

Melatonin Prevents Gut Leakiness and Liver Fibrosis Through the Gut–Liver Axis

Wiramon Rungratanawanich, Ph.D.
NIAAA, NIH

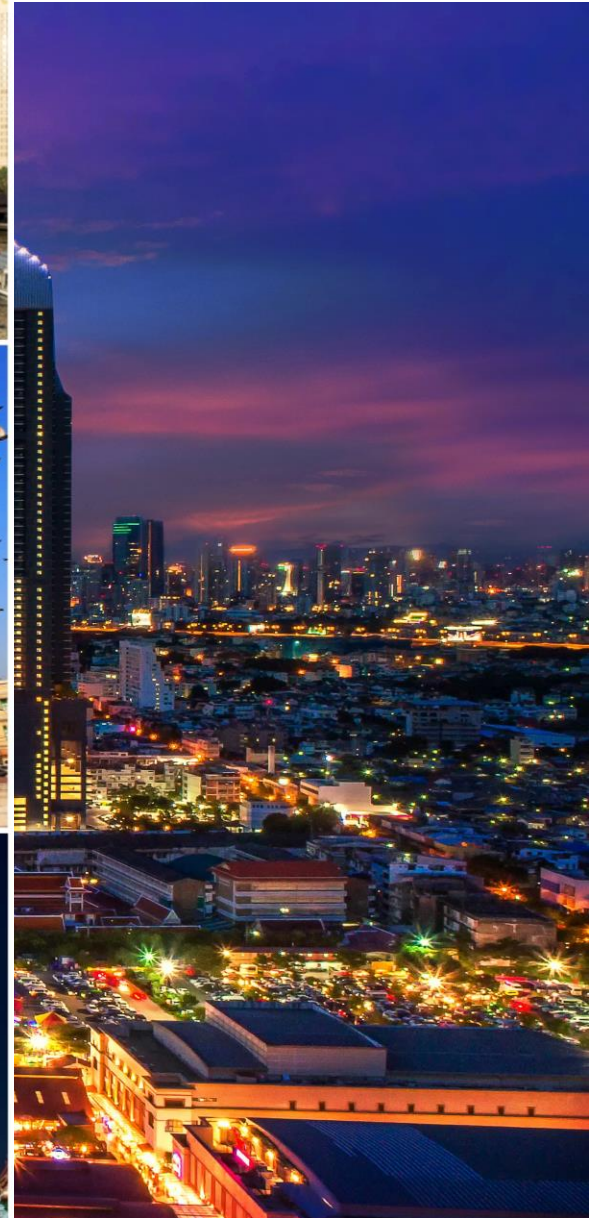
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(We-ramon)

- Research Fellow
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institutes of Health (NIH)





Pharmaceutical Sciences, Chulalongkorn University, Bangkok



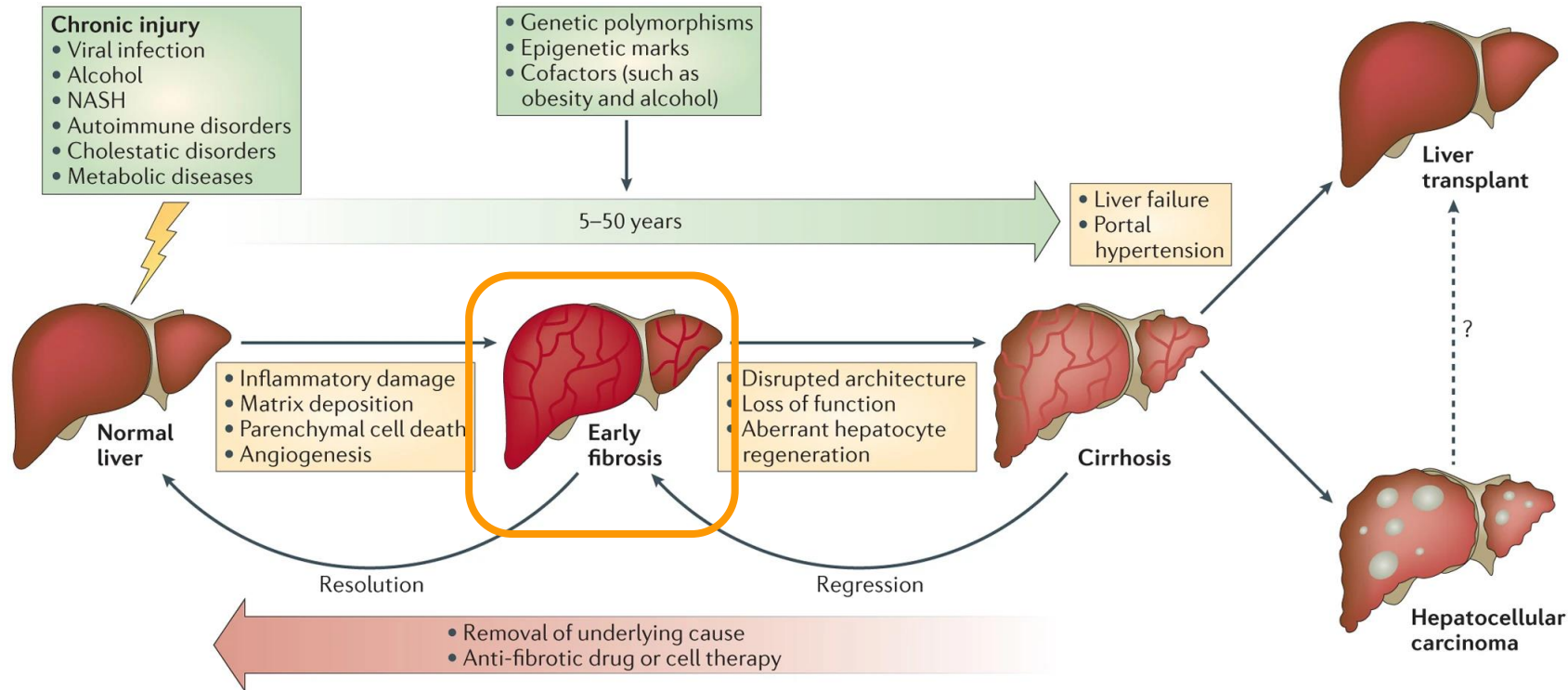
University of Bonn, Germany





Melatonin Prevents Gut Leakiness and Liver Fibrosis Through the Gut–Liver Axis

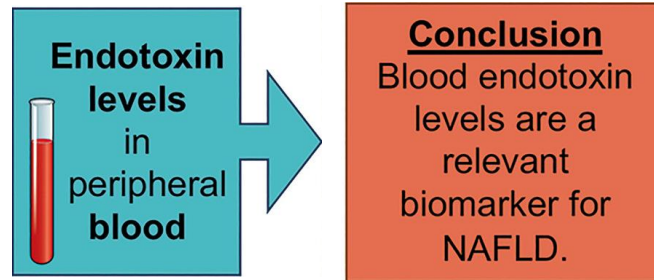
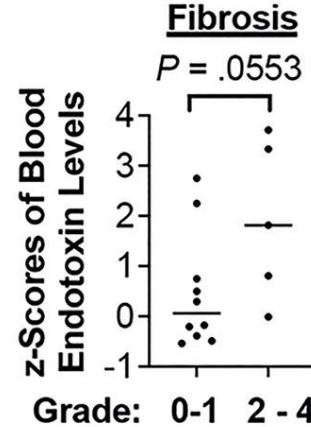
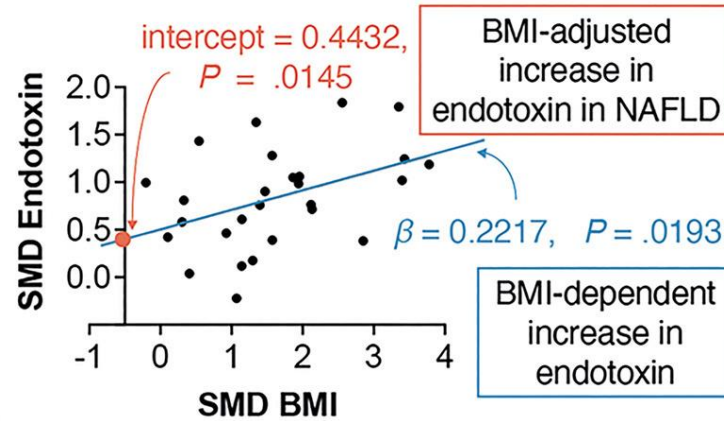
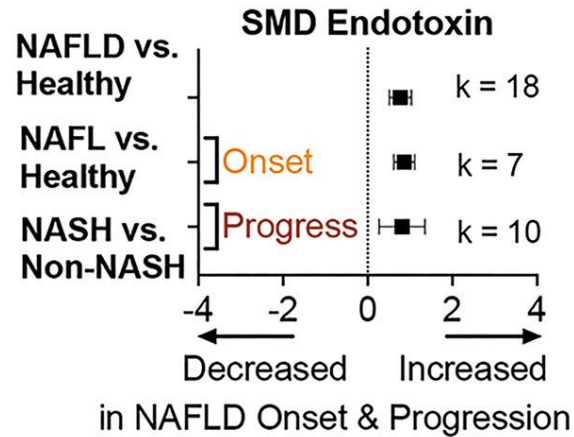
Liver fibrosis



Liver fibrosis is the consequence of several chronic liver diseases.

Once developed, it is either reversible or results in cirrhosis, liver failure, and mortality.

Liver fibrosis & Endotoxemia

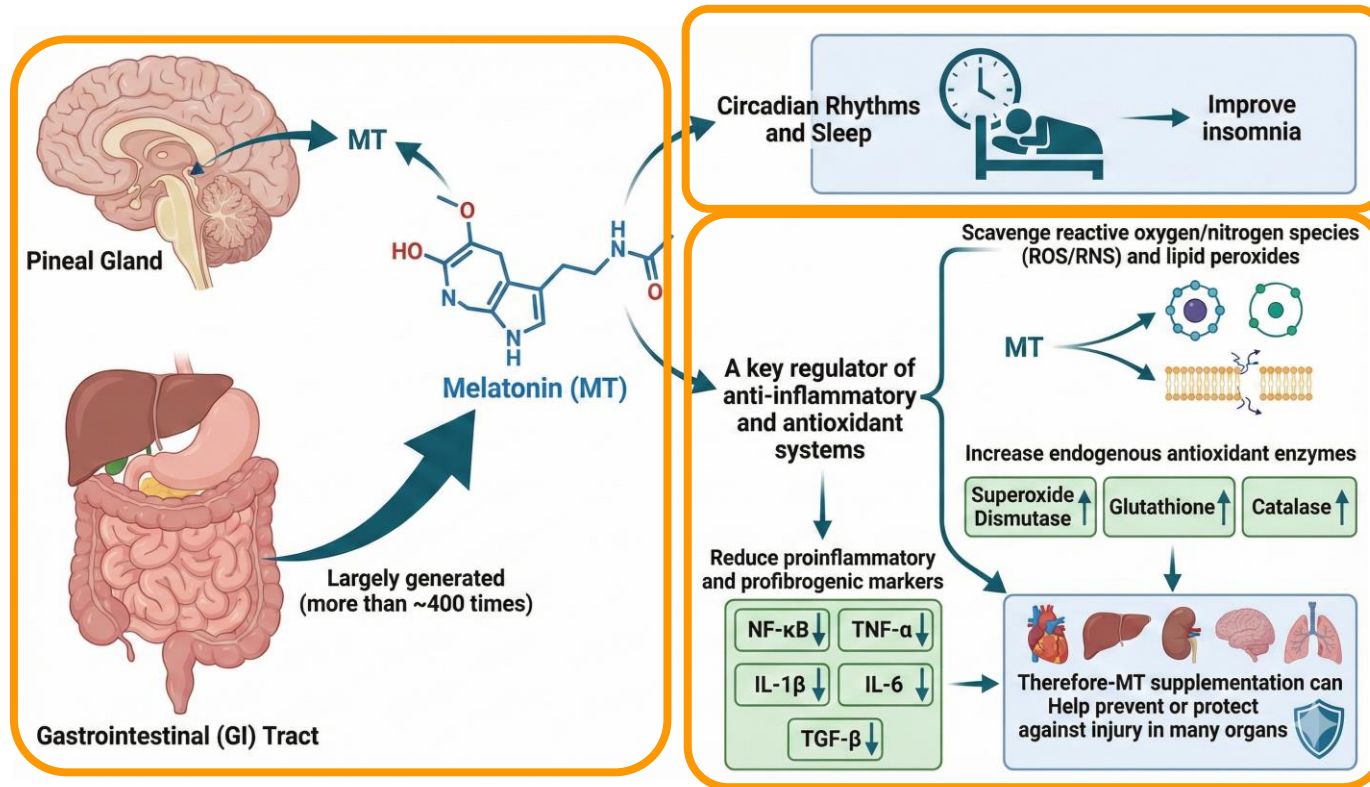


Patients with liver fibrosis and cirrhosis commonly express high endotoxin levels (a marker of gut leakiness).

Applied from: Soppert J., et al., *Clinical Gastroenterology and Hepatology*, 2023

★ ? The causal role of gut leakiness & its mechanisms underlying liver fibrosis as well as therapeutic intervention through the gut-liver axis ?

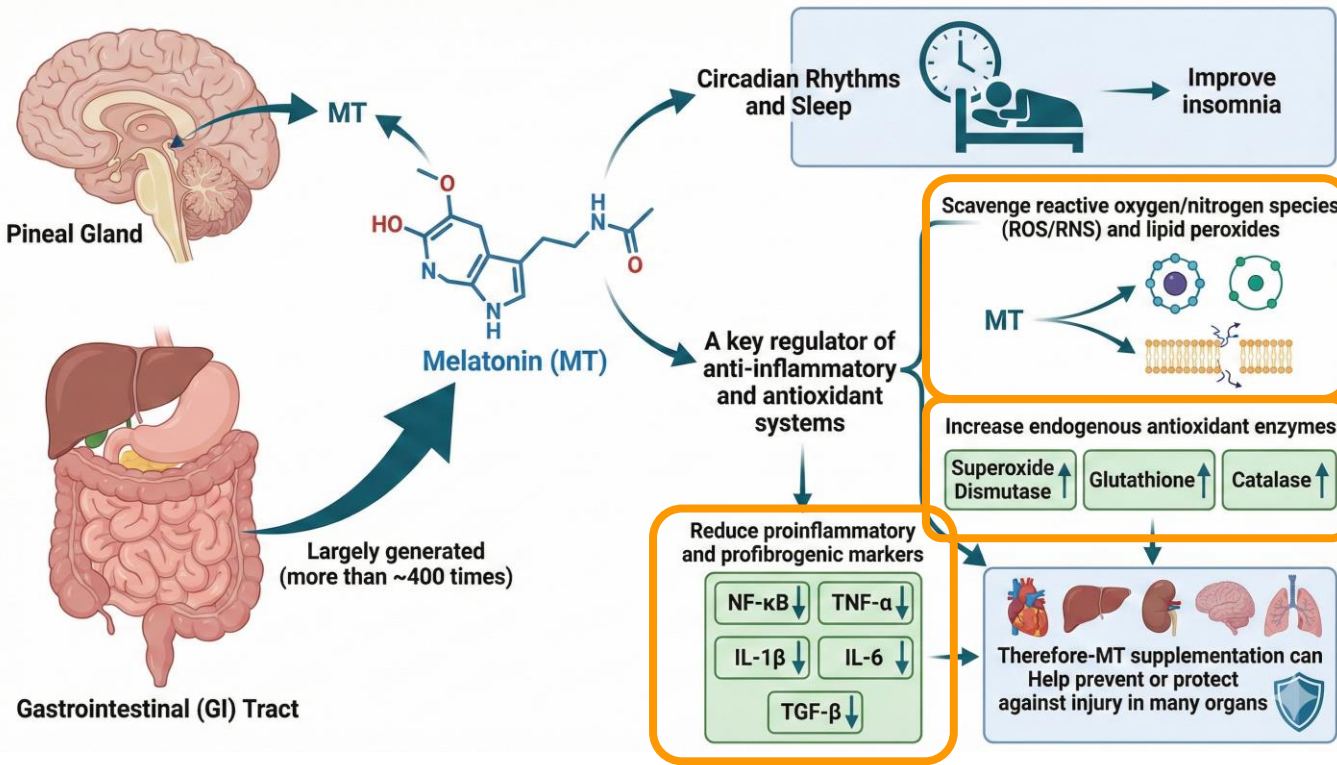
Melatonin



Melatonin:

- ✓ A hormone produced in the pineal gland
- ✓ Largely generated (more than ~400 times) in the gastrointestinal (GI) tract
- ✓ Circadian rhythms and sleep
- ✓ A key regulator of anti-inflammatory and antioxidant systems

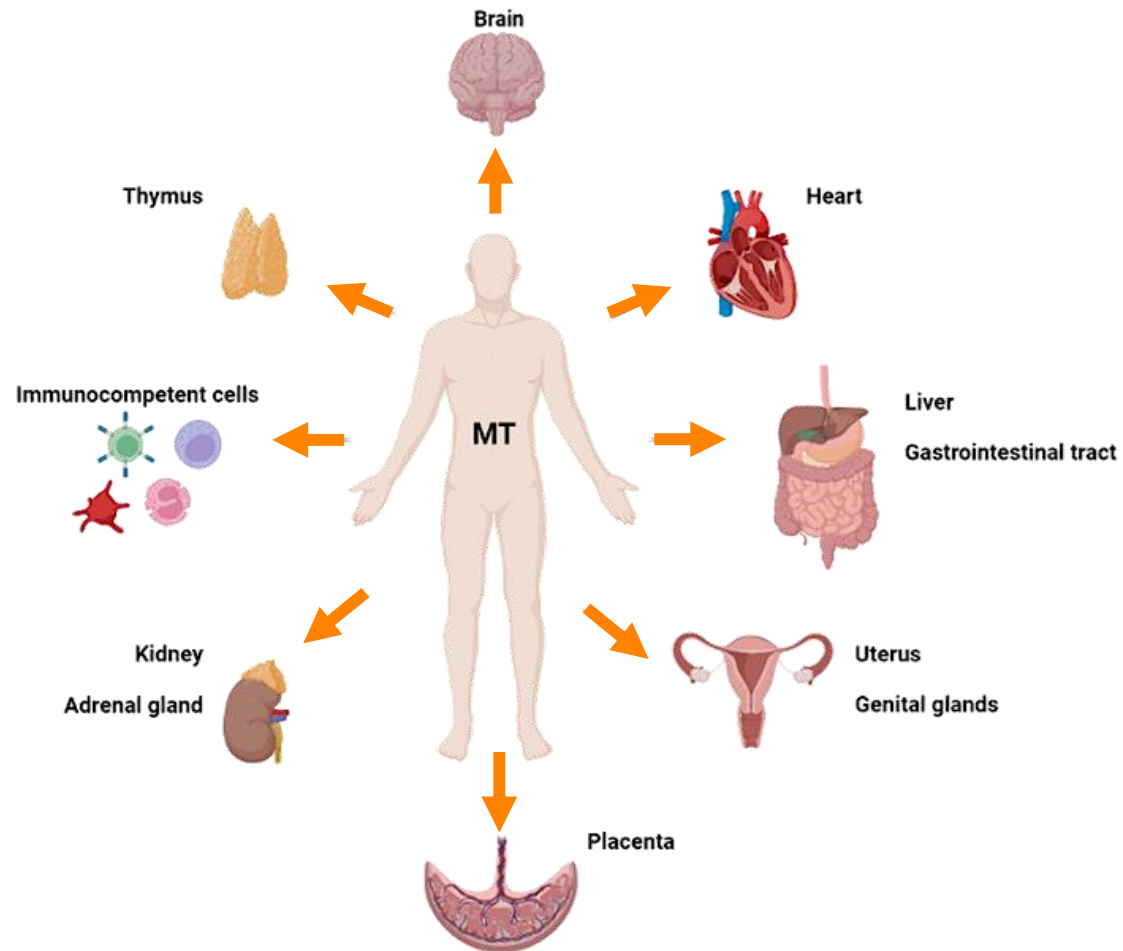
Melatonin



Melatonin:

- ✓ Scavenge reactive oxygen/nitrogen species (ROS/RNS) and lipid peroxides
- ✓ Increase endogenous antioxidant enzymes, such as superoxide dismutase, glutathione, and catalase
- ✓ Reduce proinflammatory and profibrogenic markers, including NF-κB, TNF-α, IL-1β, IL-6, and TGF-β

Melatonin



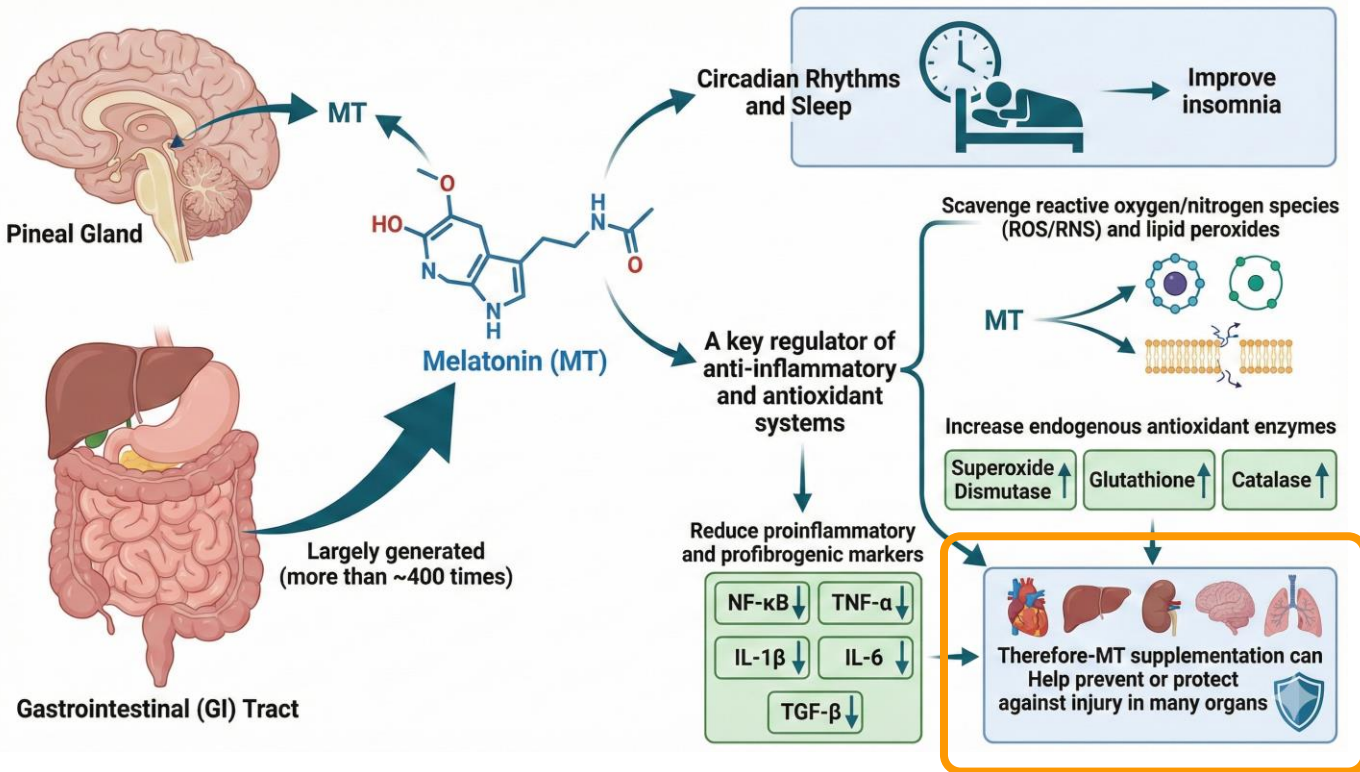
Melatonin:

- ✓ Regulate diverse physiological functions, such as immune responses and tissue/organ injury.
- ✓ Melatonin consumption (dietary supplement) can increase serum melatonin and distribute to all body compartments, as melatonin can pass through cell membranes and other barriers.

Melatonin

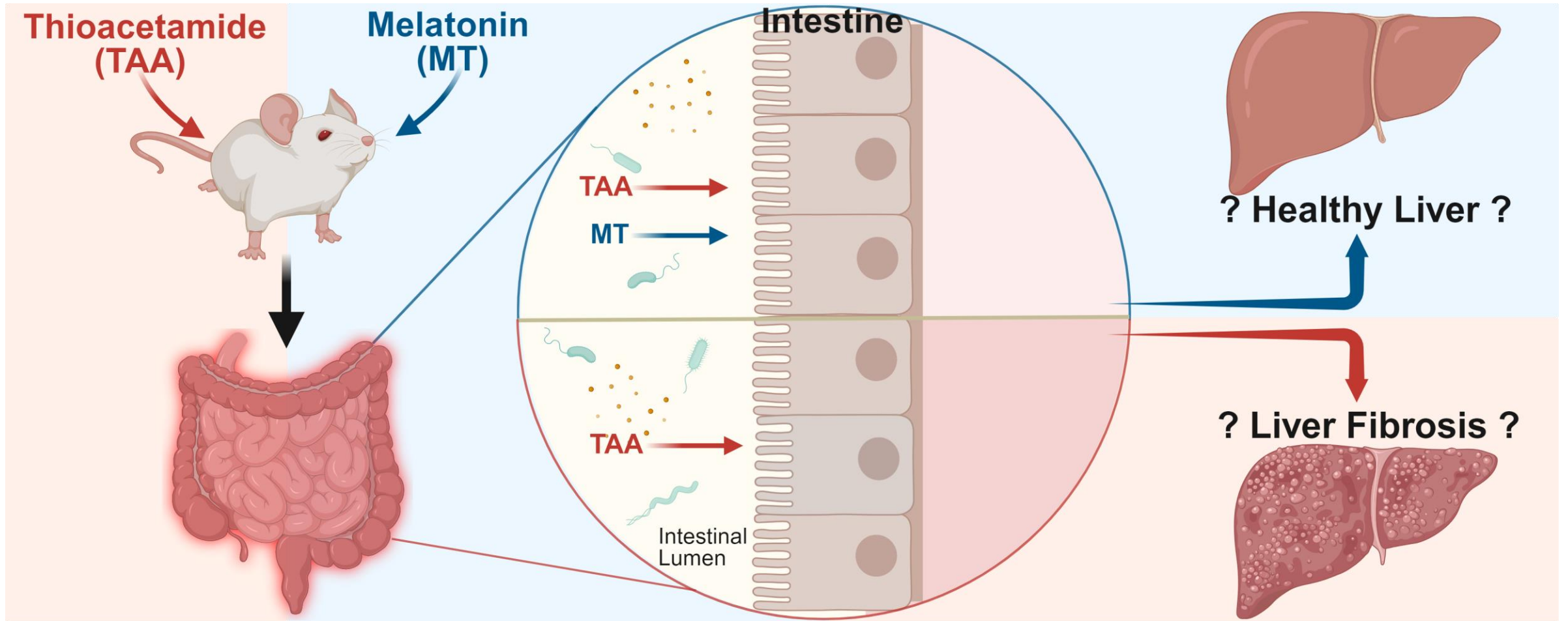
Melatonin (MT):

- ✓ Melatonin supplementation
 - Improve insomnia
 - Help prevent or protect against injury in many organs



★ ? *The mechanisms by which melatonin exerts its beneficial effects on preventing gut leakiness and liver fibrosis ?*

The Effects of Melatonin and Role of Gut Leakiness in Liver Fibrosis



★ Aim: To investigate the contributing role of gut leakiness in liver fibrosis through the gut-liver axis & the protective mechanisms of melatonin.

In vivo rat experiments

In vivo: rats

SD rats



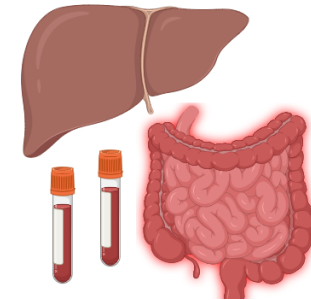
Melatonin
10 mg/kg/day,
orally



TAA
200 mg/kg, i.p.,
1, 2, 4 weeks



Tissue collection



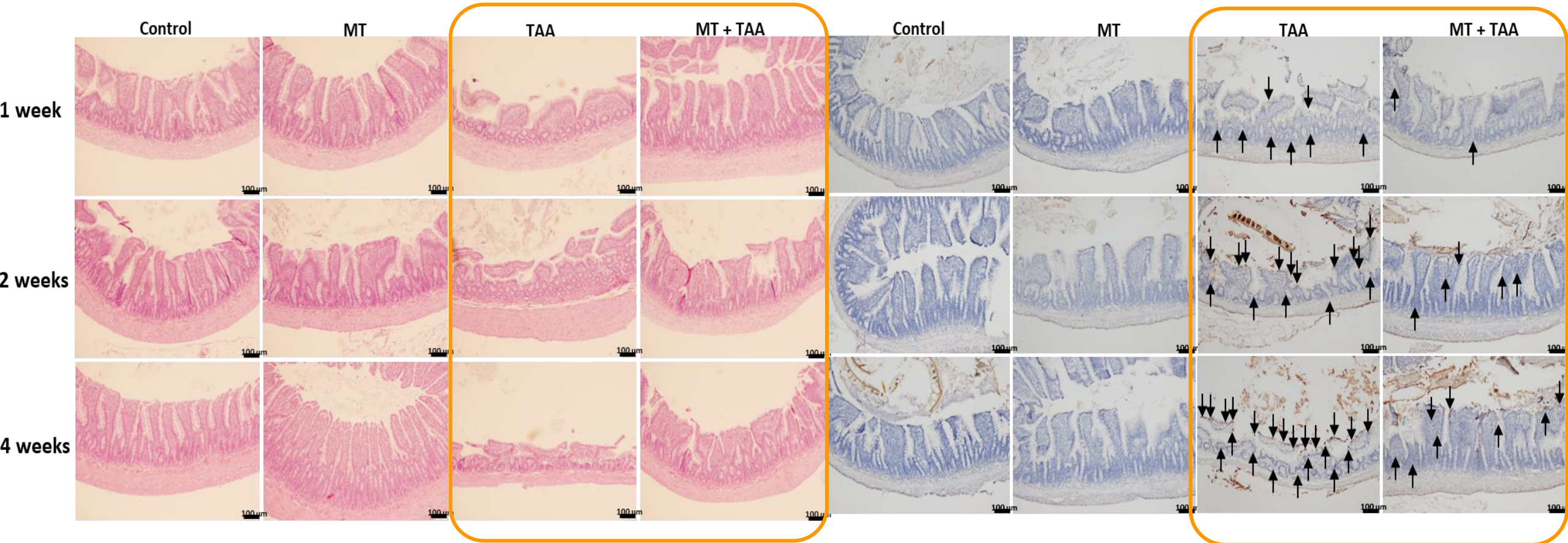
Tissue analyses:

**Histology,
biochemical
analyses**

Increased gut structural deformation and apoptosis – improved by Melatonin

Intestinal deformation

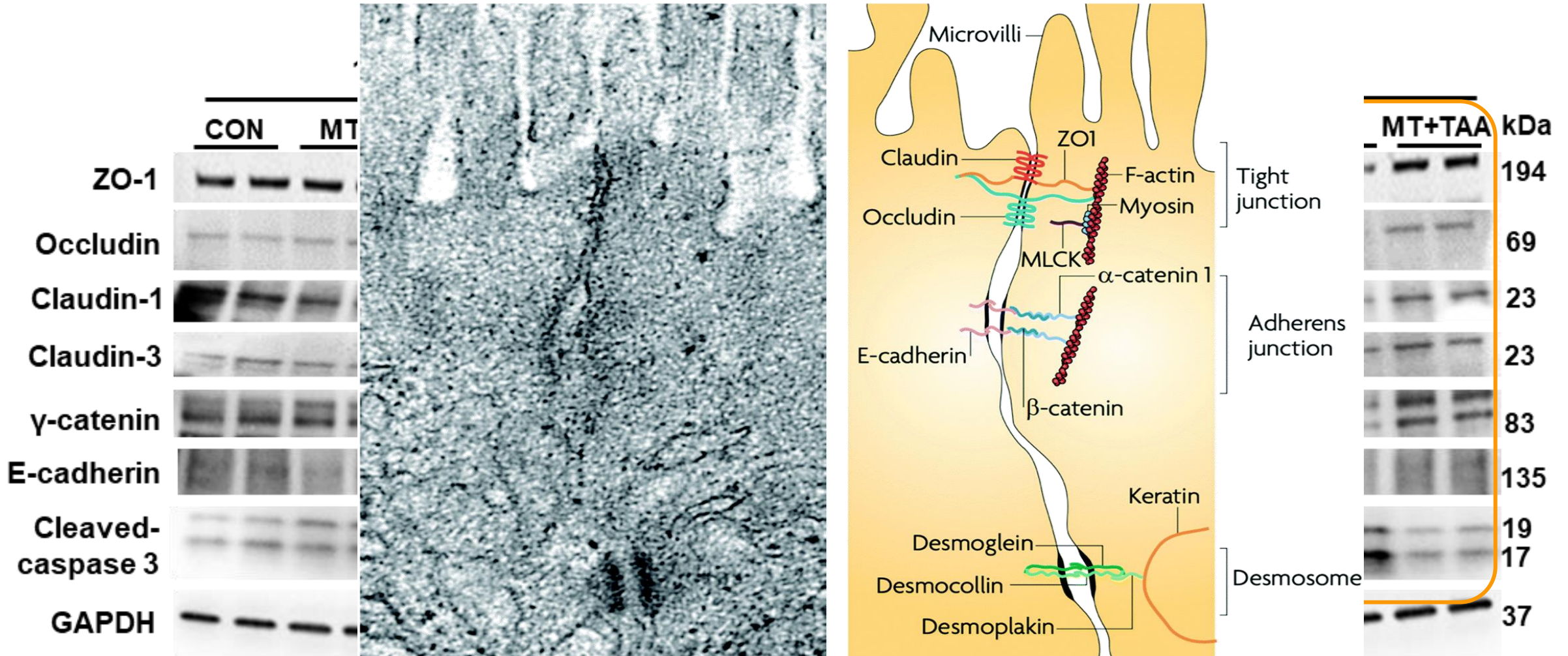
Apoptosis



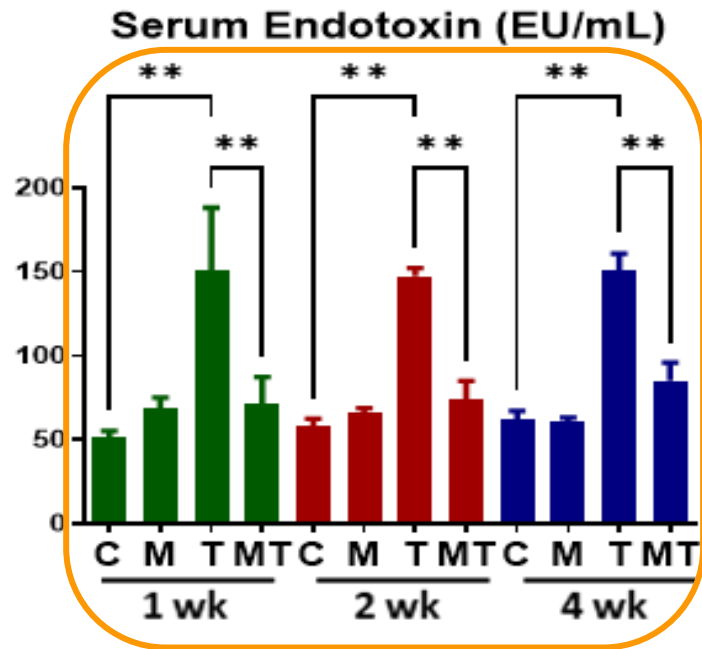
H&E staining

TUNEL staining

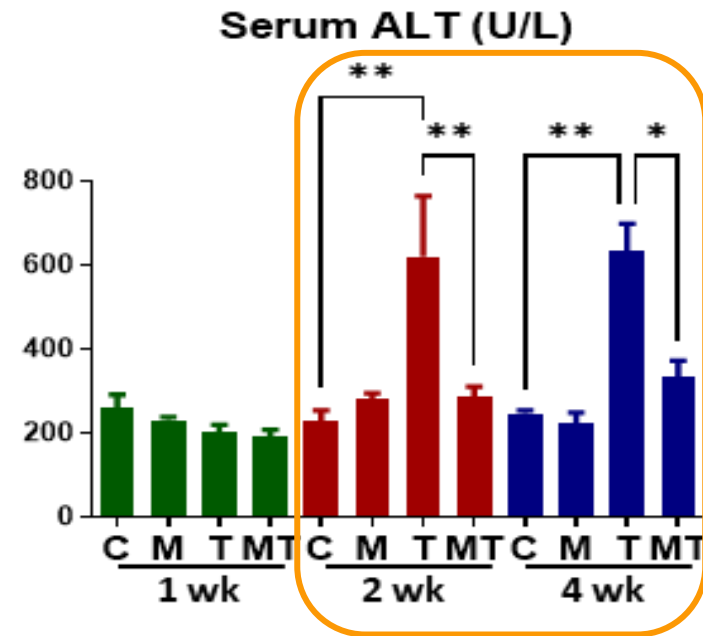
Decreased gut tight & adherens junction proteins (TJ/AJs) – improved by Melatonin



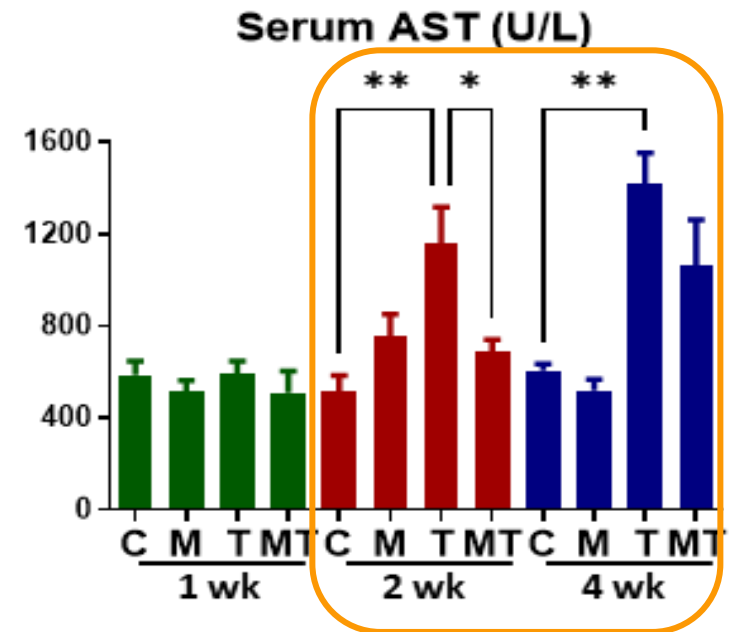
Gut leakiness and endotoxemia leads to liver injury – improved by Melatonin



(Gut leakiness)



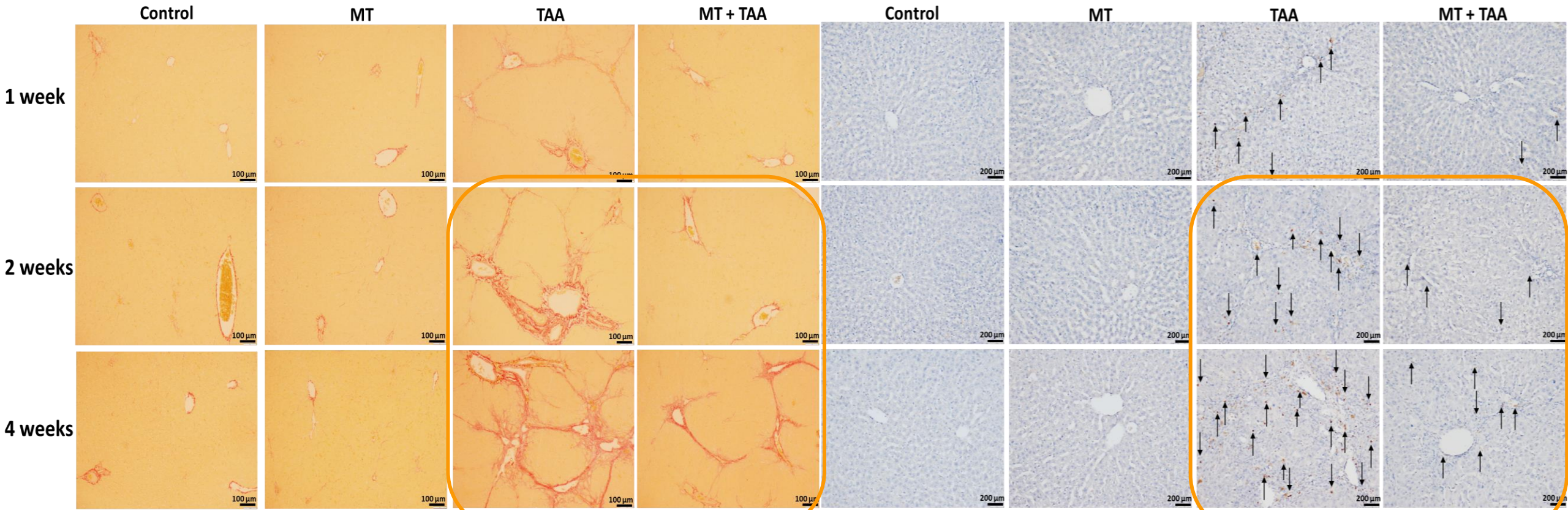
(Liver injury)



Liver fibrosis and apoptosis – improved by **Melatonin**

Fibrosis

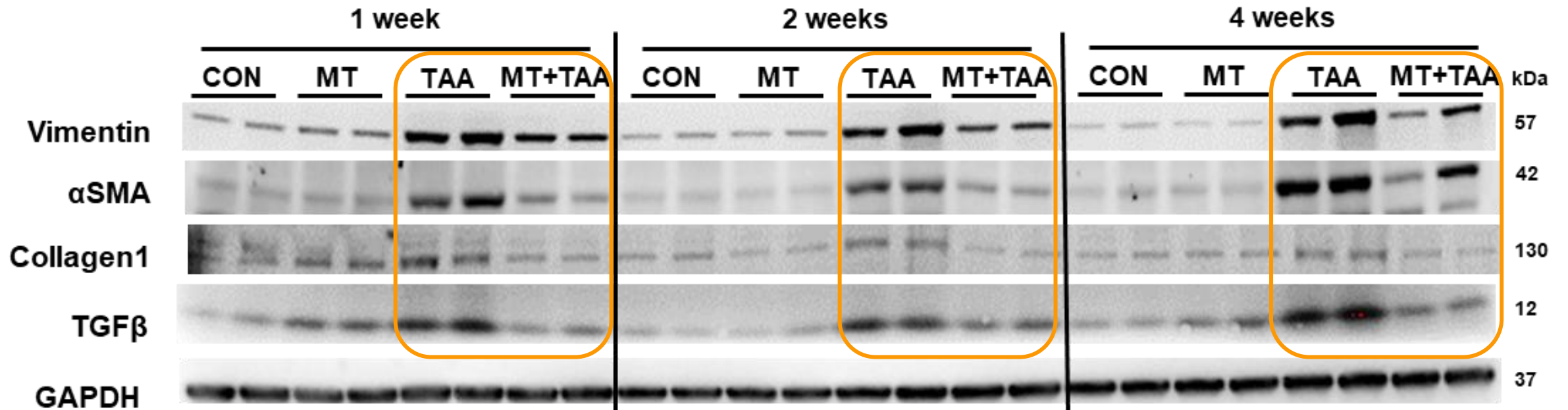
Apoptosis



Picrosirius red staining

TUNEL staining

Increased expression of proteins associated with liver fibrosis – improved by Melatonin



Liver immunoblot analyses



Underlying mechanisms?

Structural changes of proteins in liver cirrhosis and consequential changes in their function

Nikola Gligorijević, Simeon Minić, Olgica Nedić

Specialty type: Biochemistry and molecular biology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification




Nikola Gligorijević, Olgica Nedić, Department of Metabolism, University of Belgrade-Institute for the Application of Nuclear Energy, Belgrade 11080, Serbia

Simeon Minić, Centre of Excellence for Molecular Food Sciences and Department of Biochemistry, University of Belgrade-Faculty of Chemistry, Belgrade 11000, Serbia

Corresponding author: Nikola Gligorijević, PhD, Research Associate, Department of Metabolism, University of Belgrade-Institute for the Application of Nuclear Energy, Banja Luka 31b, Belgrade 11080, Serbia. nikolag@inep.co.rs

Review

Ubiquitin-Like Post-Translational Modifications (Ubl-PTMs): Small Peptides with Huge Impact in Liver Fibrosis

Sofia Lachiondo-Ortega ¹ , Maria Mercado-Gómez ^{1,†}, Marina Serrano-Maciá ^{1,†} , Fernando Lopitz-Otsoa ², Tanya B Salas-Villalobos ³, Marta Varela-Rey ¹, Teresa C. Delgado ^{1,*} , and María Luz Martínez-Chantar ¹

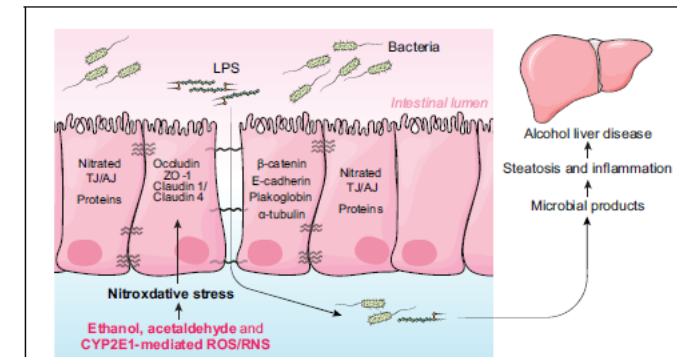
¹ Liver Disease Lab, CIC bioGUNE, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), 48160 Derio, Spain; slachiondo@cicbiogune.es (S.L.-O.); mmercado@cicbiogune.es (M.M.-G.); mserrano@cicbiogune.es (M.S.-M.); mvarrela.ciberehd@cicbiogune.es (M.V.-R.); mlmartinez@cicbiogune.es (M.L.M.-C.)

² Liver Metabolism Lab, CIC bioGUNE, 48160 Derio, Spain; flopitz@cicbiogune.es

³ Department of Biochemistry and Molecular Medicine, School of Medicine, Autonomous University of

Apoptosis of enterocytes and nitration of junctional complex proteins promote alcohol-induced gut leakiness and liver injury

Graphical abstract



Authors

Young-Eun Cho, Li-Rong Yu, Mohamed A. Abdelmegeed, Seong-Ho Yoo, Byoung-Joon Song

Correspondence

bj.song@nih.gov
(B.-J. Song)

Lay summary

Binge alcohol exposure causes gut leakiness, contributing to increased endotox-

Functional Roles of Protein Nitration in Acute and Chronic Liver Diseases

Mohamed A. Abdelmegeed and Byoung-Joon Song

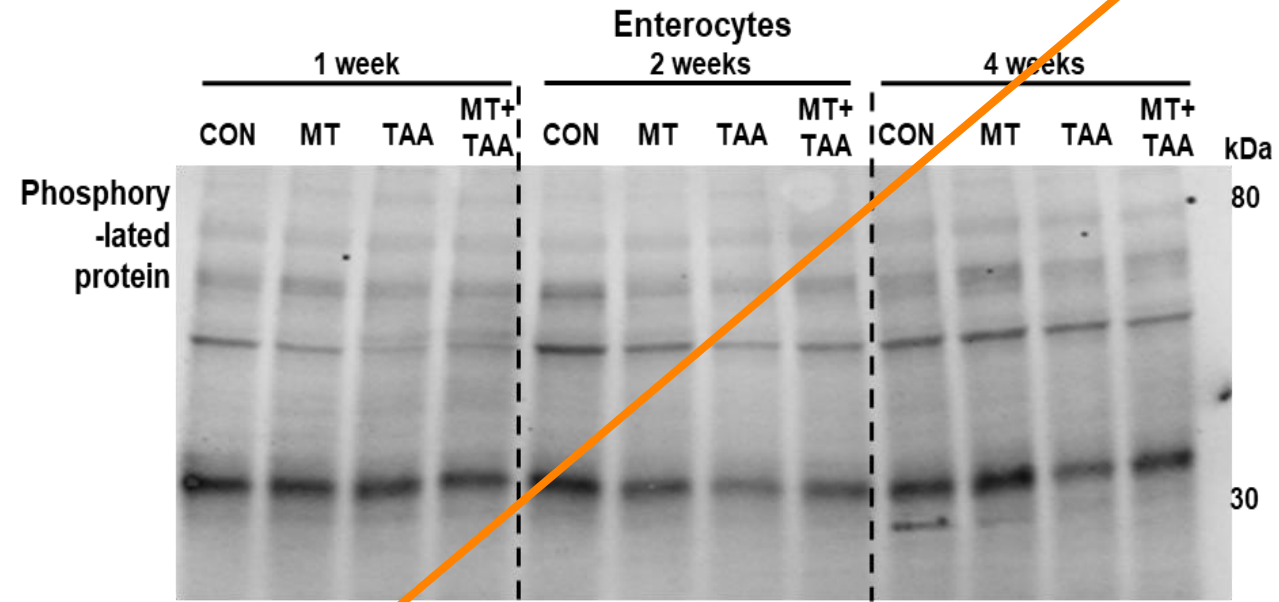
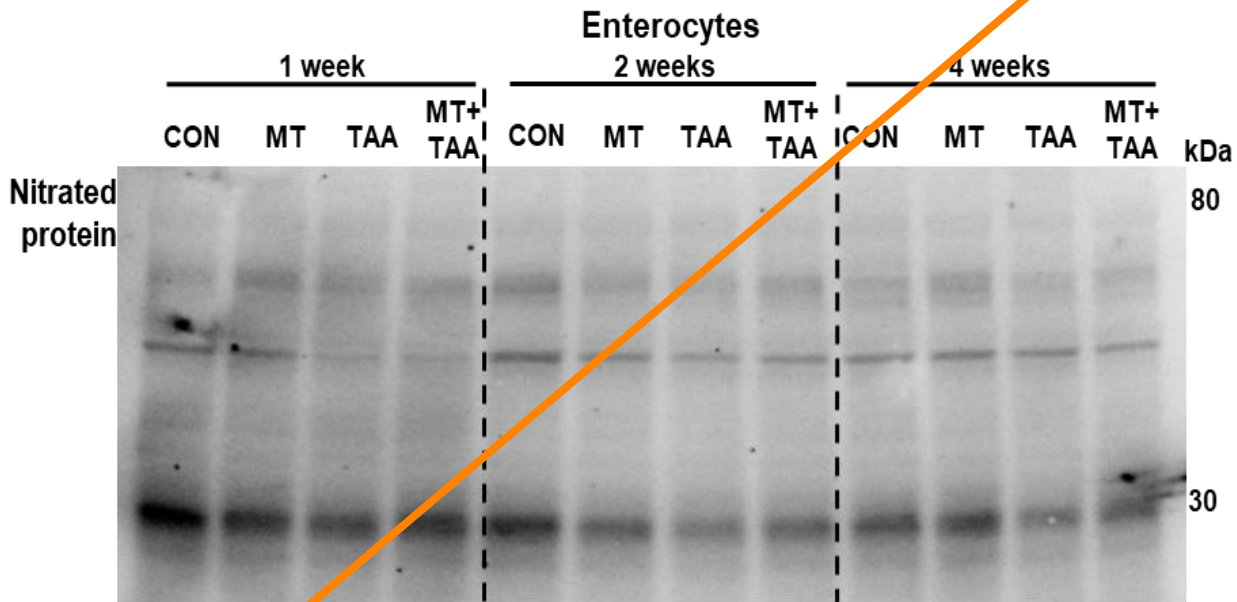
Section of Molecular Pharmacology and Toxicology, Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, 9000 Rockville Pike, Bethesda, MD 20892-9410, USA

Correspondence should be addressed to Mohamed A. Abdelmegeed; abdelmegeedm@mail.nih.gov and Byoung-Joon Song; bj.song@nih.gov

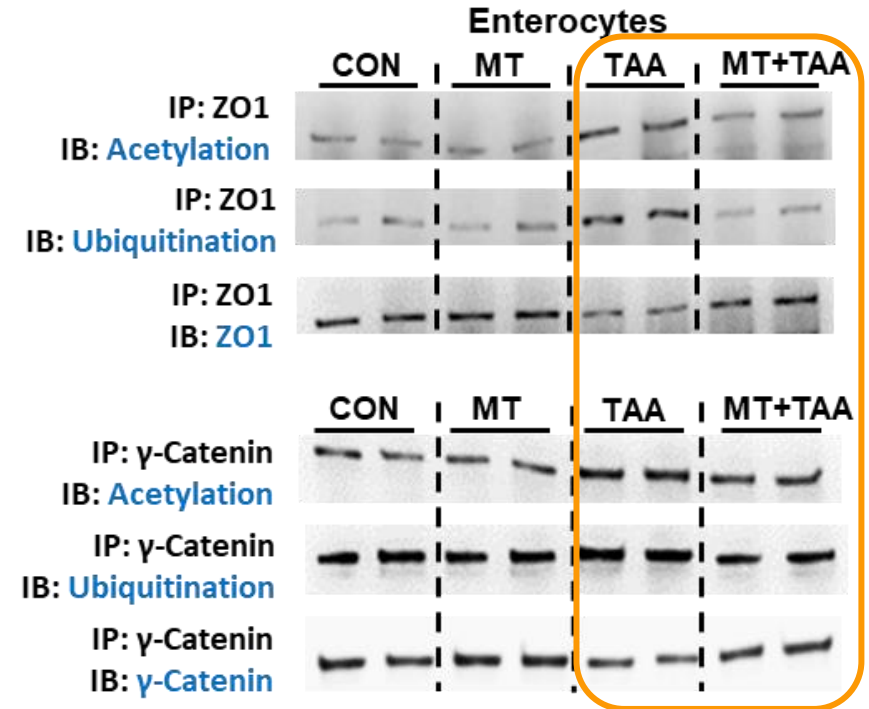
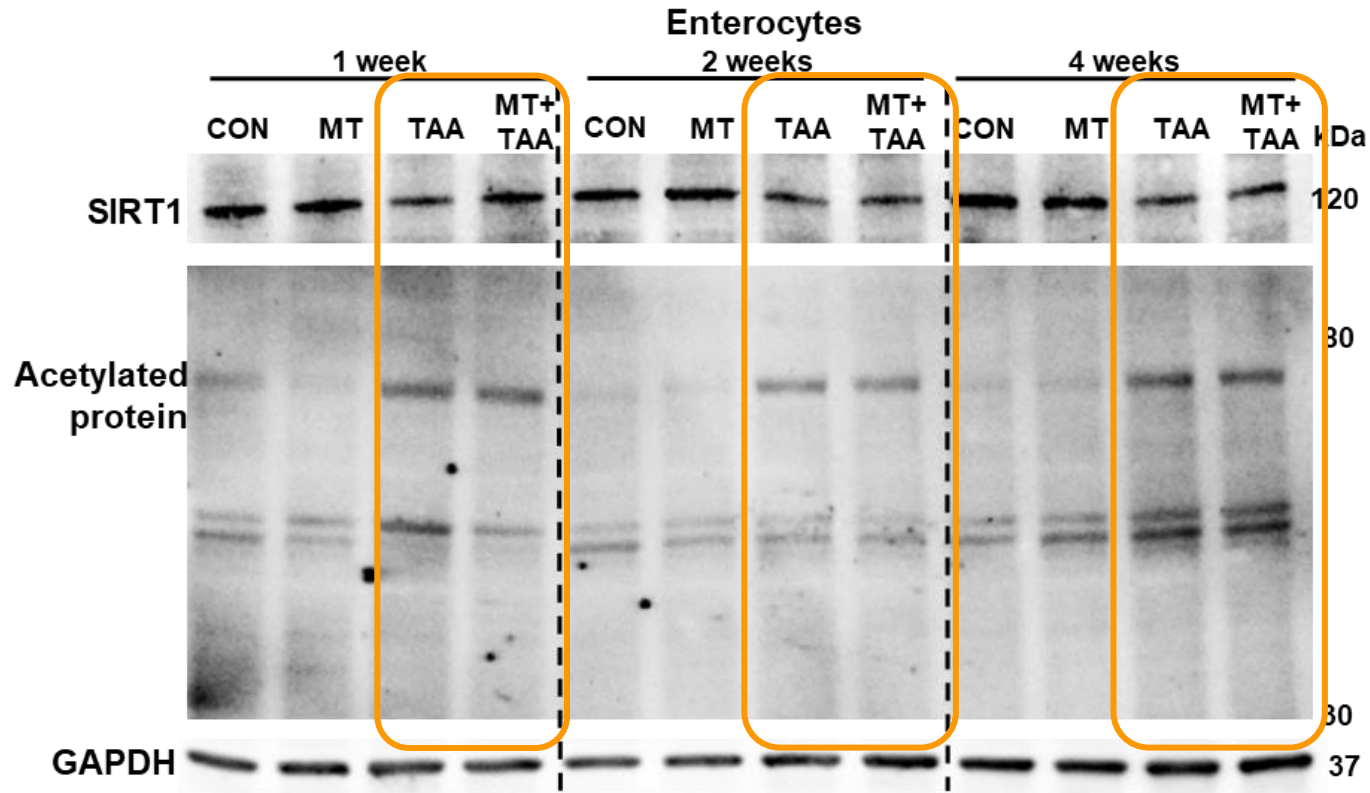
Received 12 February 2014; Revised 1 April 2014; Accepted 4 April 2014; Published 30 April 2014

Aberrant protein function from post-translational modifications (PTMs) in gut leakiness and liver injury

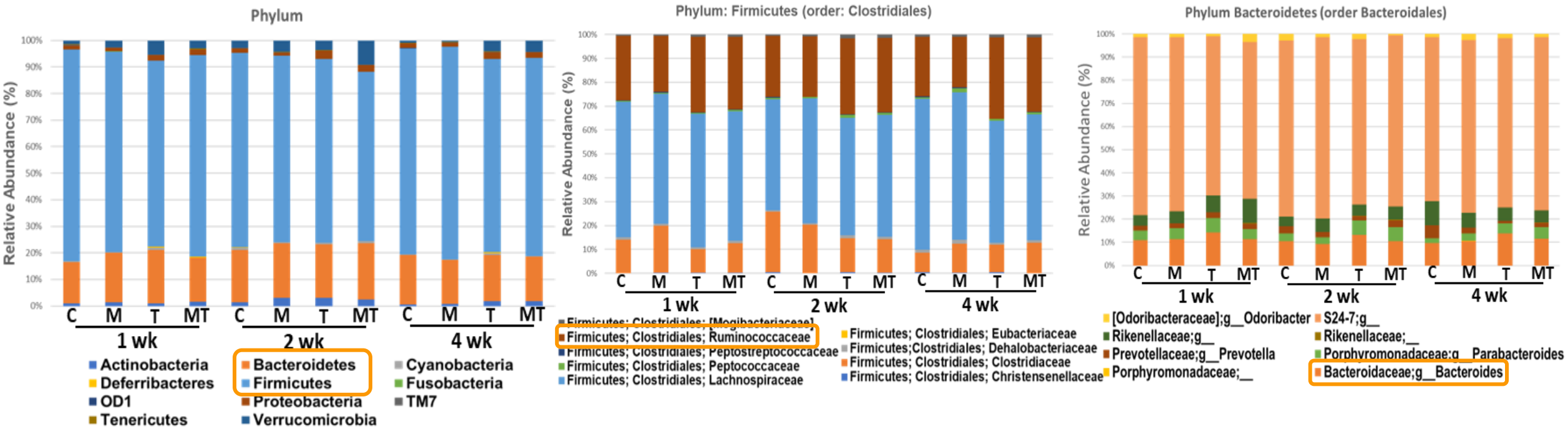
Gut post-translational modifications (PTMs)



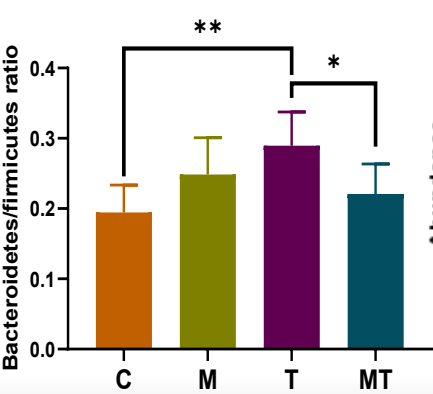
Increased **gut** protein acetylation – improved by **Melatonin**



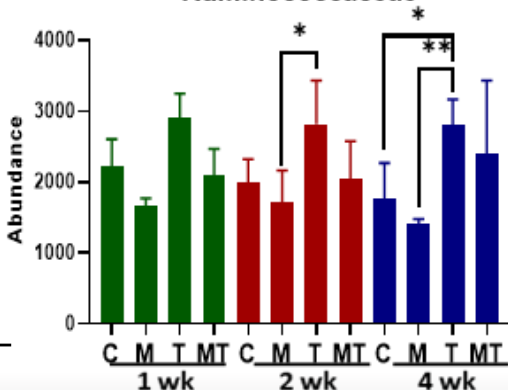
Increased gut dysbiosis and decreased short-chain fatty acids – improved by Melatonin



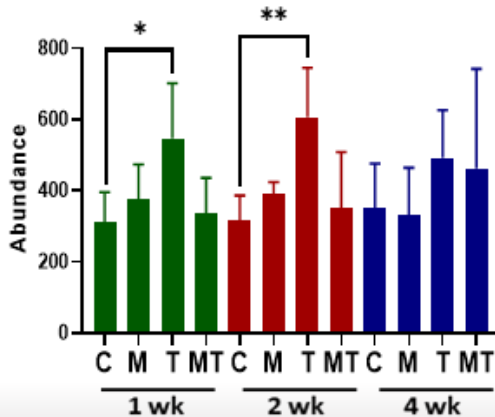
Bacteroidetes/Firmicutes ratio



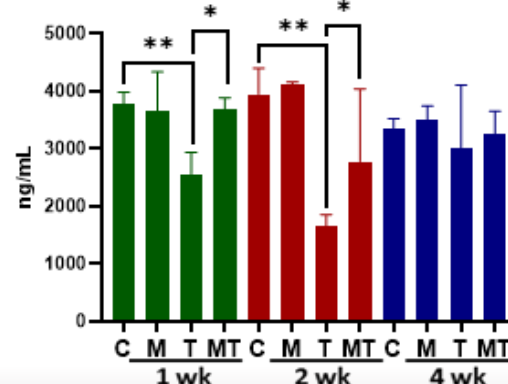
Ruminococcaceae



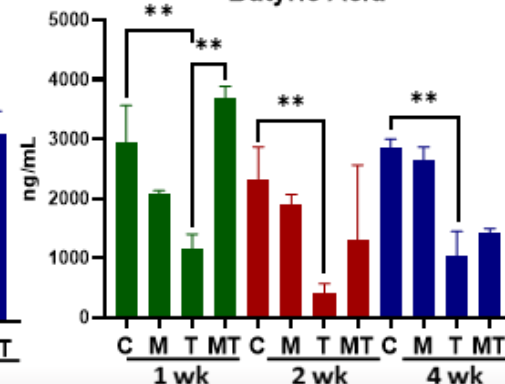
Bacteroides



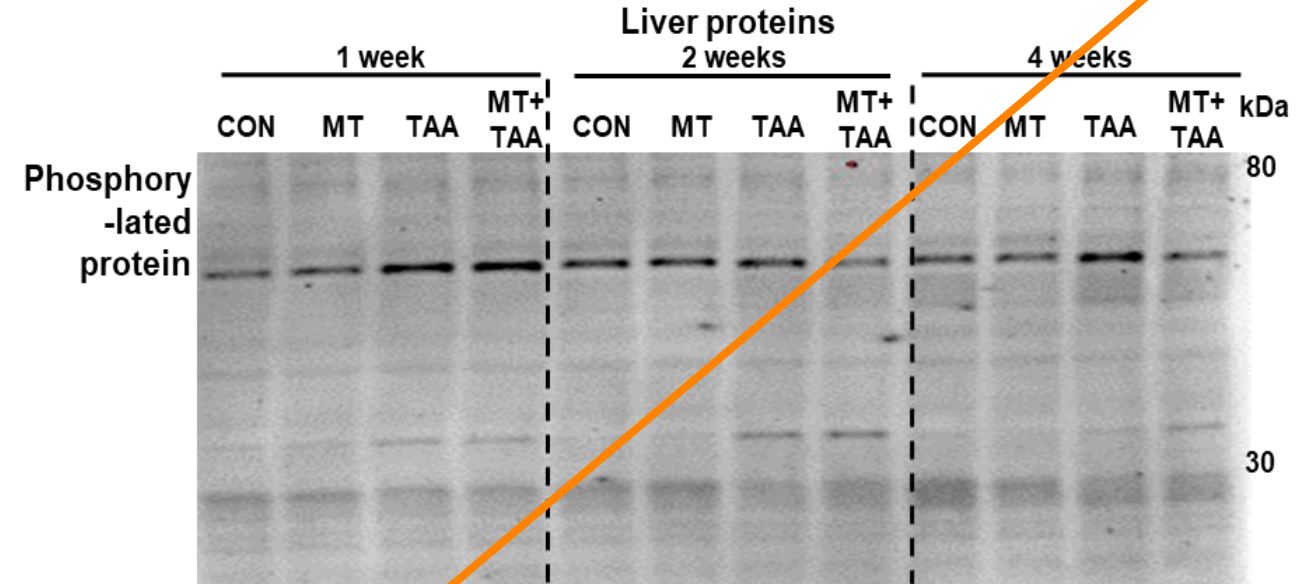
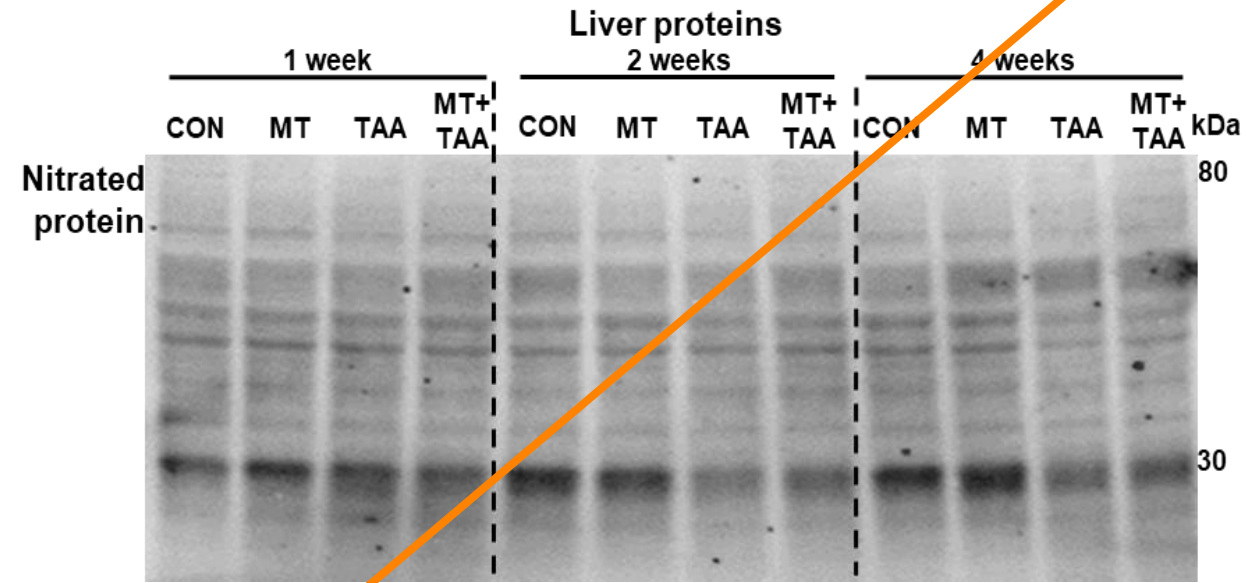
Acetic Acid



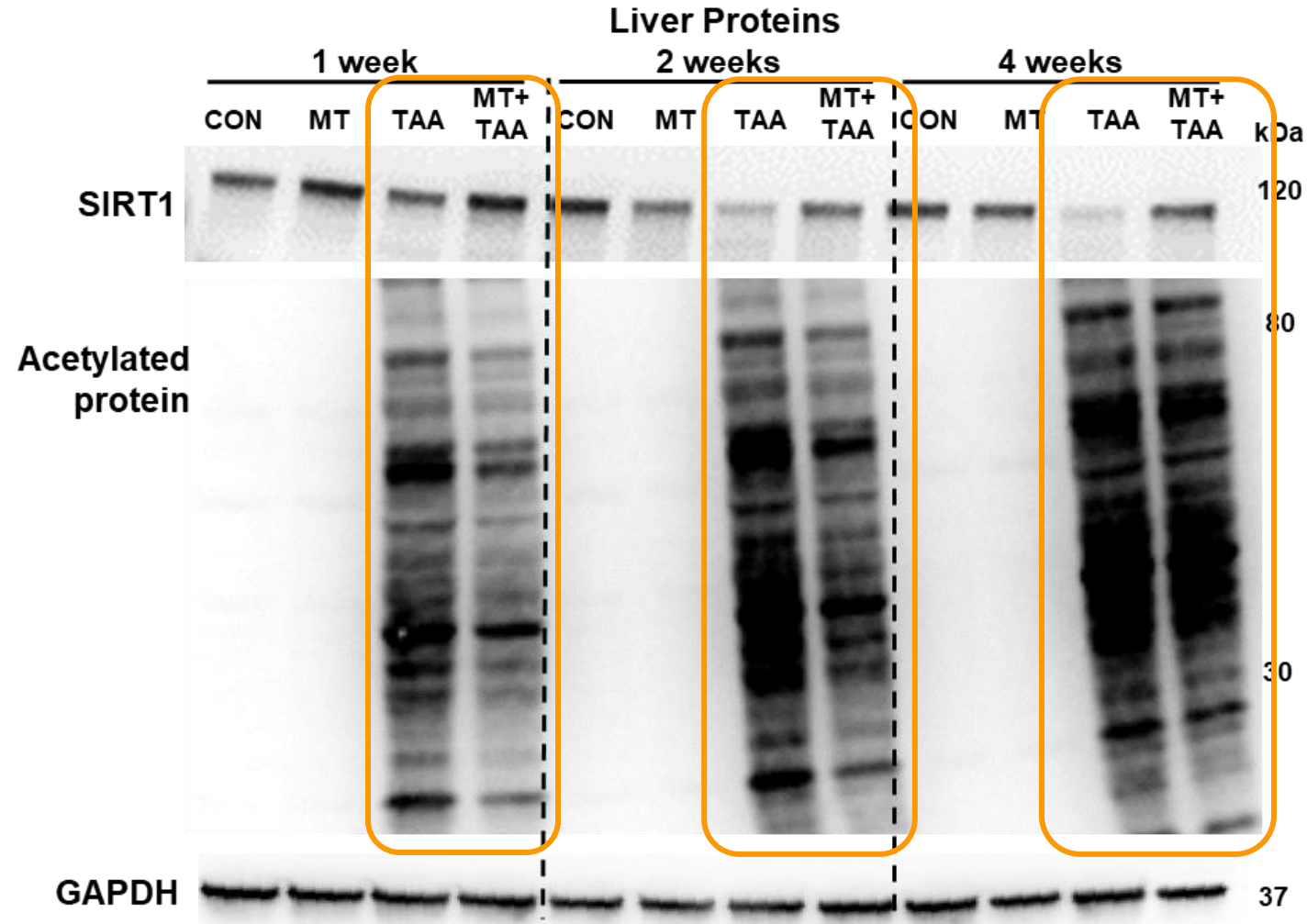
Butyric Acid



Liver post-translational modifications (PTMs)



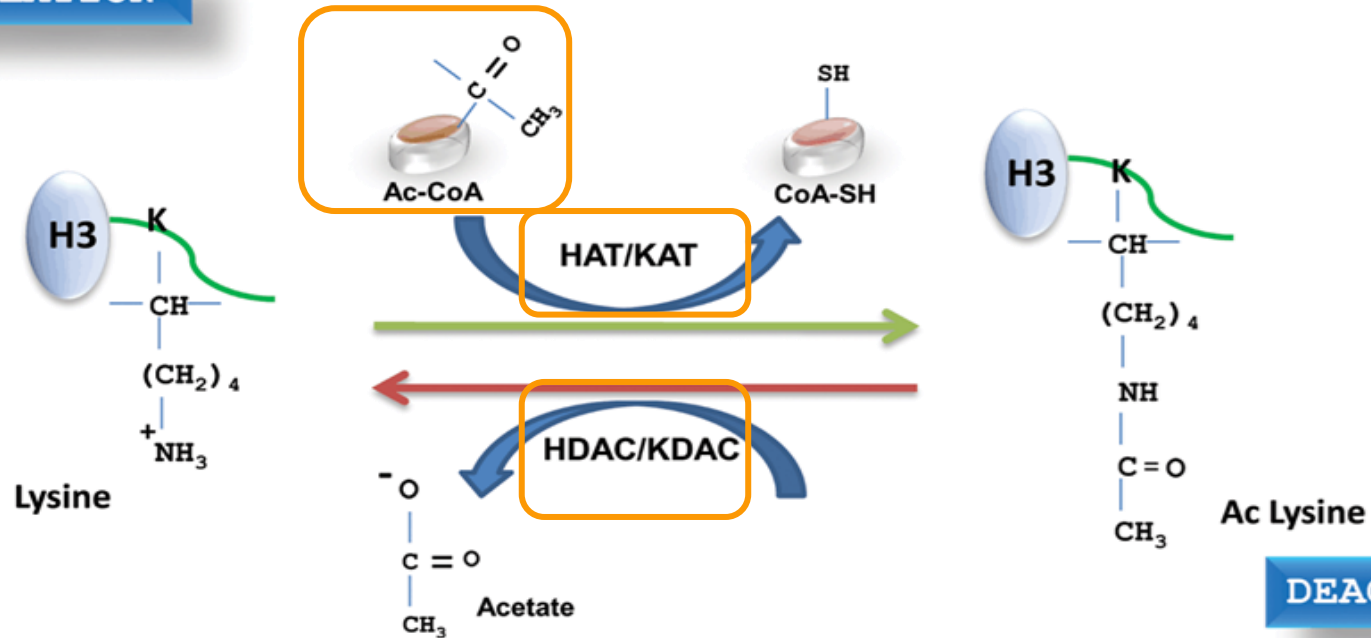
Increased **liver** protein acetylation – improved by **Melatonin**



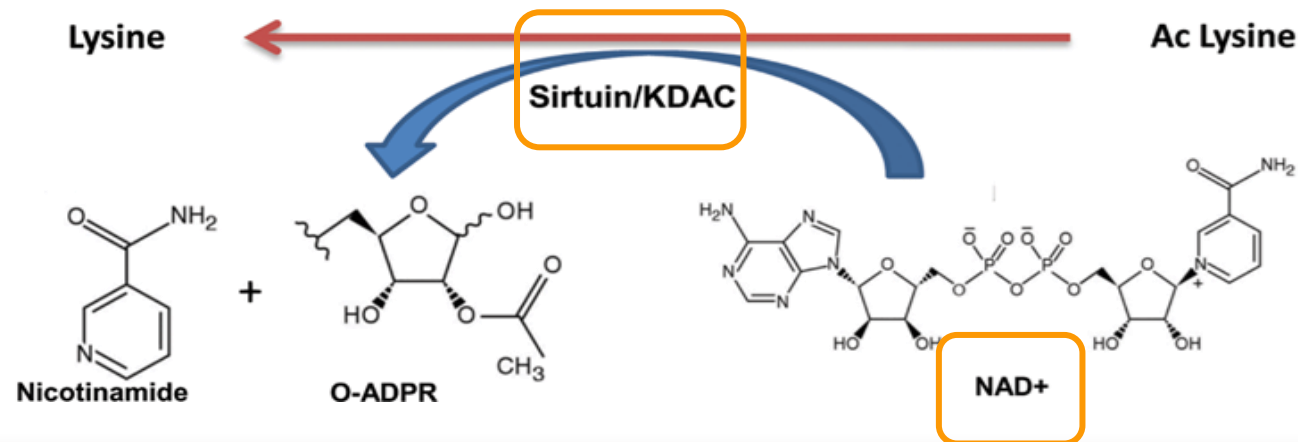
Protein acetylation?

Protein acetylation and deacetylation processes

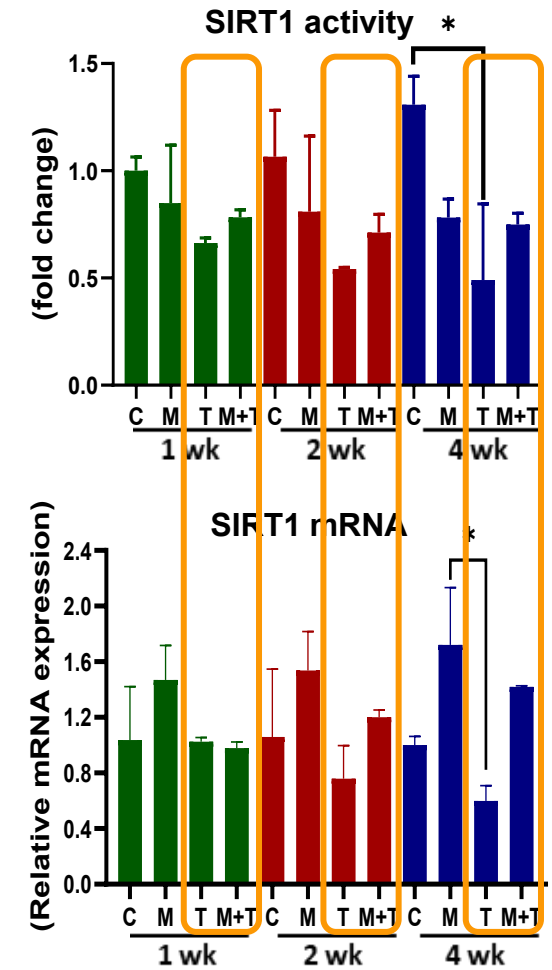
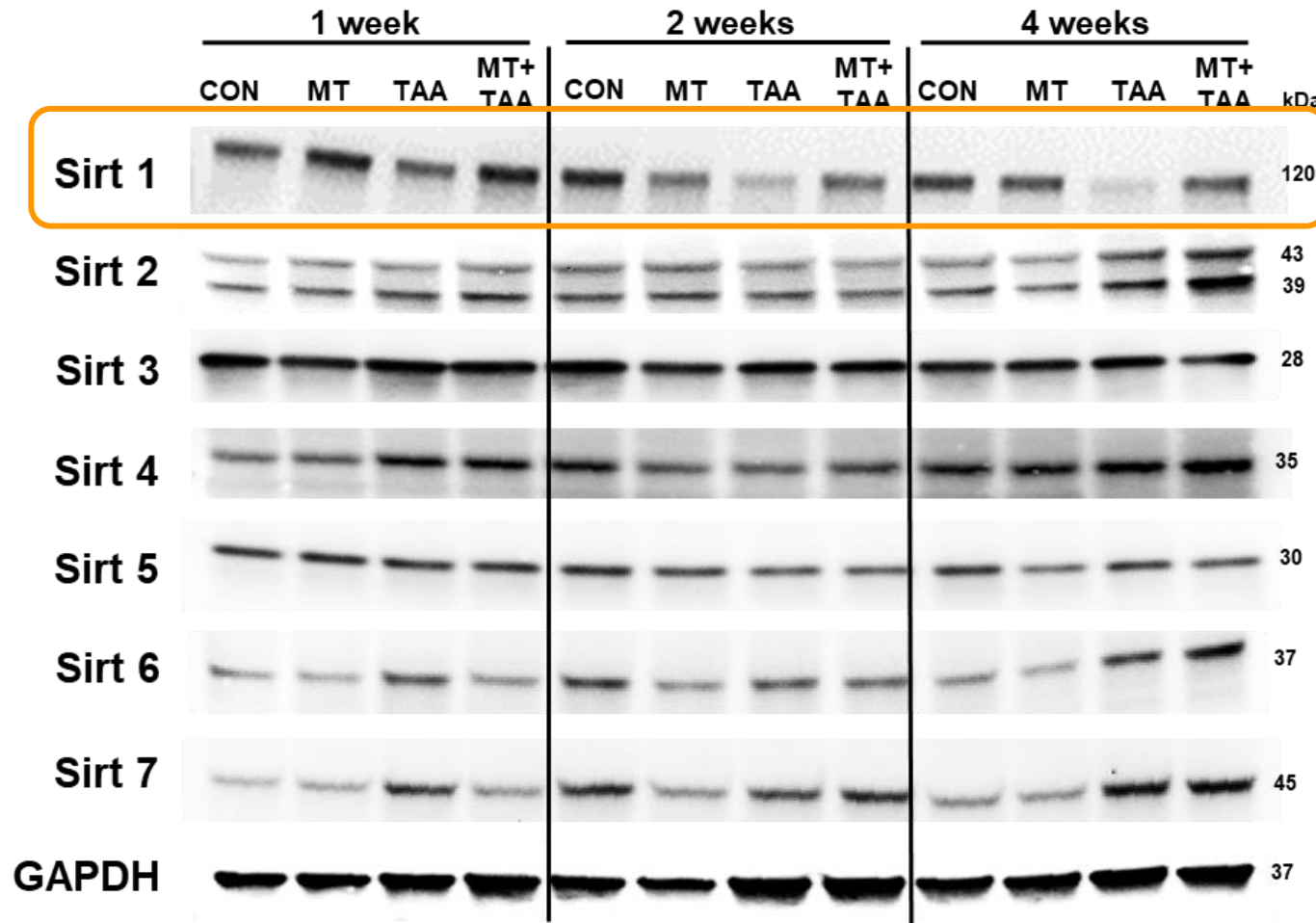
ACETYLATION



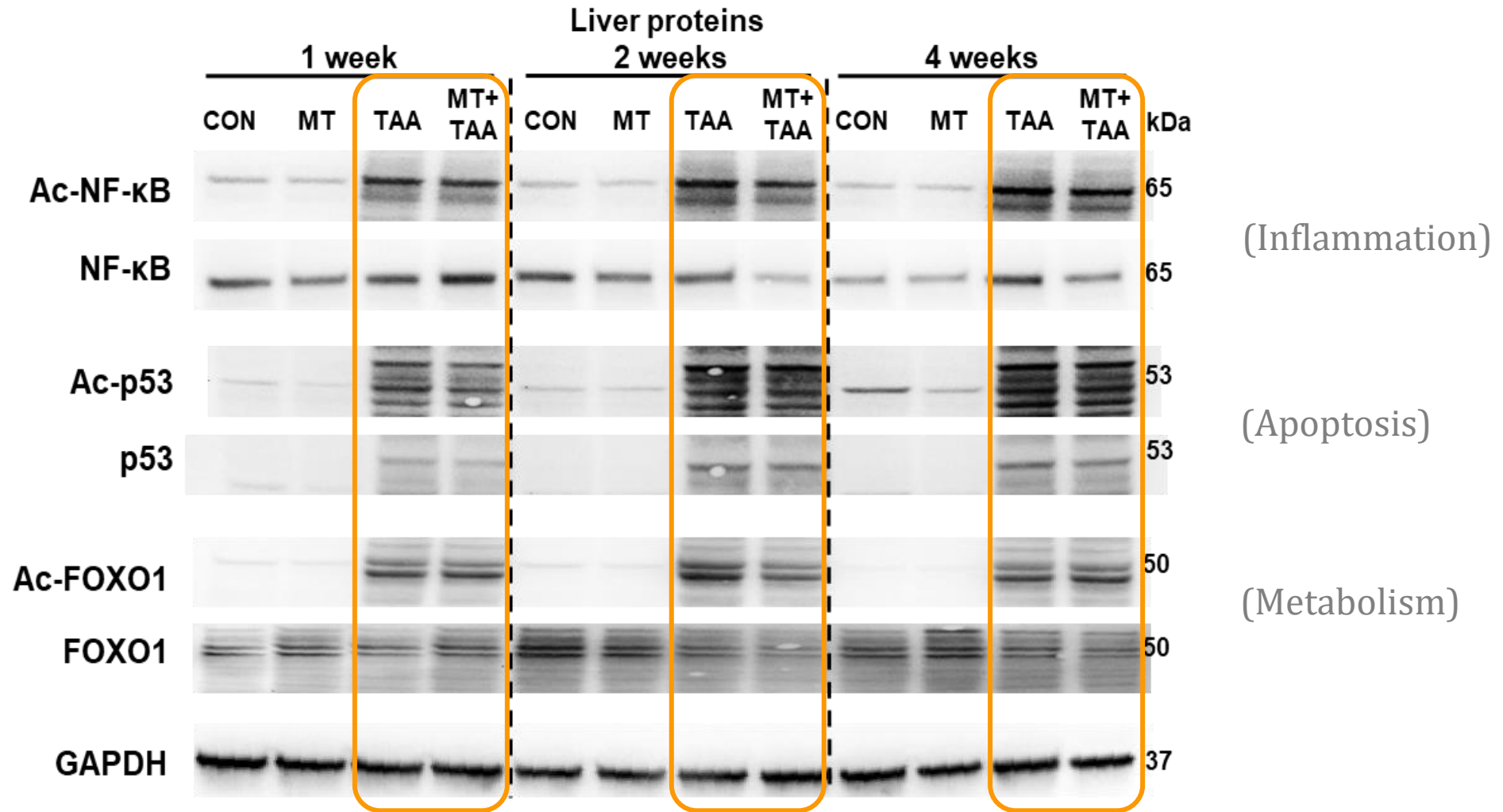
Class III deacetylase



Liver protein acetylation is specific for a reduction in Sirt1 deacetylase – improved by Melatonin



Increased acetylation of Sirt1-targeted proteins – improved by **Melatonin**



The role of Sirt1 in gut leakiness and liver fibrosis?

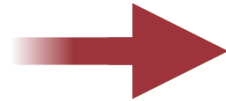
In vivo mouse experiments

In vivo: tissue-specific KO mice

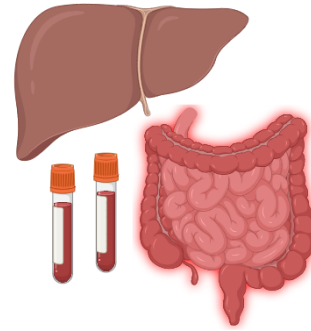
Intestinal-specific *Sirt1*-KO mice



TAA
200 mg/kg, i.p.,
4 weeks



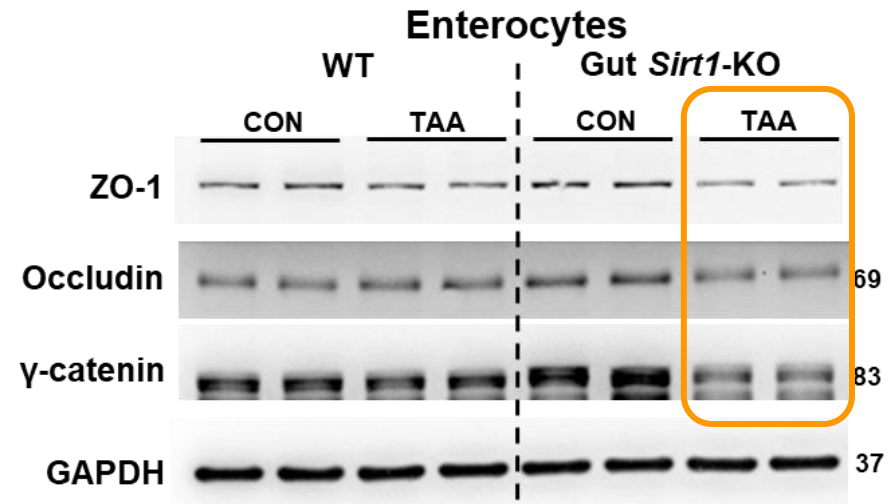
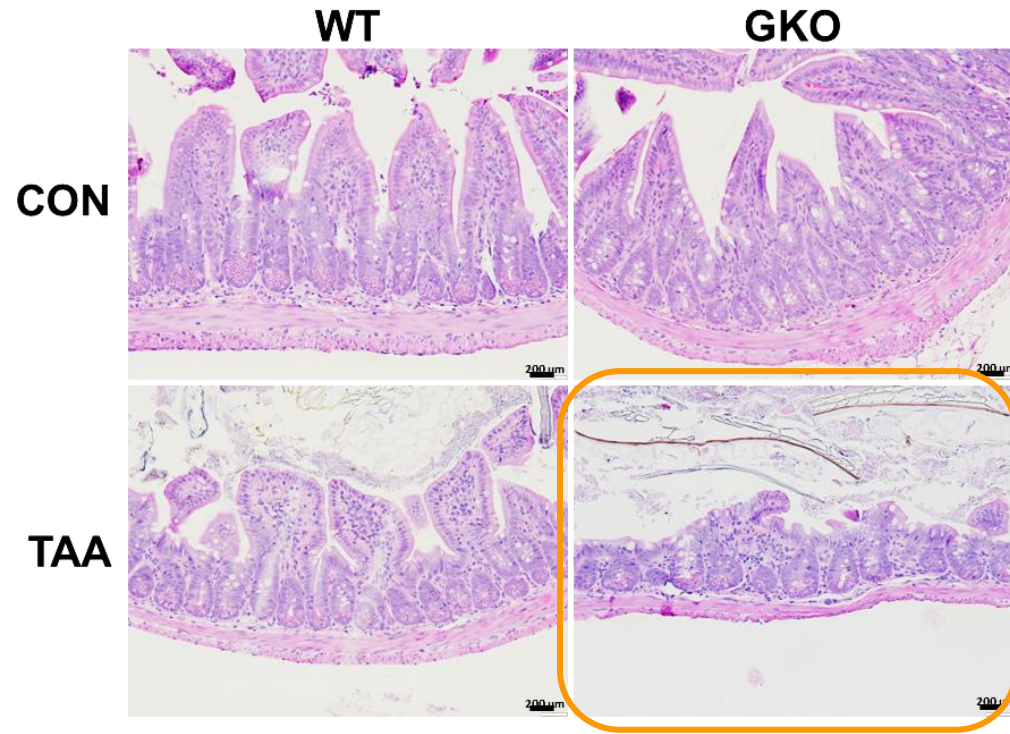
Tissue collection



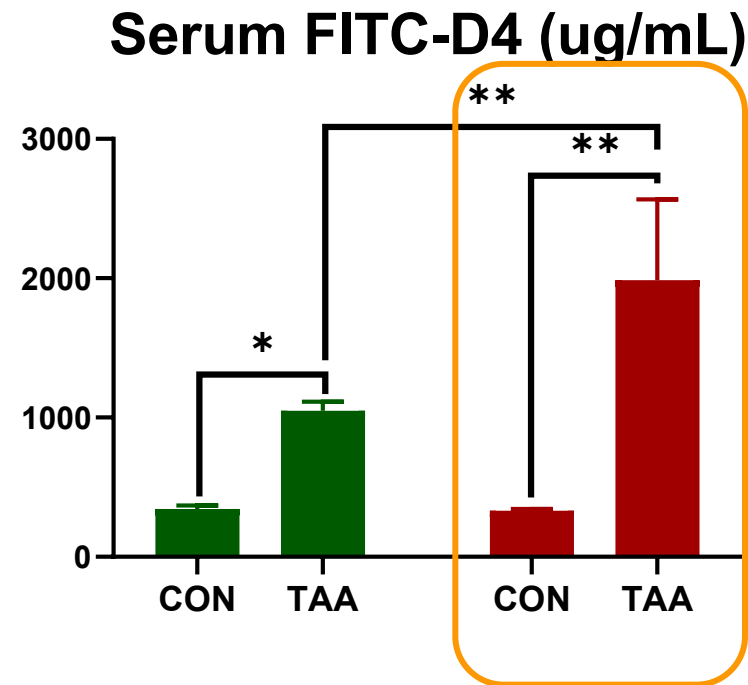
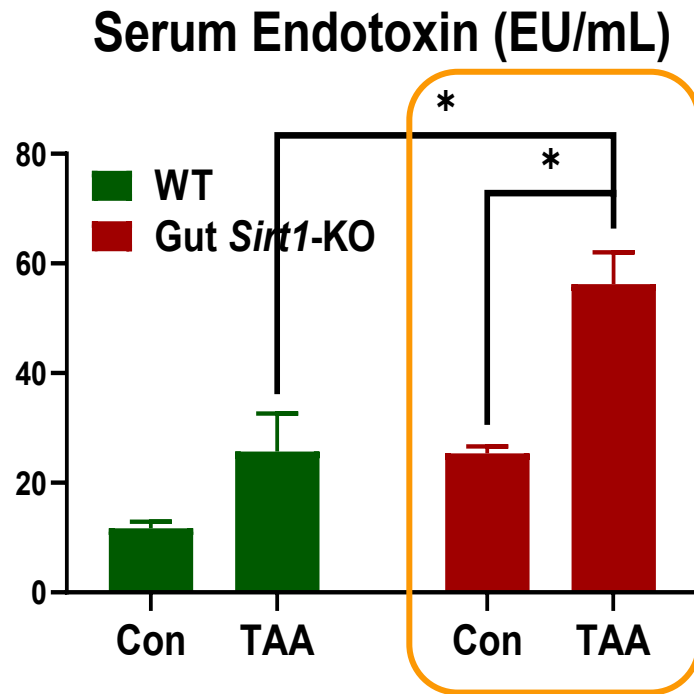
Tissue analyses:

**Histology,
biochemical
analyses**

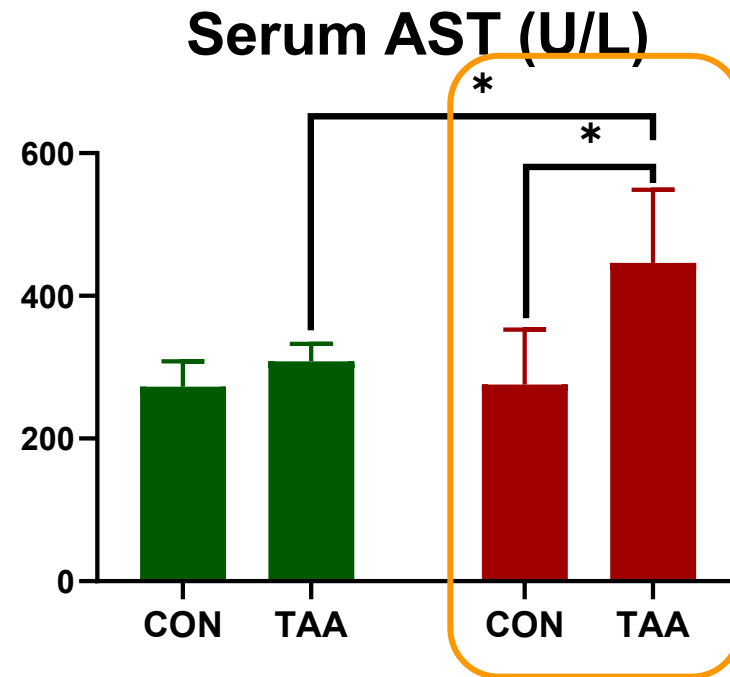
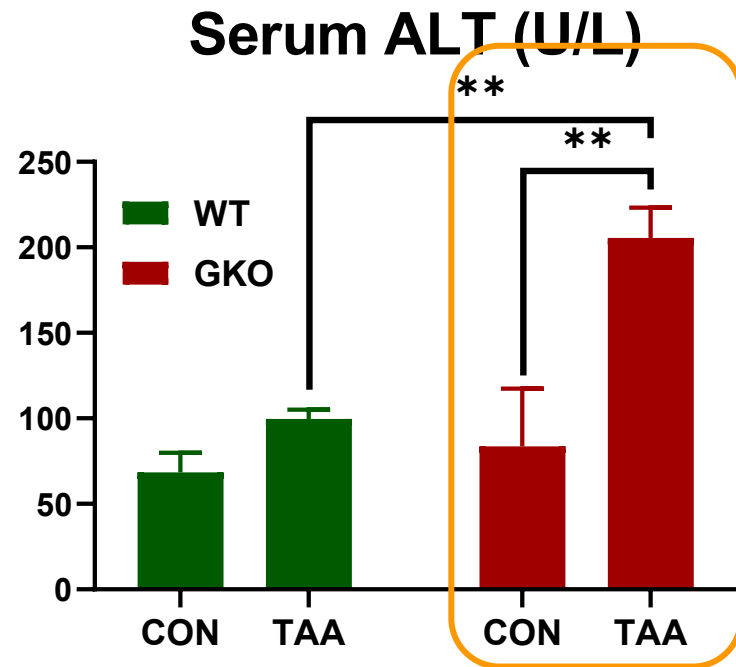
Gut-specific Sirt1-KO (GKO) mice are susceptible to TAA-induced gut leakiness



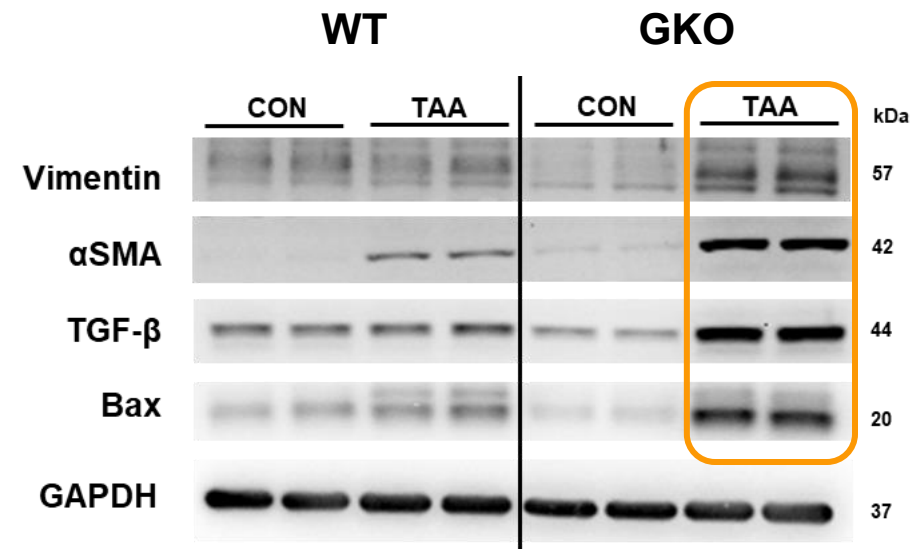
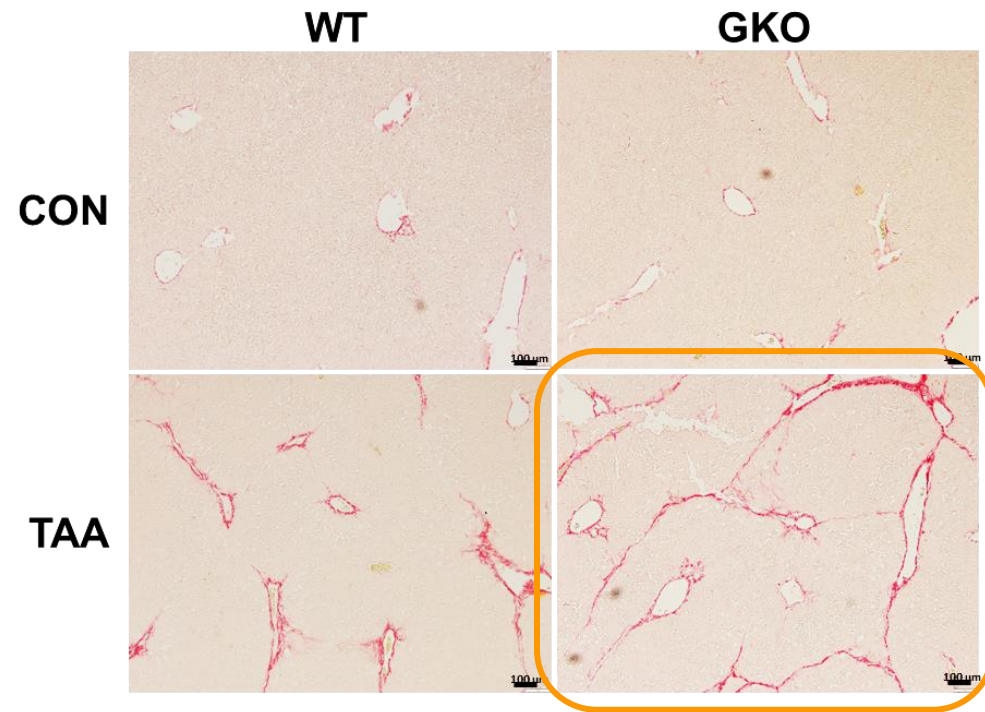
GKO mice are susceptible to TAA-induced gut leakiness



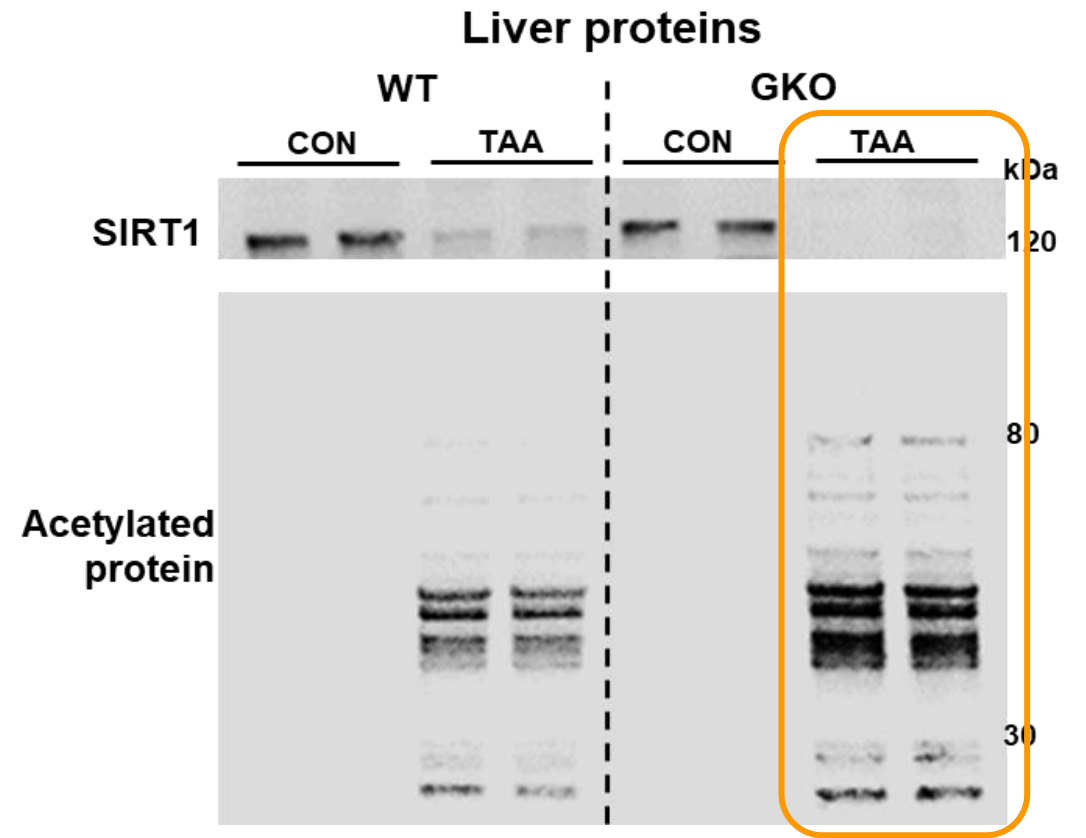
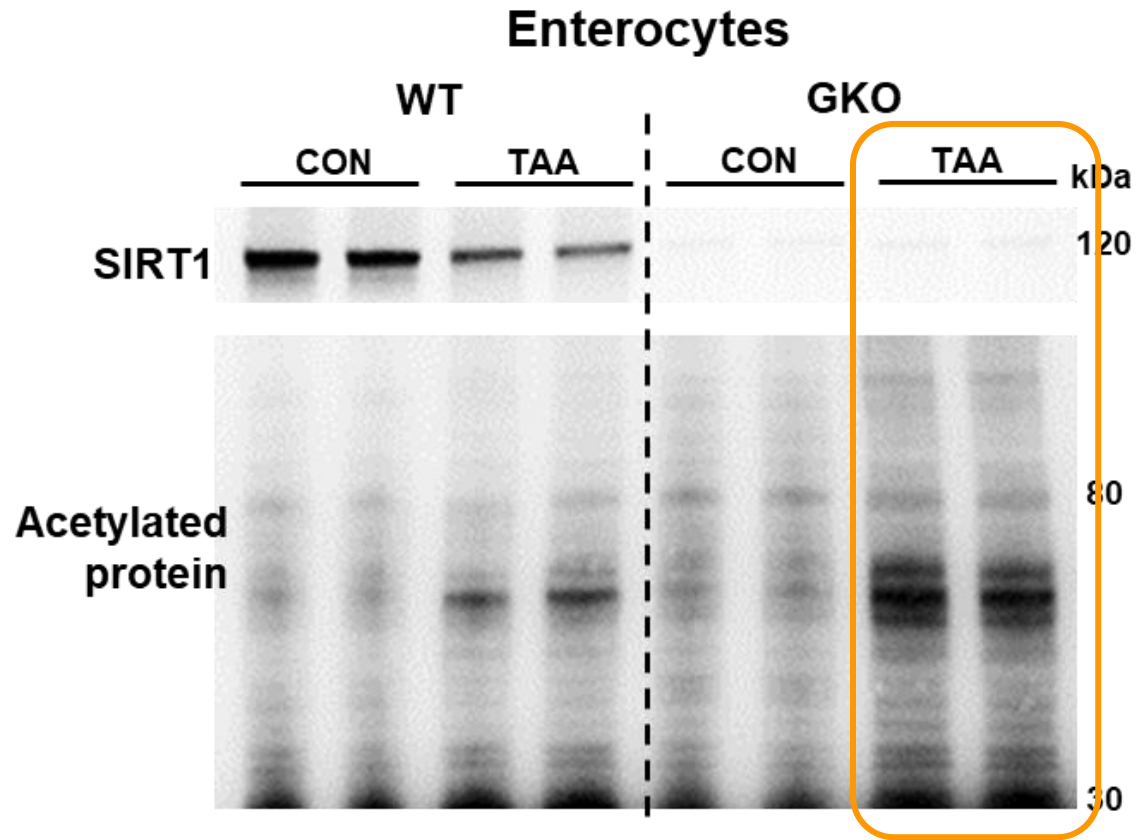
Increased **liver** injury markers in TAA-treated **GKO** mice



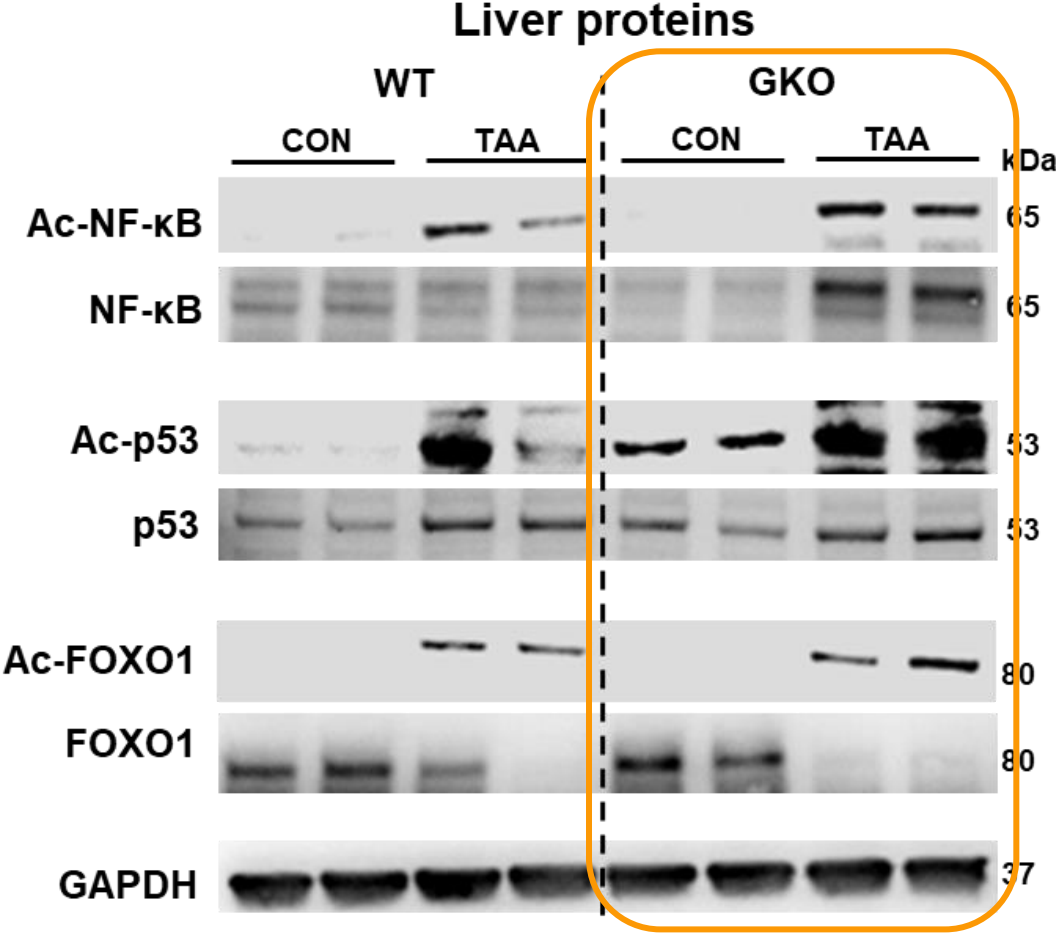
GKO mice are susceptible to TAA-induced liver fibrosis



Increased **gut** and **liver** protein acetylation in **GKO** mice



Increased acetylation of Sirt1-targeted proteins in **GKO** mice

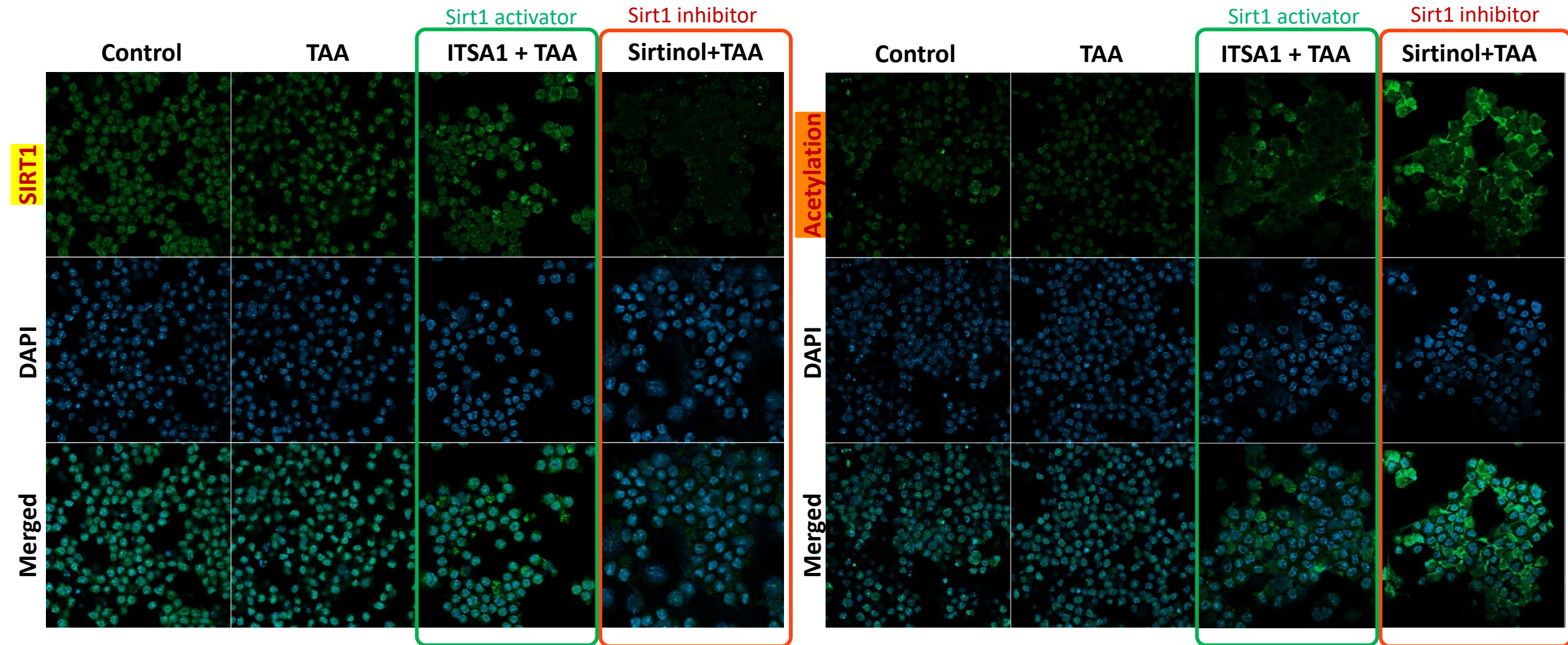


***In vitro* study?**

Decreased Sirt1 & increased protein acetylation in hepatocytes

Hepatic AML12 cells

Hepatic AML12 cells



Decreased **intestinal** Sirt1 expression – improved by **Melatonin**

Human intestinal T84 cells

Human intestinal T84 cells

Sirt1 activator

Sirt1 inhibitor

Sirt1 activator

Sirt1 inhibitor

Control

TAA

ITSA1 + TAA

Sirtinol+TAA

MT

MT+TAA

ITSA1+MT+TAA

Sirtinol+MT+TAA

SIRT1

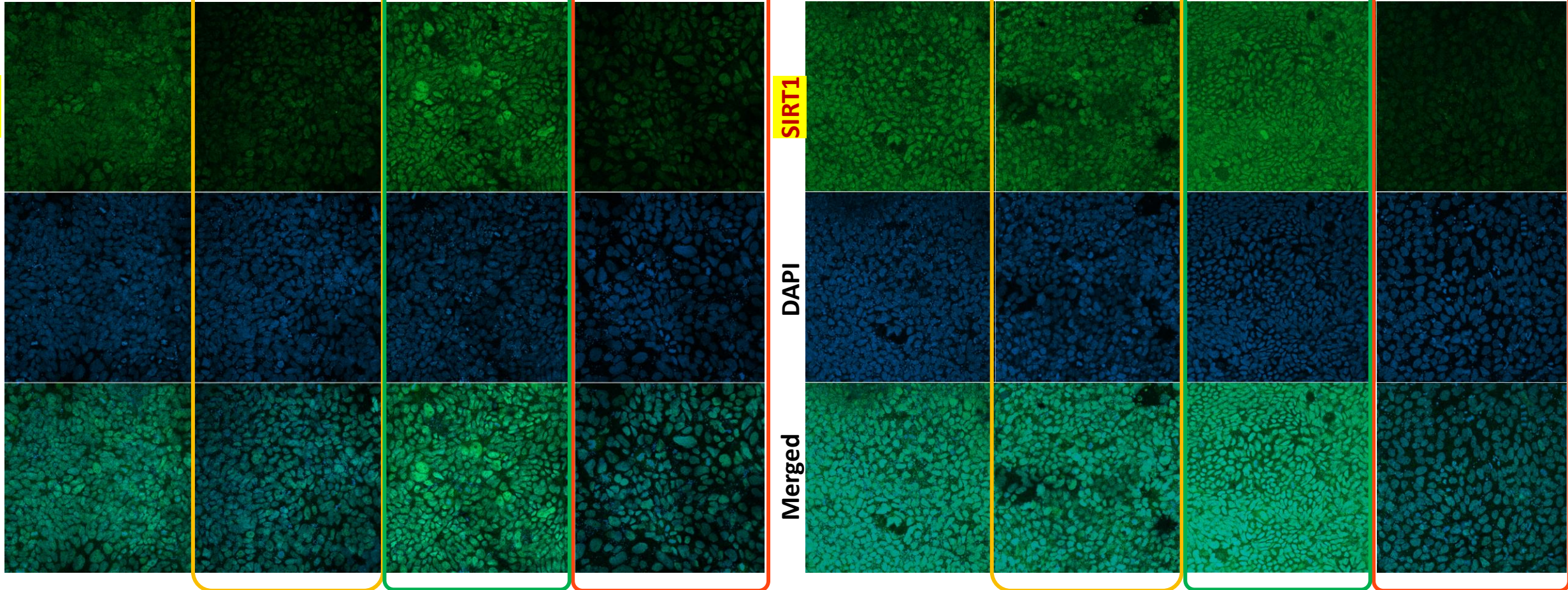
SIRT1

DAPI

DAPI

Merged

Merged



Decreased **intestinal** TJ/AJ expression – improved by **Melatonin**

Human intestinal T84 cells

Human intestinal T84 cells

Sirt1 activator

Sirt1 inhibitor

Sirt1 activator

Sirt1 inhibitor

Control

TAA

ITSA1 + TAA

Sirtinol+TAA

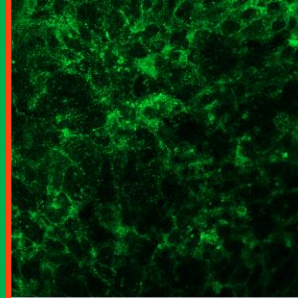
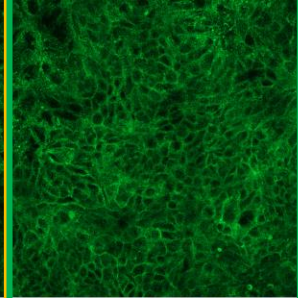
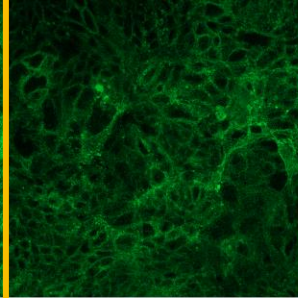
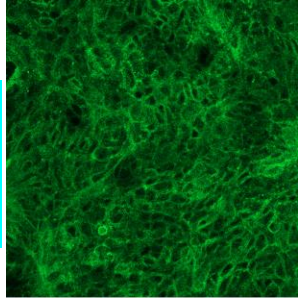
MT

MT+TAA

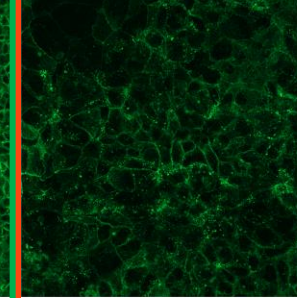
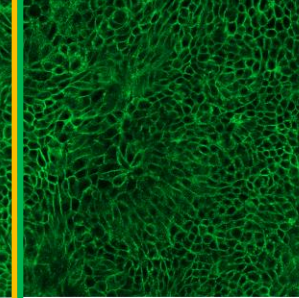
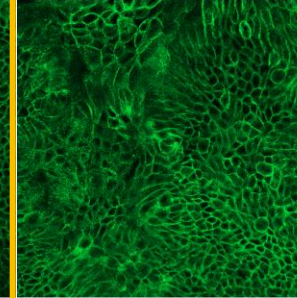
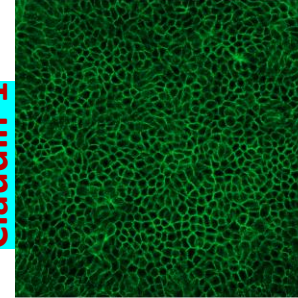
ITSA1+MT+TAA

Sirtinol+MT+TAA

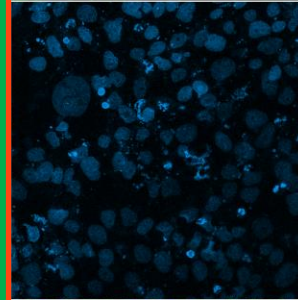
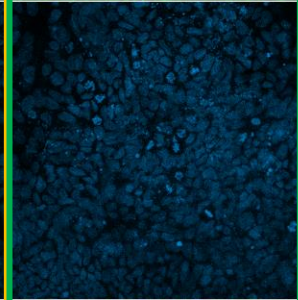
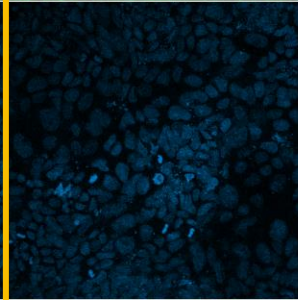
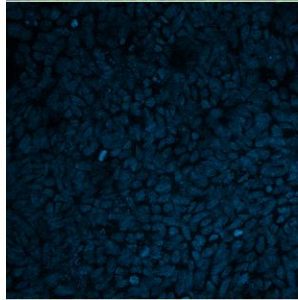
Claudin-1



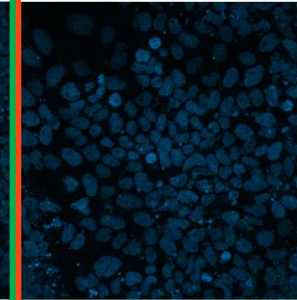
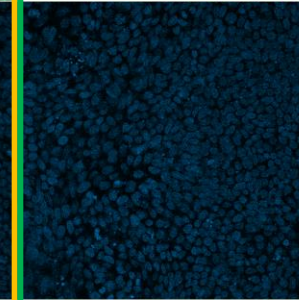
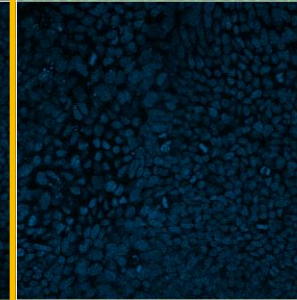
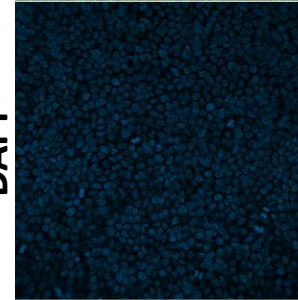
Claudin-1



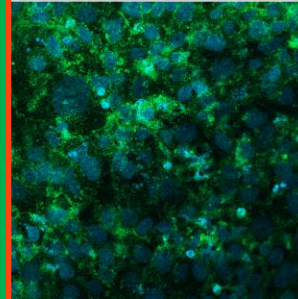
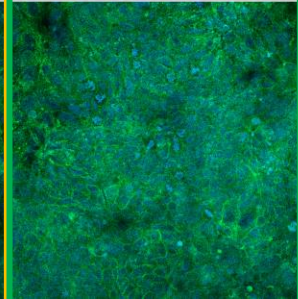
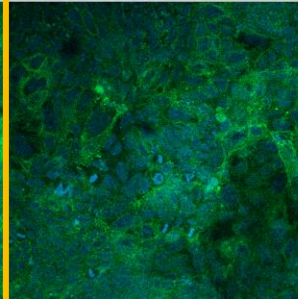
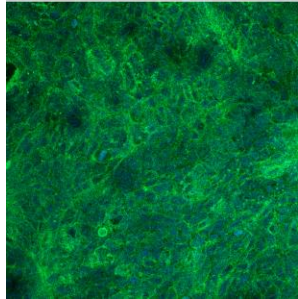
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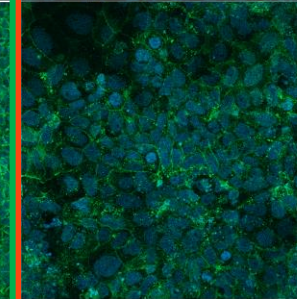
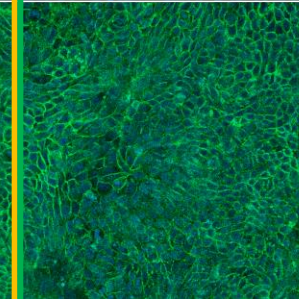
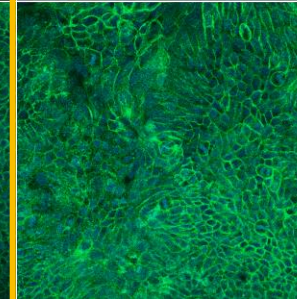
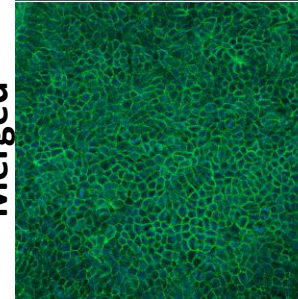
DAPI



Merged



Merged



Decreased **intestinal** TJ/AJ expression – improved by **Melatonin**

Human intestinal T84 cells

Human intestinal T84 cells

Sirt1 activator

Sirt1 inhibitor

Sirt1 activator

Sirt1 inhibitor

Control

TAA

ITSA1 + TAA

Sirtinol+TAA

MT

MT+TAA

ITSA1+MT+TAA

Sirtinol+MT+TAA

γ-Catenin

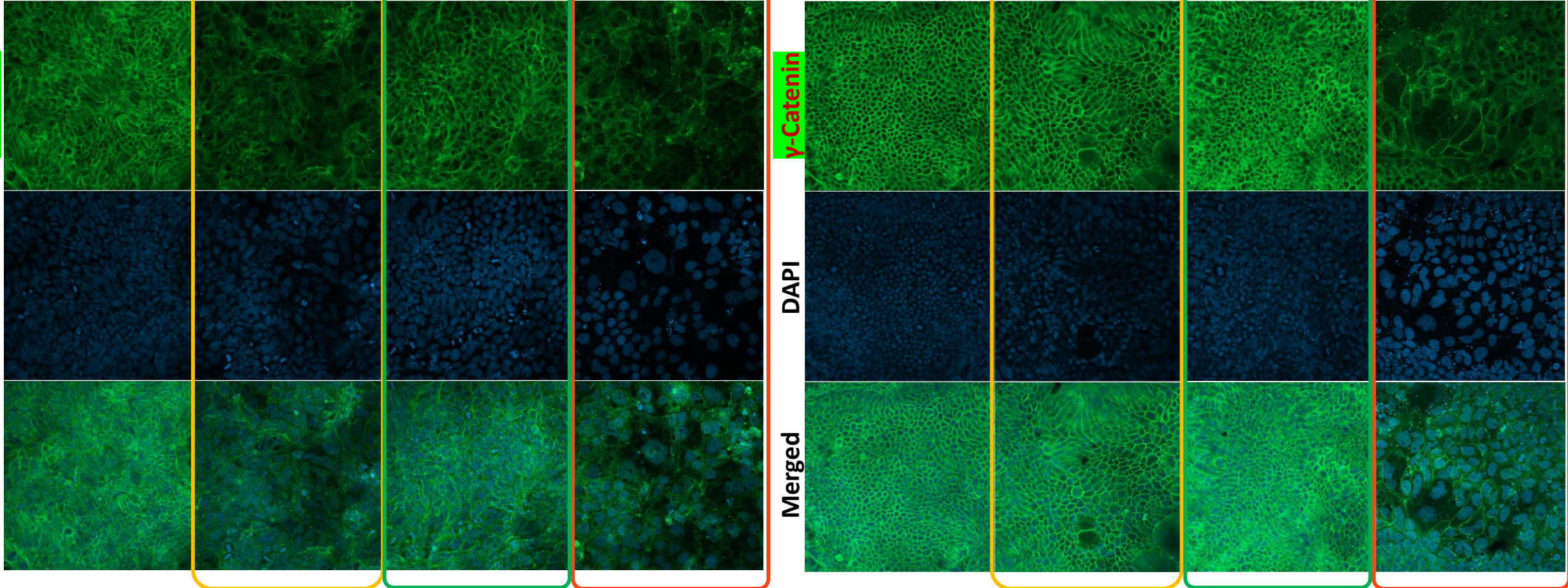
γ-Catenin

DAPI

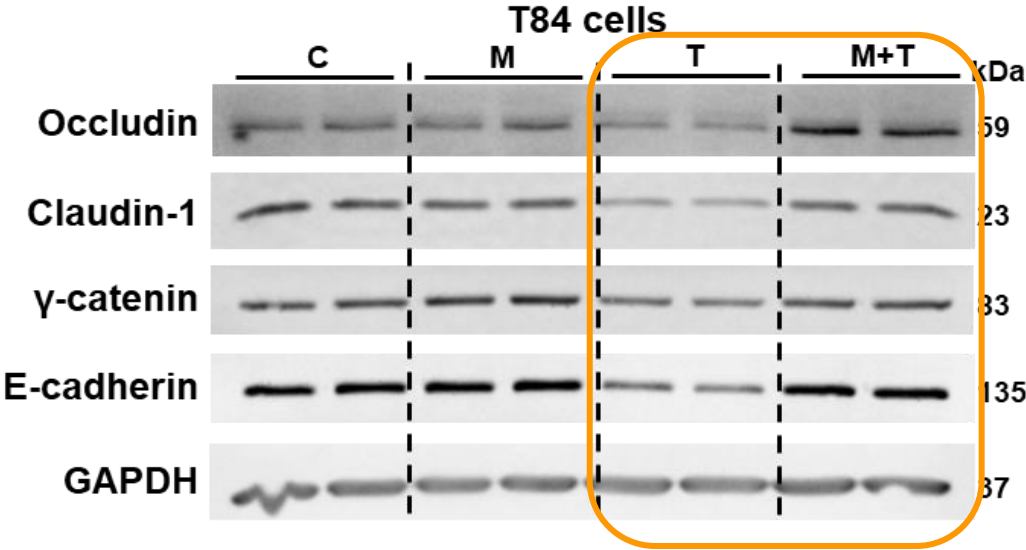
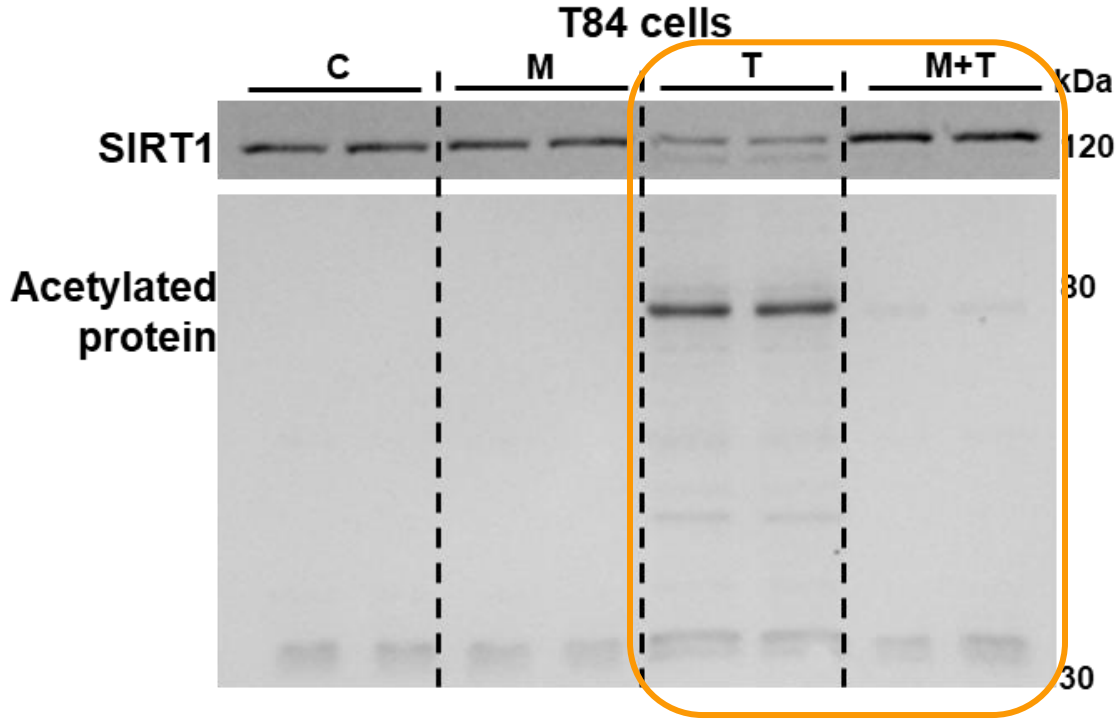
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Merged

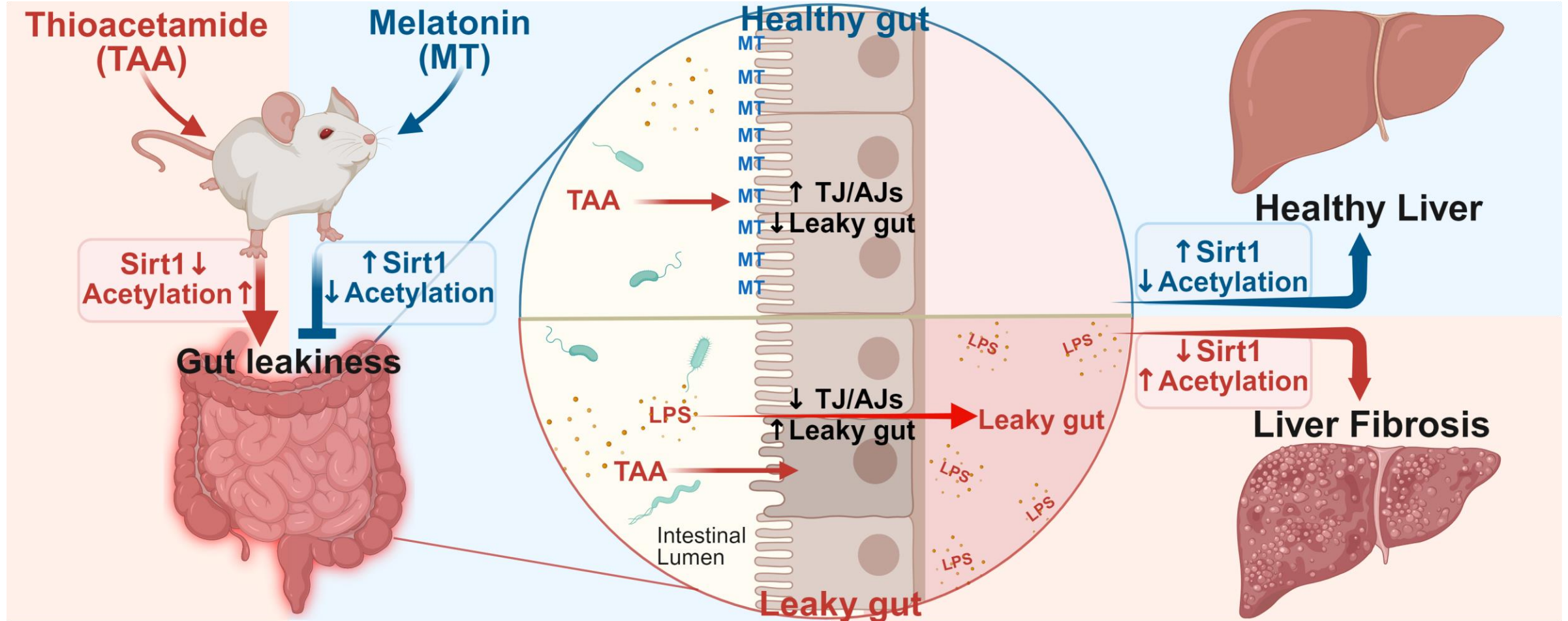
Merged



Decreased **intestinal** Sirt1 & TJ/AJ expression – improved by **Melatonin**



Melatonin Prevents Gut Leakiness and Liver Fibrosis Through the Gut–Liver Axis



★ Melatonin Prevents TAA–Induced Gut Leakiness and Liver Fibrosis Through the Gut–Liver Axis via Modulating Sirt1-Related Deacetylation of Gut Junctional Complex and Hepatic Proteins.

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*Thank
you*

