidney injury (PI18/01133)

Role of **faty acid binding proteins (FABPs)** proteins in mitocondrial dysfunction and associated innate immune activation (PI21/01453)

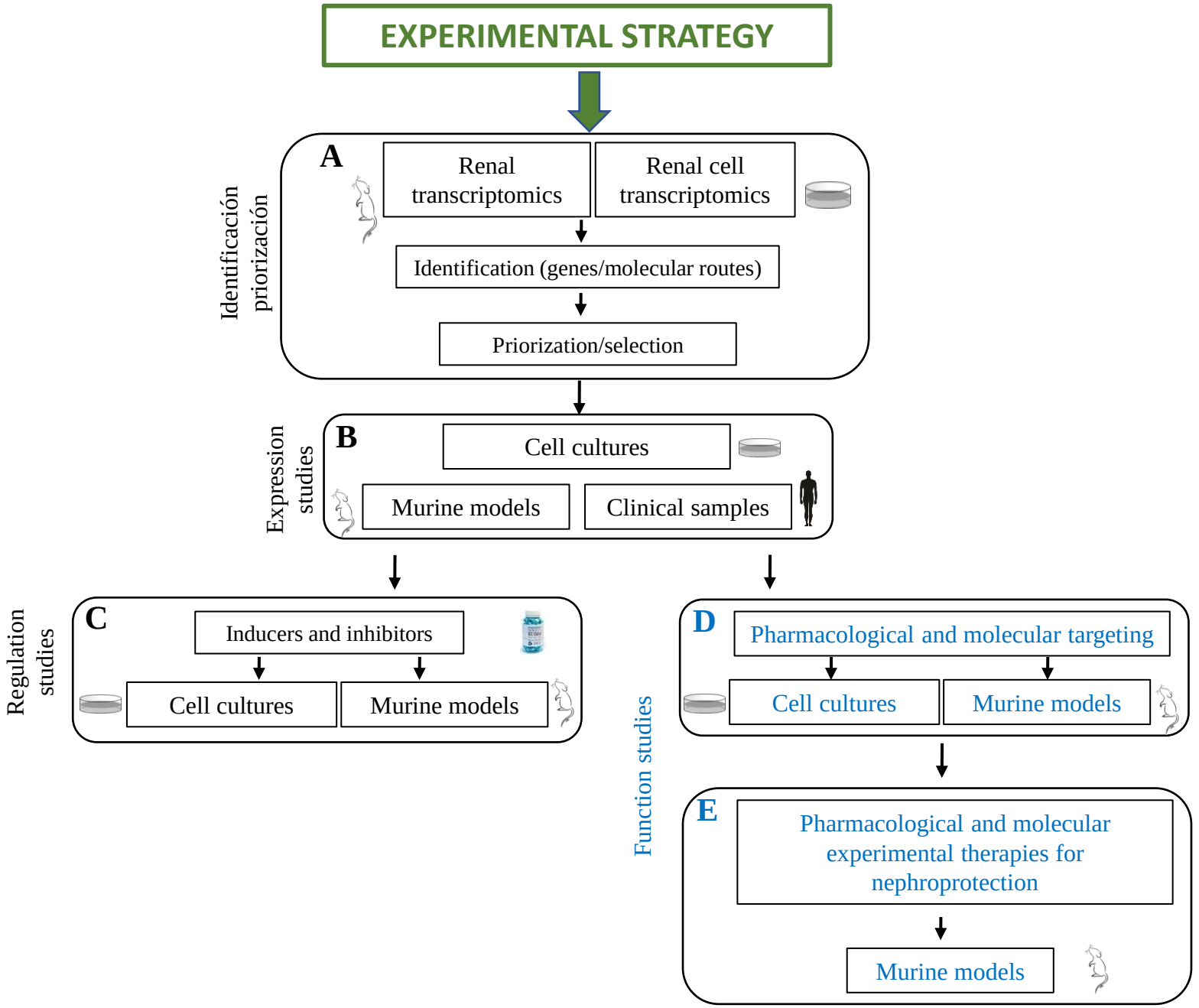
THE JOURNAL OF Pathology

A Journal of The Pathological Society Understanding Disease

Original Paper

CCL20 blockade increases the severity of nephrotoxic folic acid-induced acute kidney injury

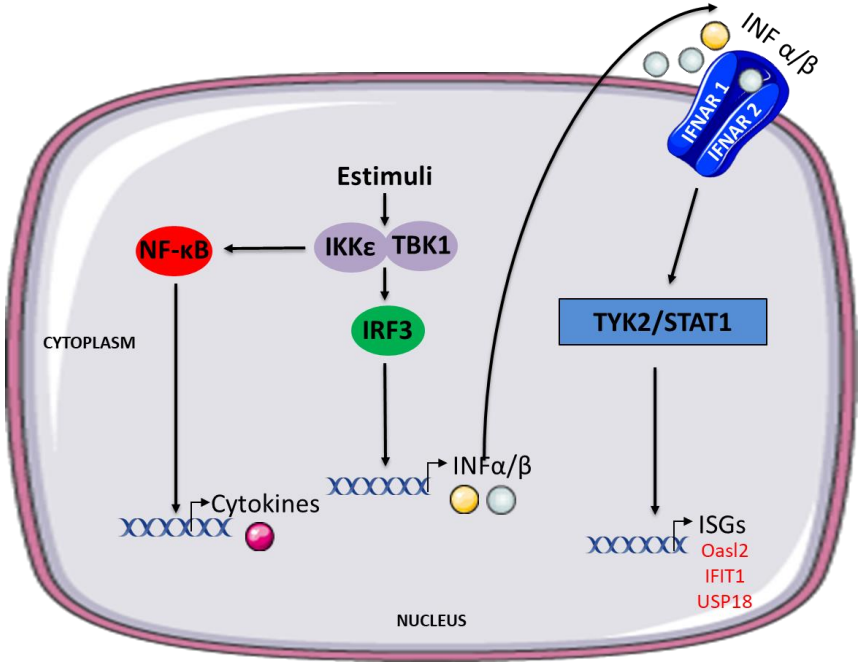
Cristian González-Guerrero, José Luis Morgado-Pascual, Pablo Cannata-Ortiz, María Angeles Ramos-Barron, Carlos Gómez-Alamillo, Manuel Arias, Sergio Mezzano, Jesús Egido, Marta Ruiz-Ortega, Alberto Ortiz, Adrián M Ramos ... See fewer authors

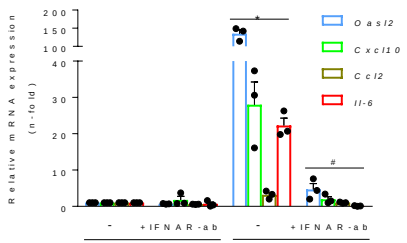

EXPERIMENTAL STRATEGY
A
Renal transcriptomics
Renal cell transcriptomics
Identification (genes/molecular routes)
Priorization/selection
Identificación priorización
B
Cell cultures
Murine models
Clinical samples
Expression studies
C
Inducers and inhibitors
Cell cultures
Murine models
Regulation studies
D
Pharmacological and molecular targeting
Cell cultures
Murine models
E
Pharmacological and molecular experimental therapies for nephroprotection
Murine models
Function studies

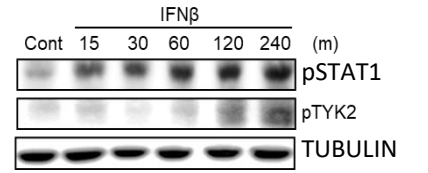
INFα/β and proinflammatory inducers (TWEAK, LPS) activate the T1-IFN pathway by engaging non-canonical IKKs TBK1 and IKKε in tubular cells and kidney

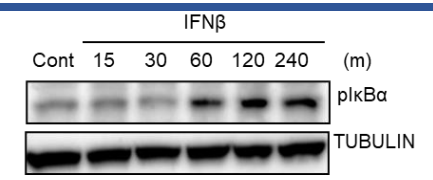
TYPE 1 INTERFERONS (IFNα-IFNβ)

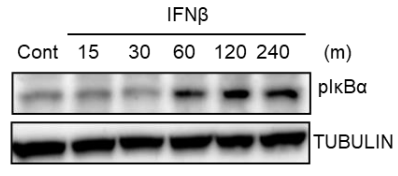
- Promote the antiviral response through the transcription of interferon-stimulated genes (ISG)
- Involved in microbial infection but also in human inflammatory pathology (autoimmune, autoinflammatory, chronic)
- Induced for nucleic acids, cyclic dinucleotides, and endotoxins from microorganisms and damaged/stressed host cells

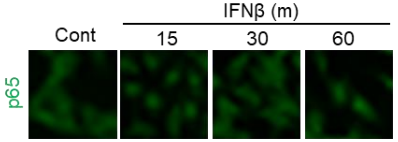


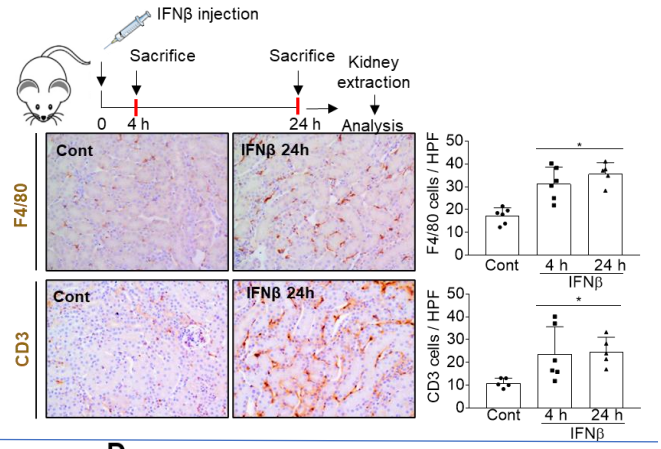


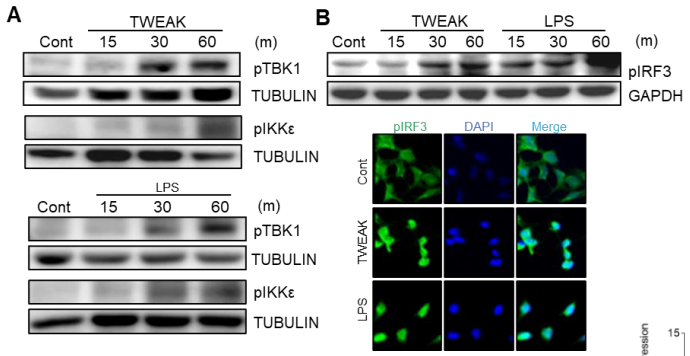


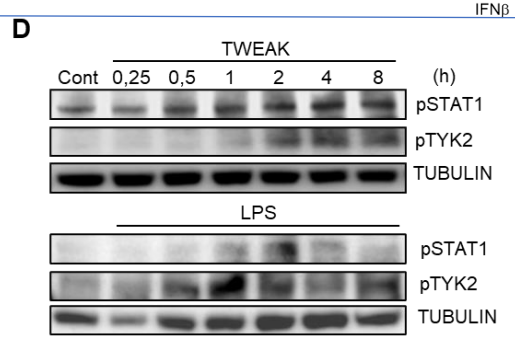


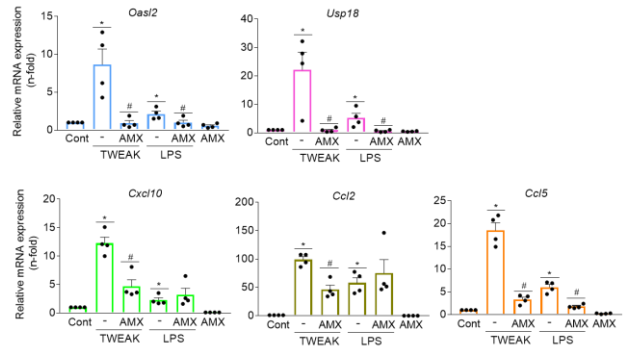




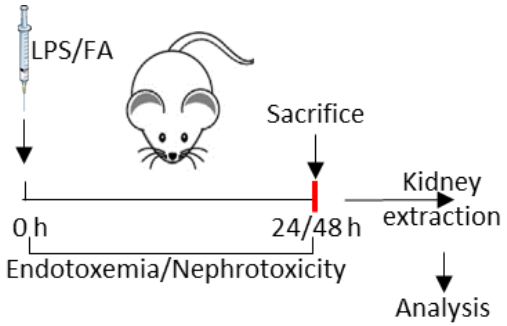


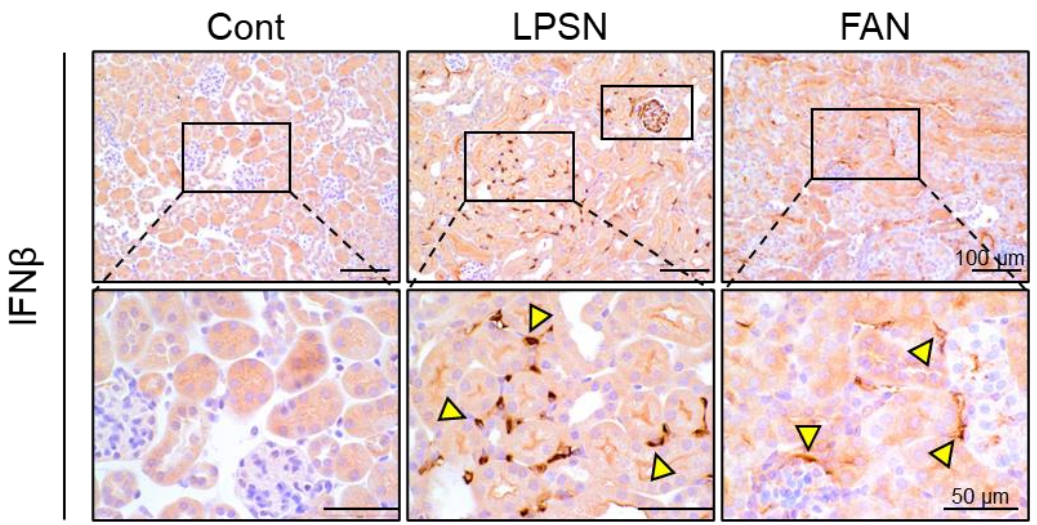


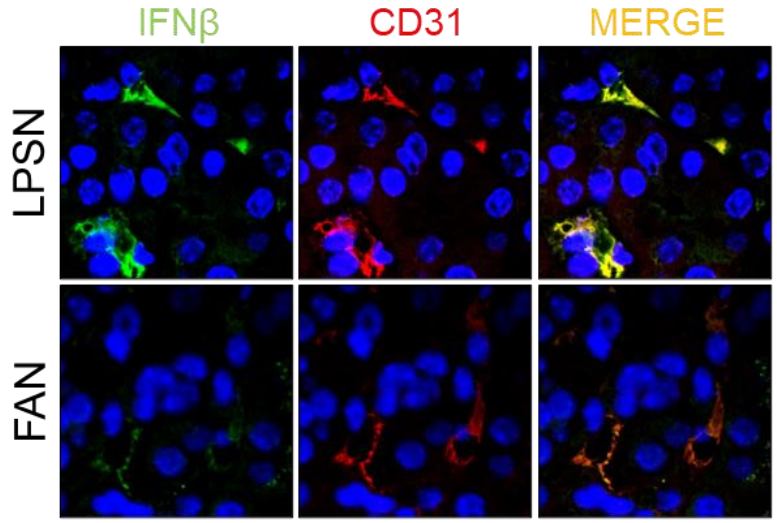


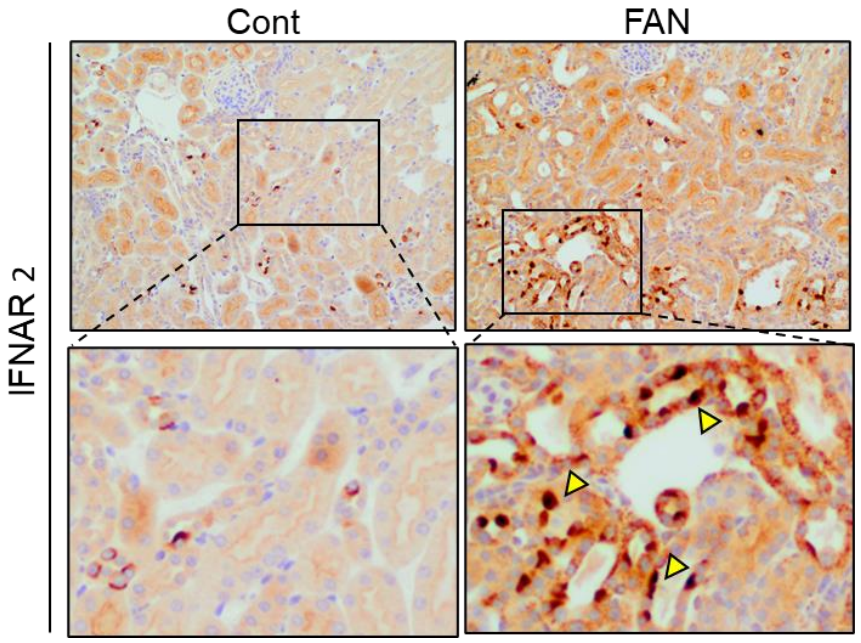


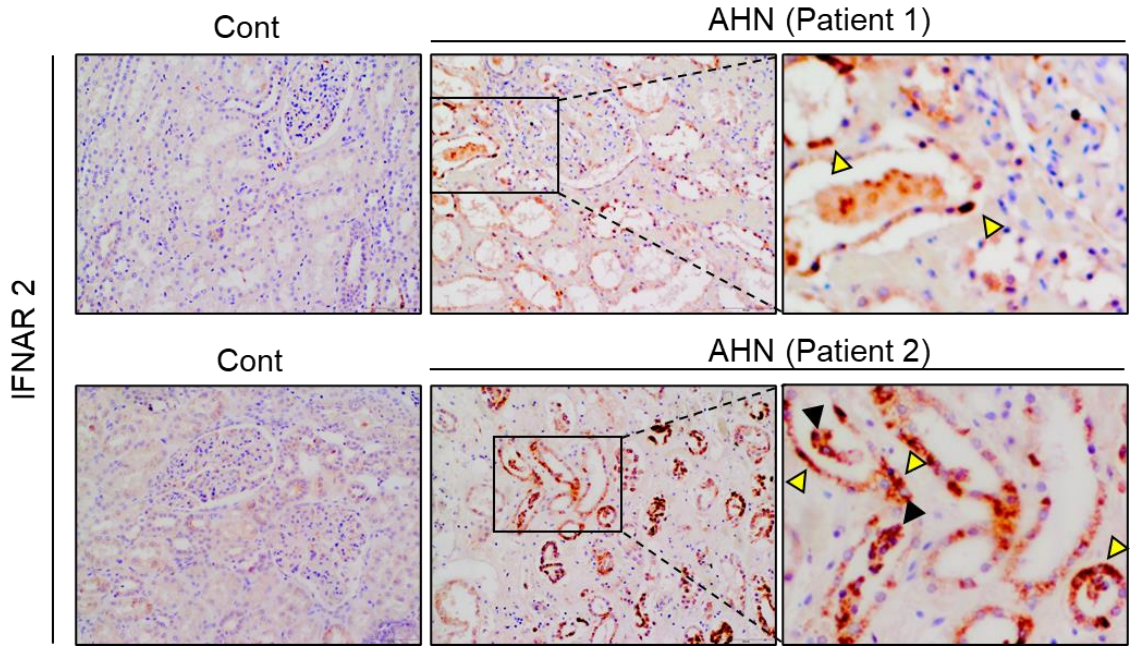
IFNα/β, TWEAK and LPS activate the T1-IFN pathway by engaging the TBK1 and IKKε in tubular cells and kidney tissue



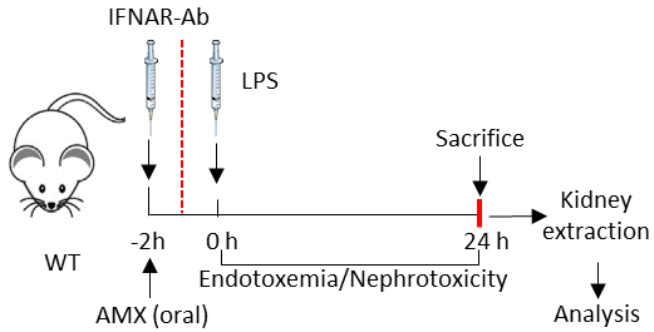


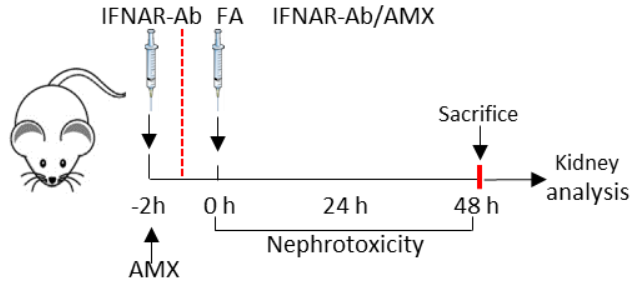


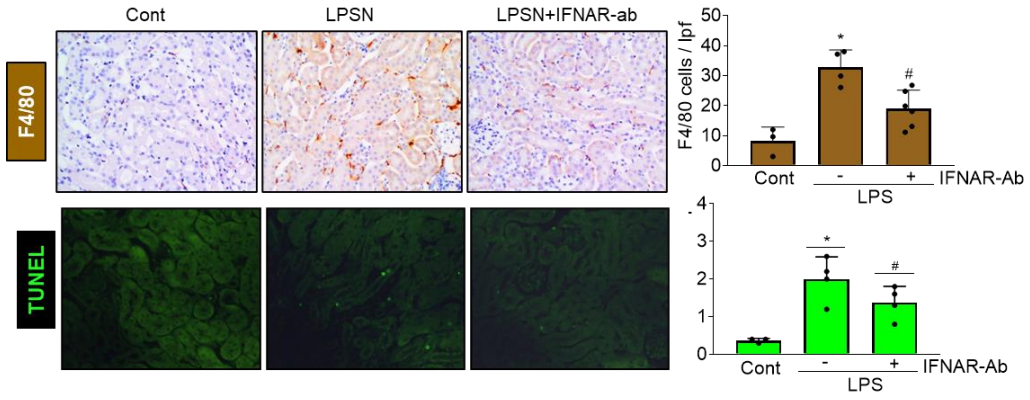


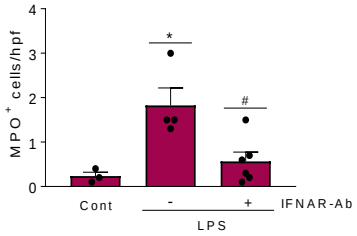


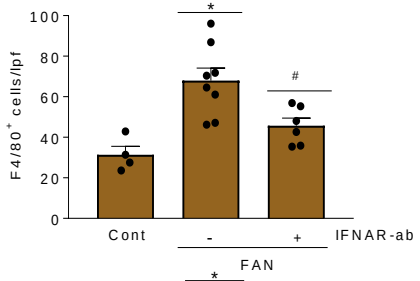
IFNα/β, TWEAK and LPS activate the T1-IFN pathway by engaging the TBK1 and IKKε in tubular cells and kidney tissue

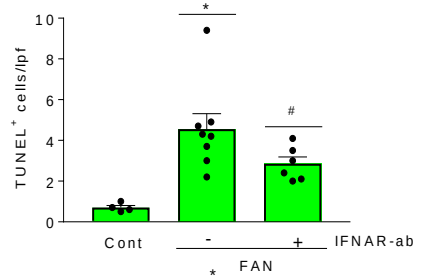


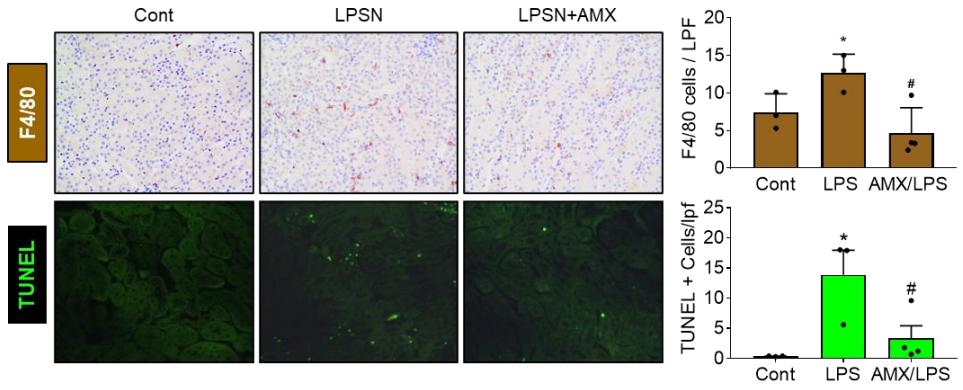


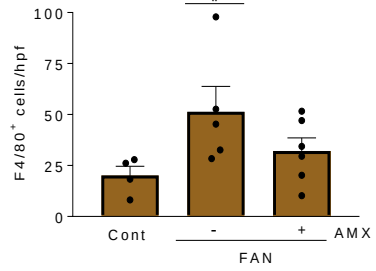


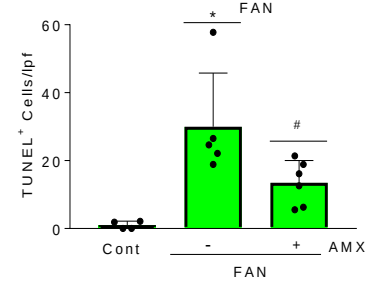


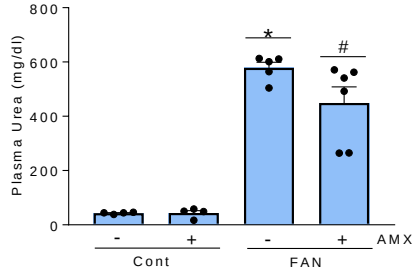








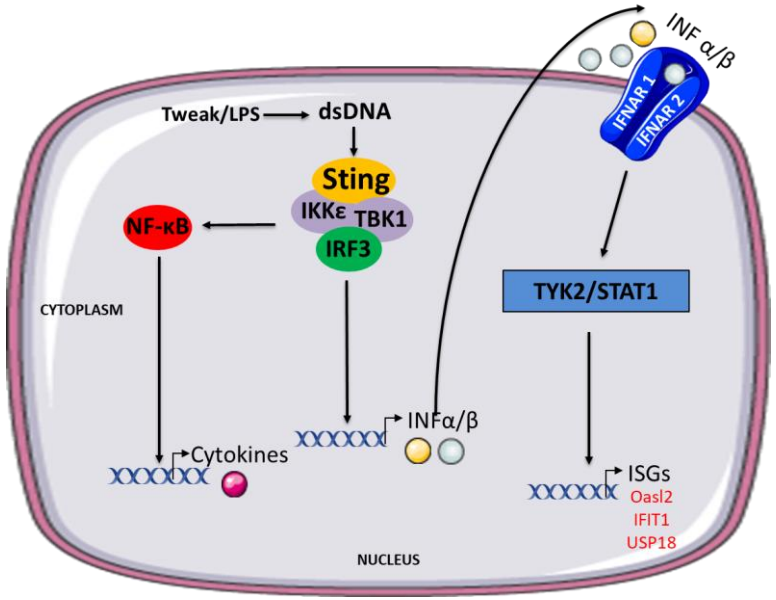


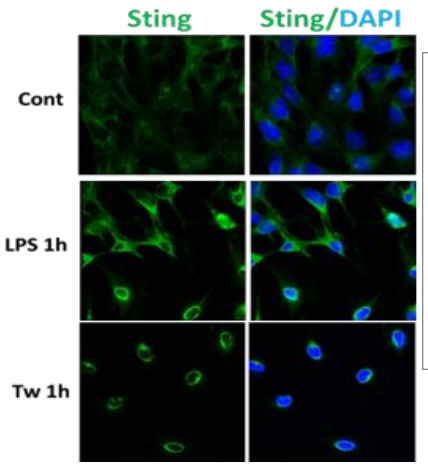


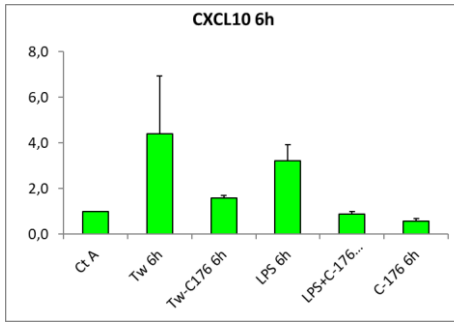
Sting mediates TWEAK and LPS-induced NF-κB- and T1-INF pathway-dependent inflammation and antiviral responses in tubular cells and kidney tissue

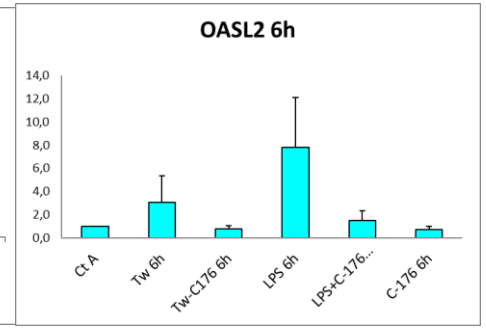
Stimulator of Interferon Genes (STING)

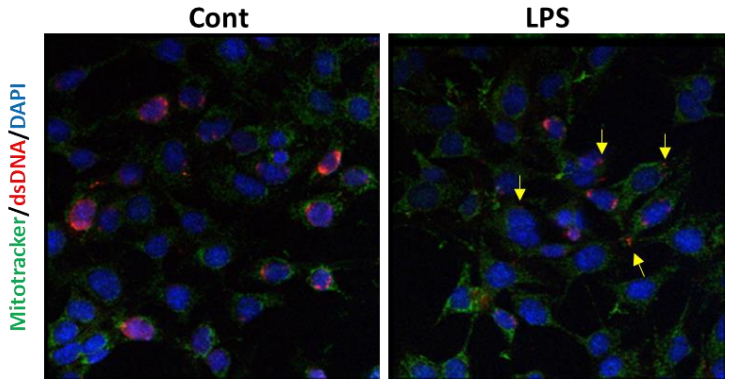
- Recognizes dsDNA from microrganisms and self dsDNA (mtDNA in cytoplasm, gDNA) from the interaction of this nucleic acids with cGAS/cGAMP
- Resides in the RE and translocates to Golgi under interaction with dsDNA, where it forms a platform to TBK1 and IRF3 recruitment and activation
- Involved in microbial infection but also in human inflammatory pathology by promoting T1-INF- and NF-κB-dependent iSG and inflammatory cytokine programs

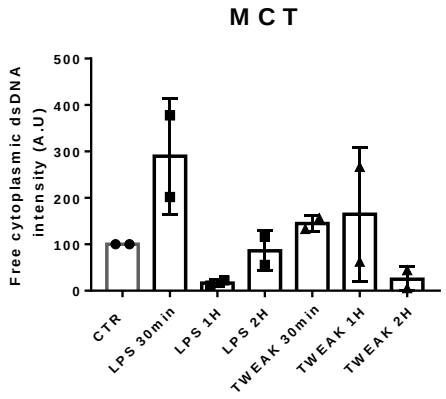


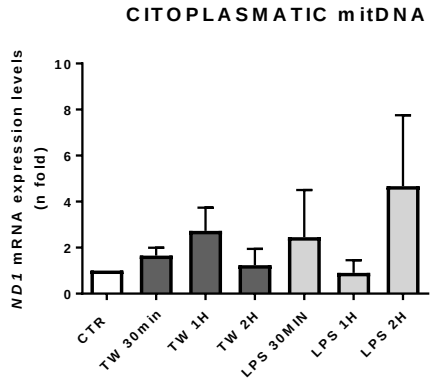


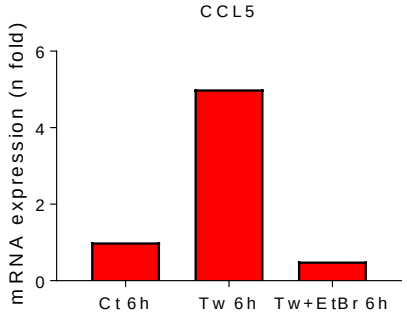


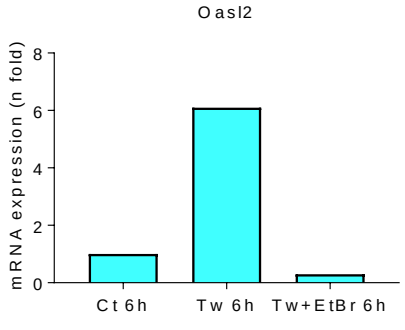




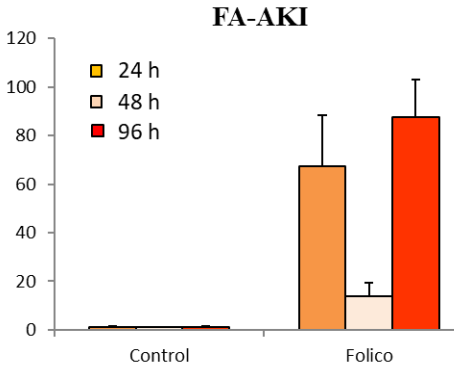


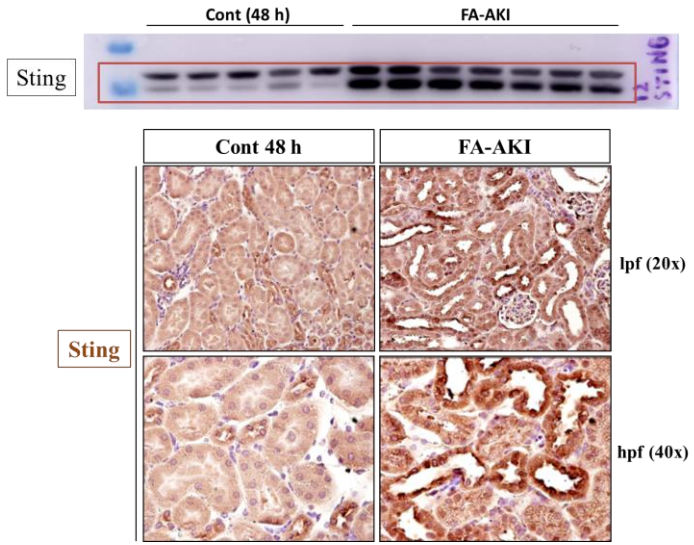


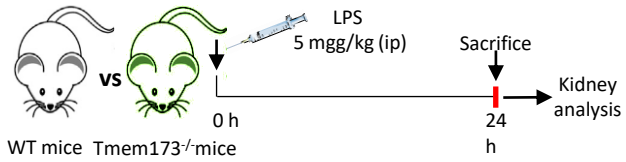


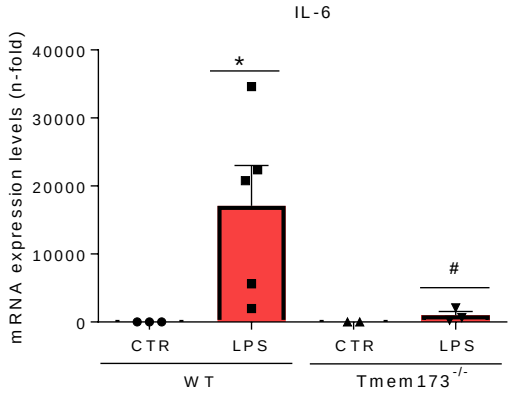


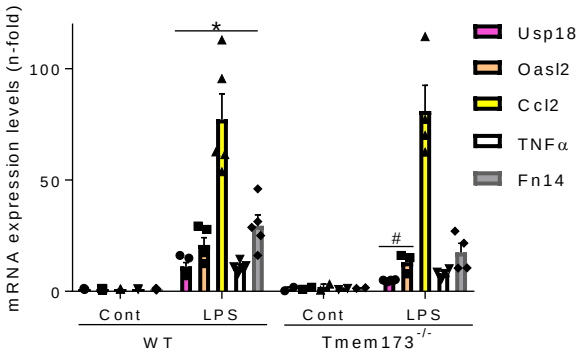
Kidney inflammation is reduced in Sting-KO mice

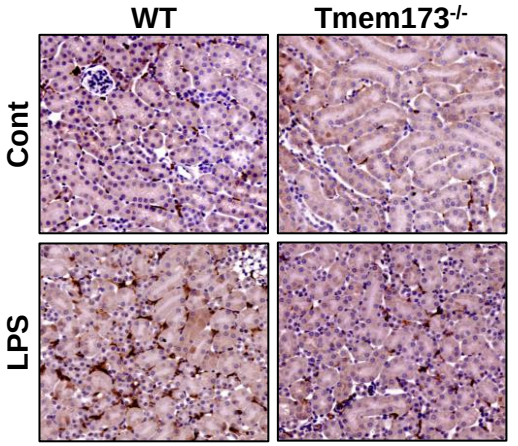


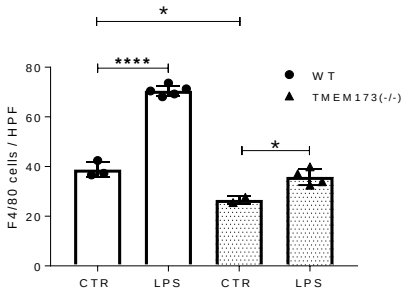




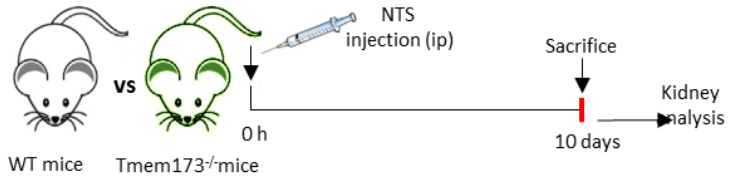


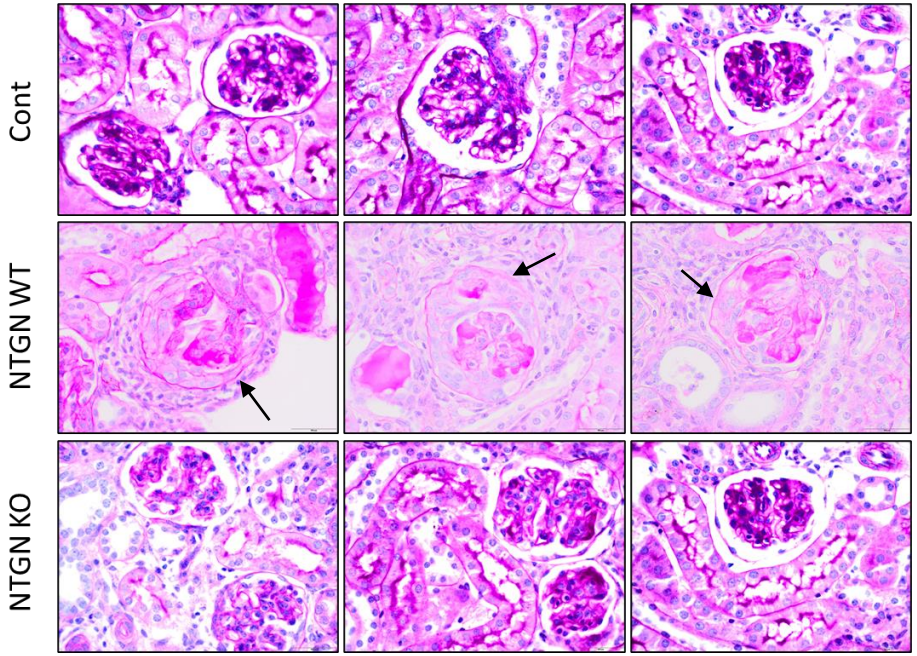


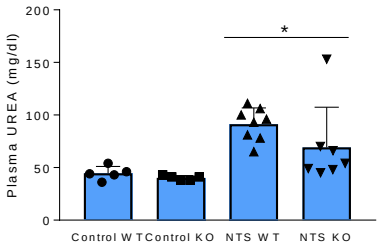


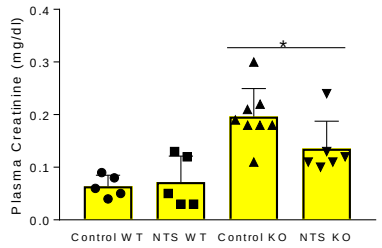


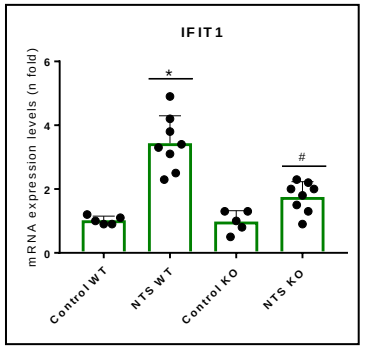
Sting is involved in promoting nephrotoxic autoimmune glomerulonephritis

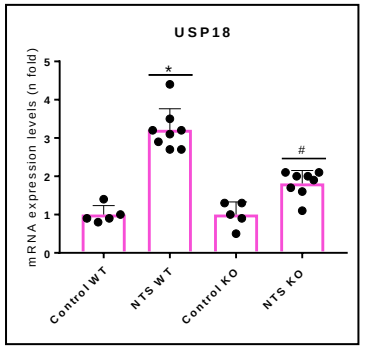


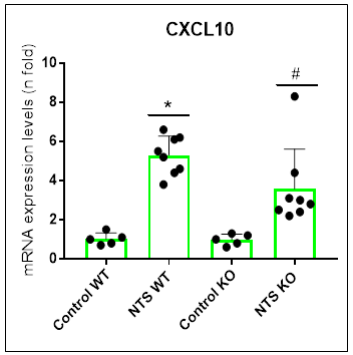


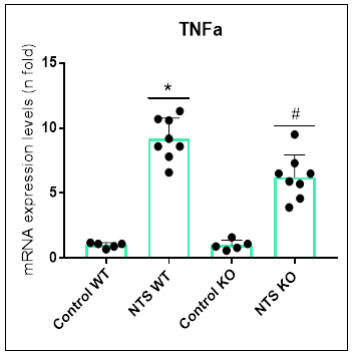


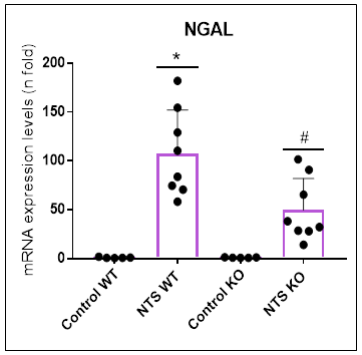


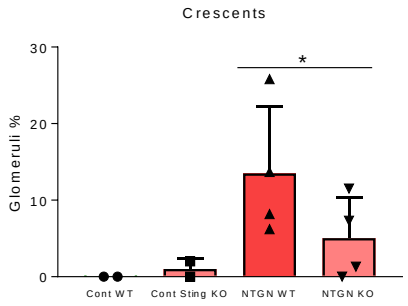


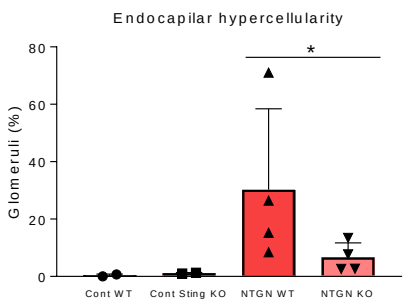


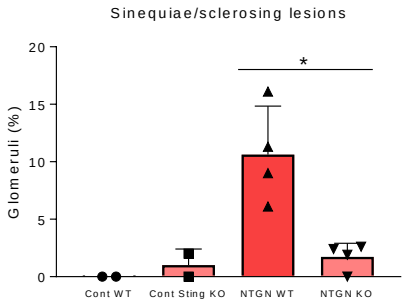


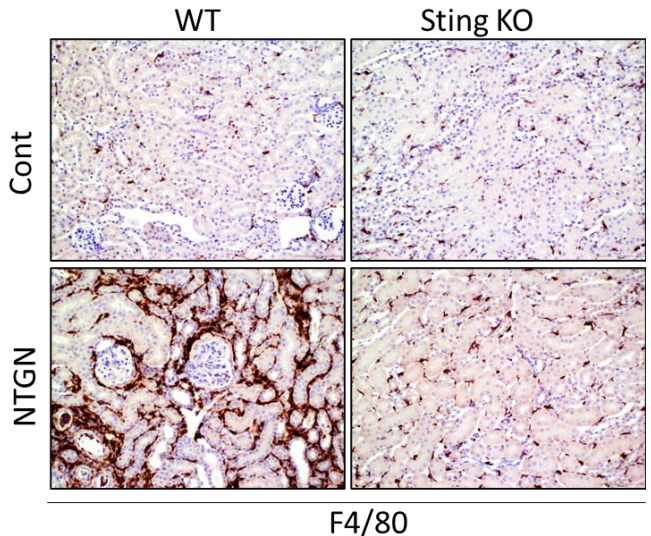


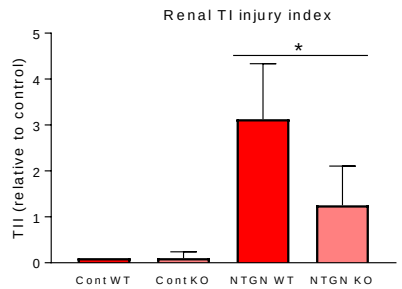




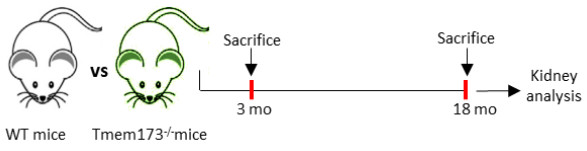


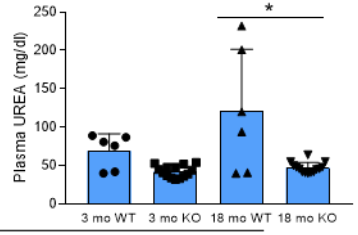


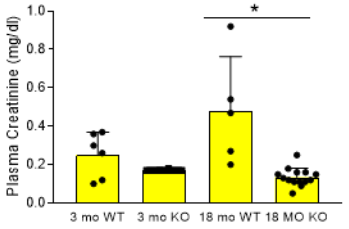


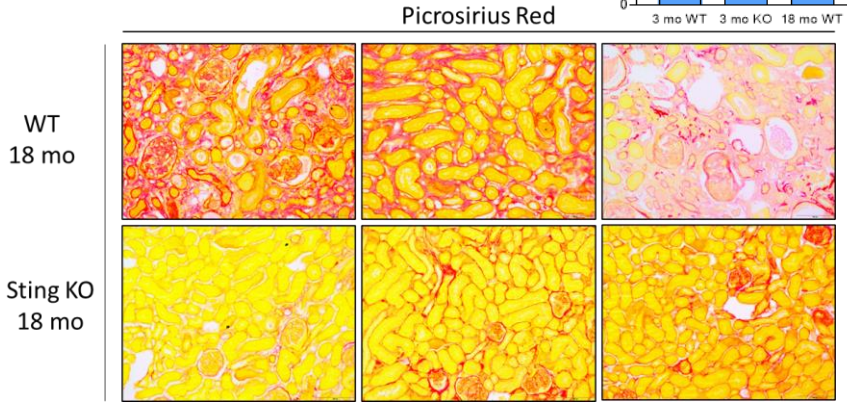


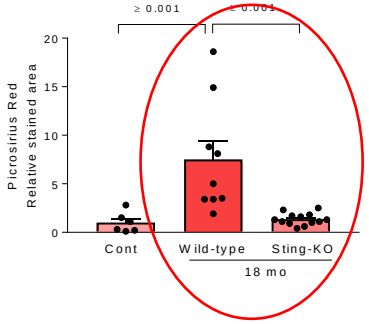
Sting is involved in promoting spontaneous kidney aging

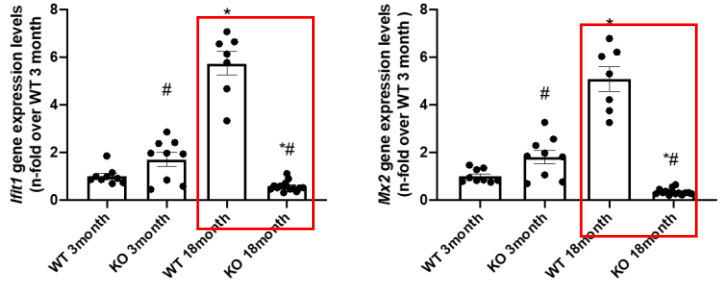


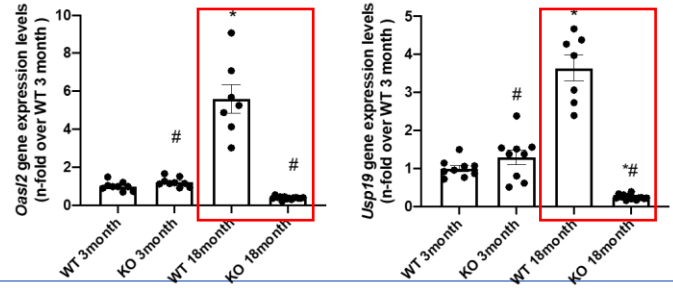


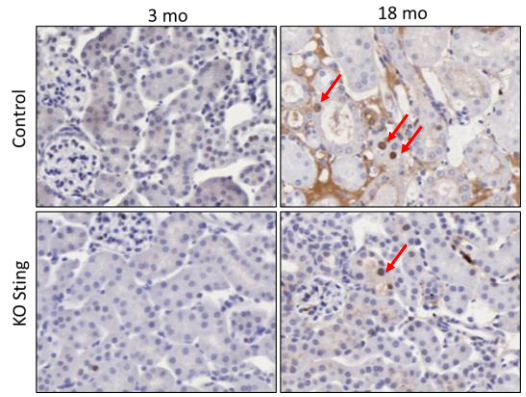


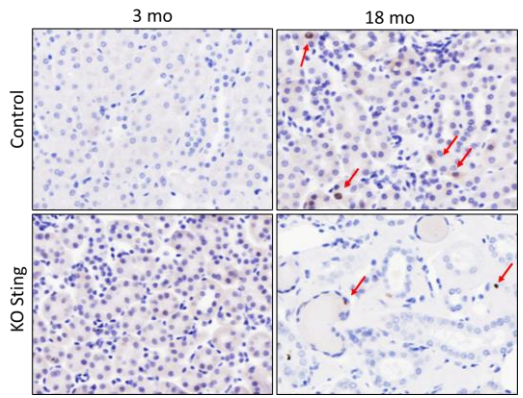


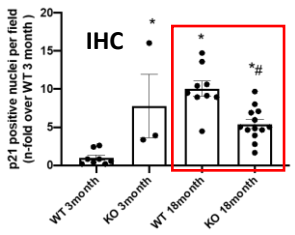


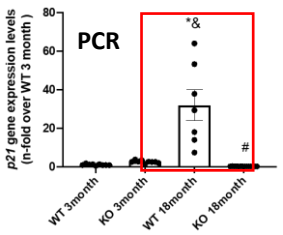


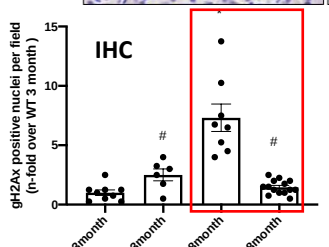


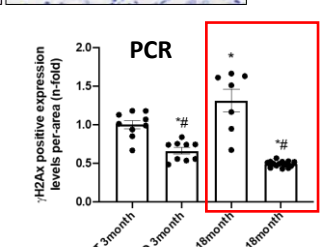


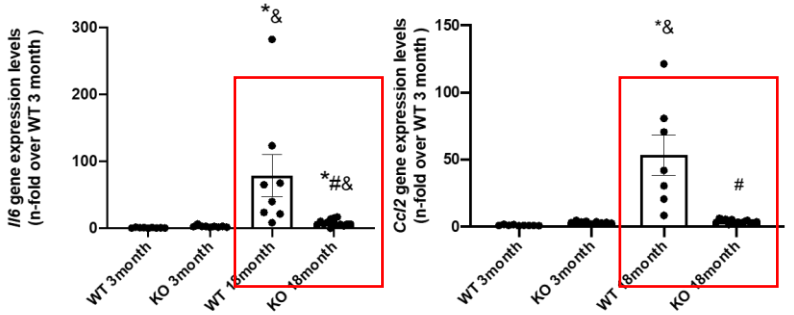


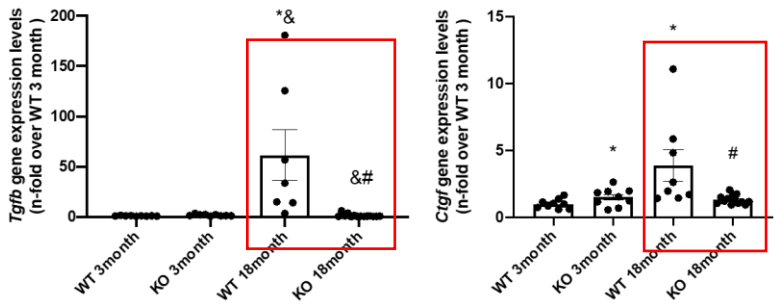




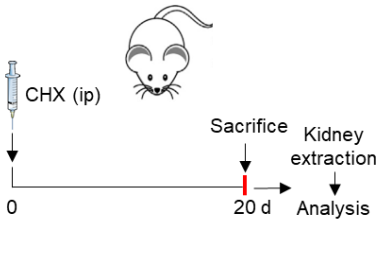


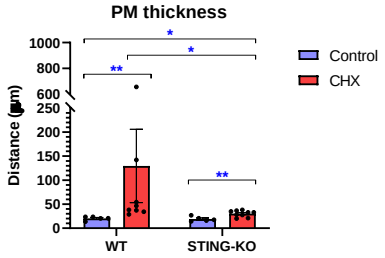


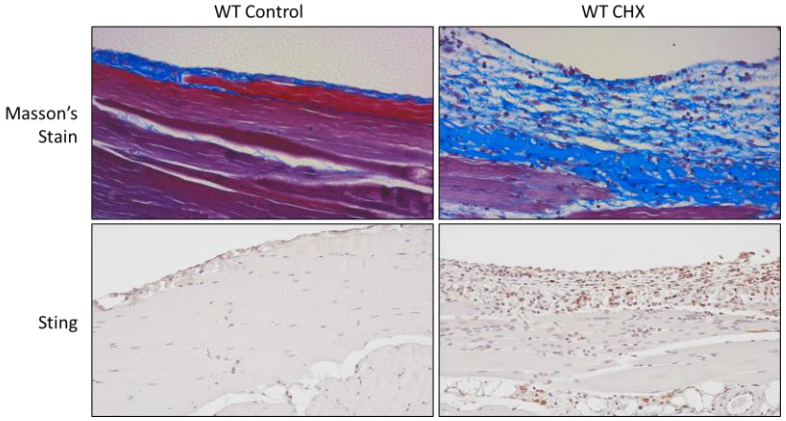


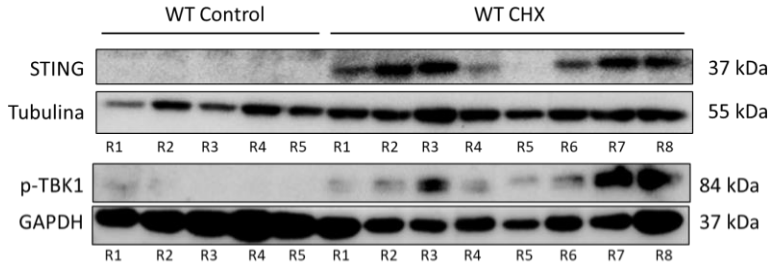


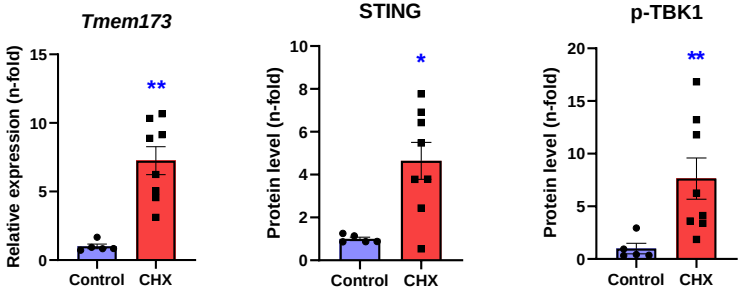
Sting promotes inflammation, oxidative stress and fibrosis in a model of peritoneal injury

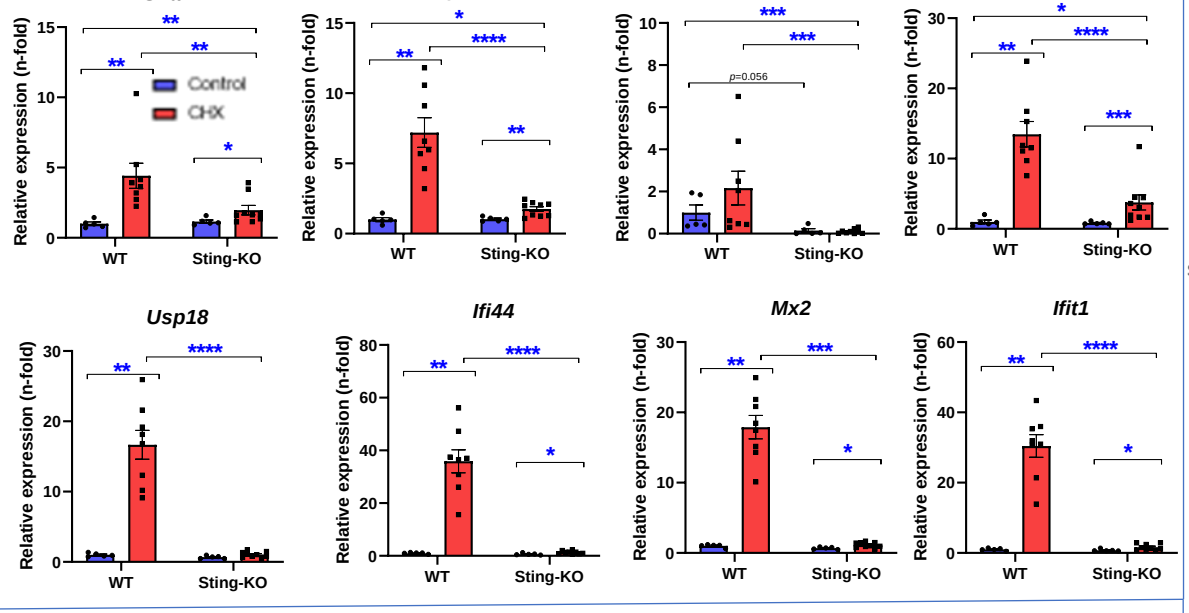


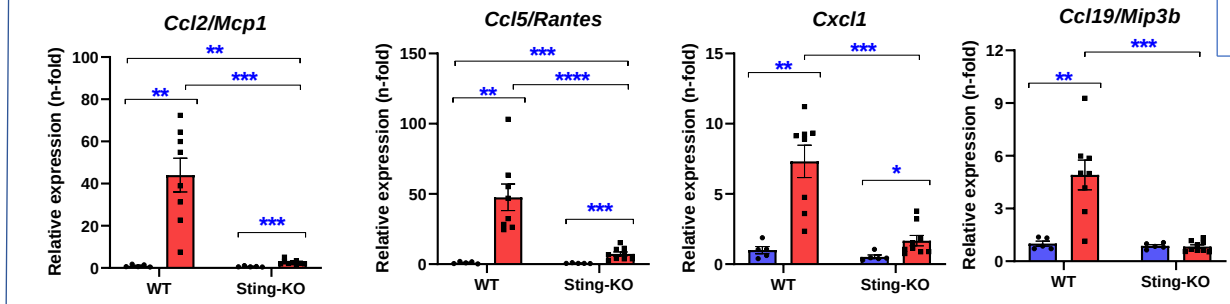


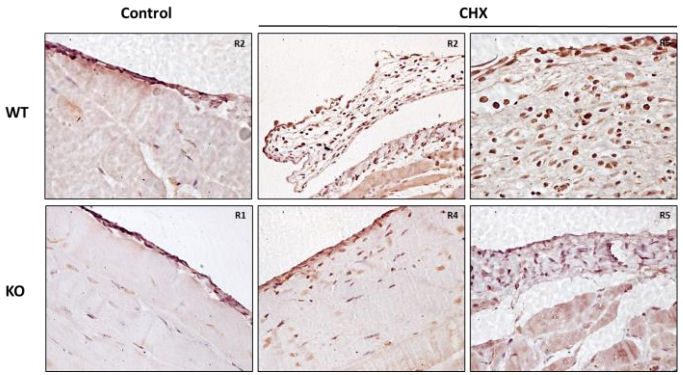


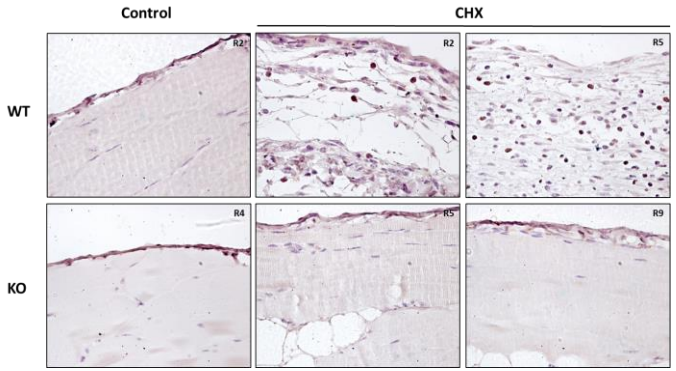


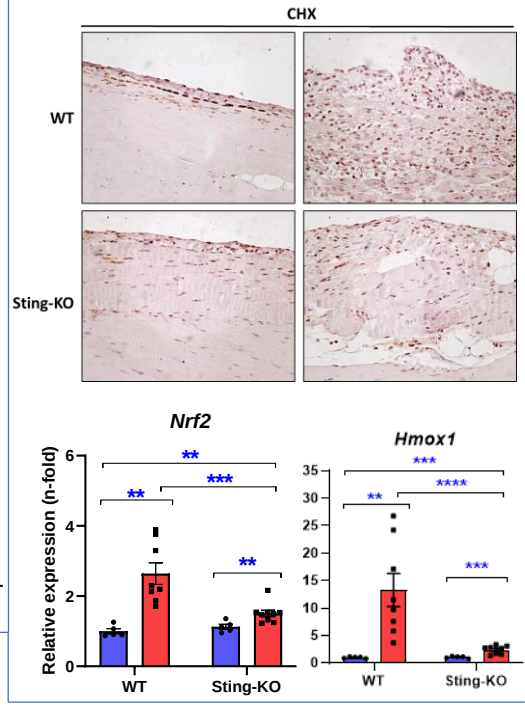


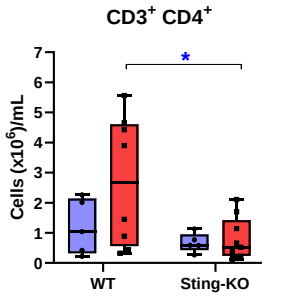


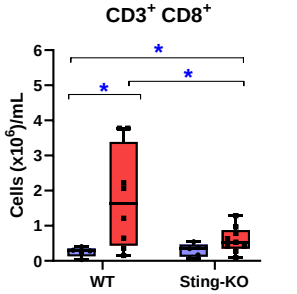












Dr AM Ramos (PhD) (IP)

Estudiantes predoctorales
Biol/Ma Gina Córdoba David
Lcdo/Ma Jorge García Jiménez

Tecn. Susana Carrasco Navarro

Colaboradores
Dra Marta Ruiz-Ortega y cols (UAM-IIS)
Pablo Cannata Ortiz (FJD)

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(University of Hamburg)
(CCR6 KO mice, NTS)

Dr Prof. Gokan Hotamisligil
(Sabrİ Ülker Center, Harvard University)
(FABPs KO mice)

NATIONAL CONGRESSES

SEBM

1) Upstream and downstream activation of the type 1 interferon pathway promotes kidney inflammation

Córdoba David G, García Giménez J, Ortiz A, Ramos AM.

2) Sting triggers NF-κB-dependent proinflammatory effects in renal tubular cells and kidney injured tissue

García Giménez J, Córdoba David G, Ortiz A, Ramos AM.

SEN

1) **STING participa en el proceso de senescencia celular renal asociado al envejecimiento renal**

Lucia Tejedor-Santamaria1,2, Laura Marquez-Expósito1,2, Gina Córdoba-David2,3, Vanessa Marchant1,2, Jorge García-Giménez2,3, Antonio Tejera1,2,Pamela Basantes1, Alberto Ortiz2,3, Marta Ruiz-Ortega1,2 y Adrián Mario Ramos2,3

INTERNATIONAL CONGRESSES

ERA-EDTA

1) Noncanonical IKKs, TBK1 and IKKε, and the type 1 interferon pathway activate inflammation and cell death in tubular cells and support renal injury

Gina Córdoba-David, Jorge García Giménez, Alberto Ortiz, Adrián M. Ramos.

2) The absence of STING prevents peritoneal damage in a murine model of peritoneal fibrosis

Vanessa Marchant[1,2], Jorge García-Giménez[2,3], Guadalupe González-Mateo[3], Valeria Kopytina[3], Irene Rubio-Soto[1,2], Manuel López-Cabrera[3], Adrián M. Ramos[2,4], Marta Ruiz-Ortega[1,2].