The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

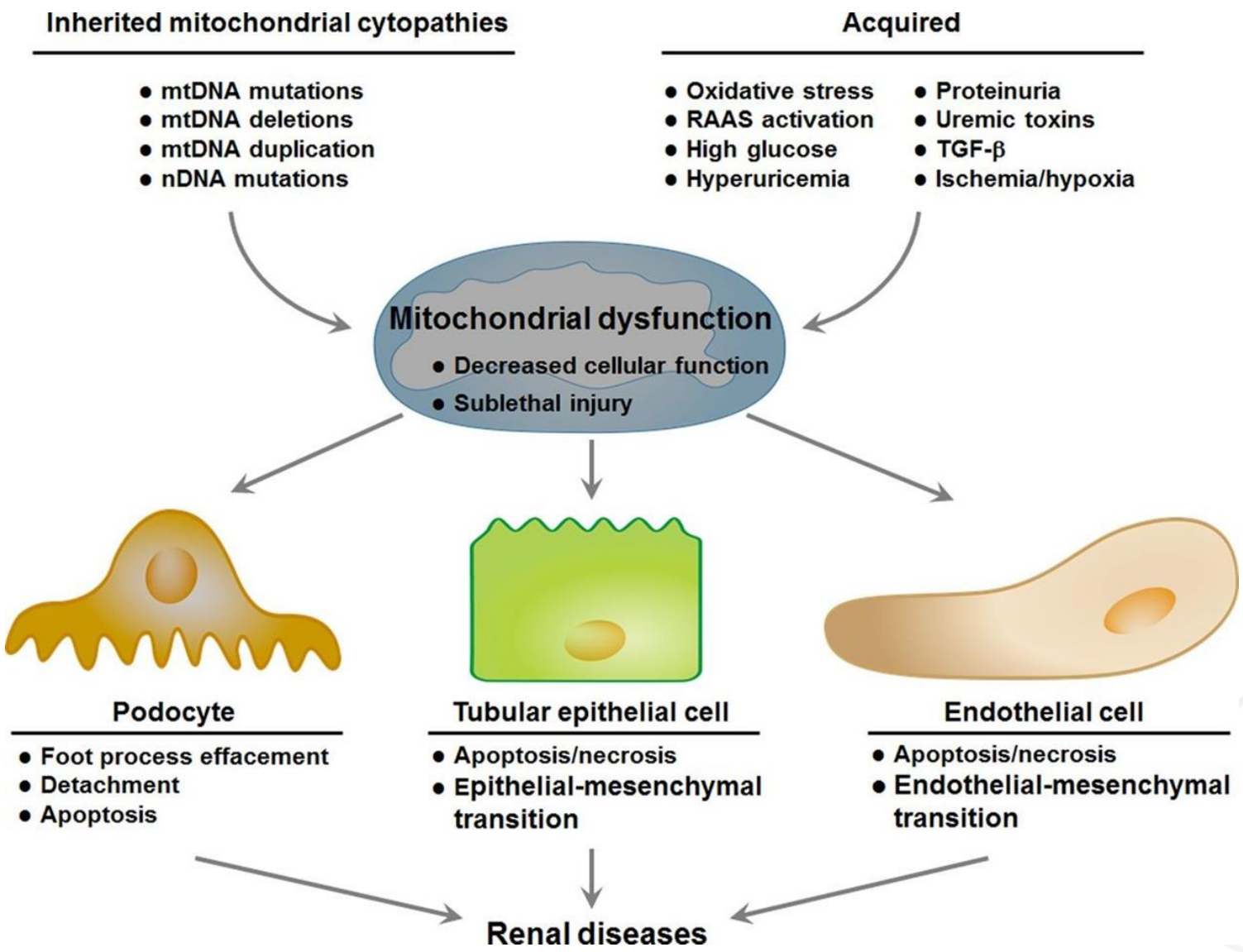
12-15 December 2023
Homa Hotel, Tehran

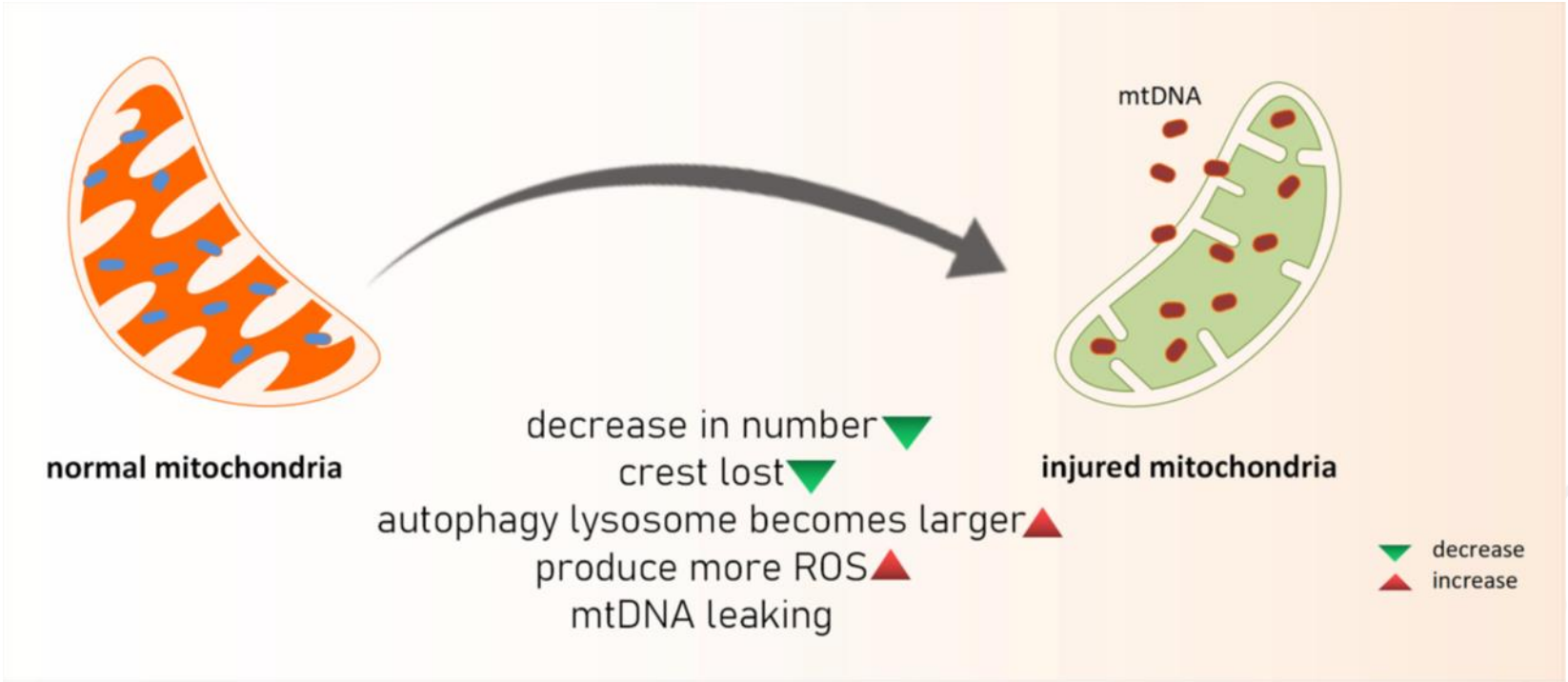
Mitochondrial damage & kidney diseases

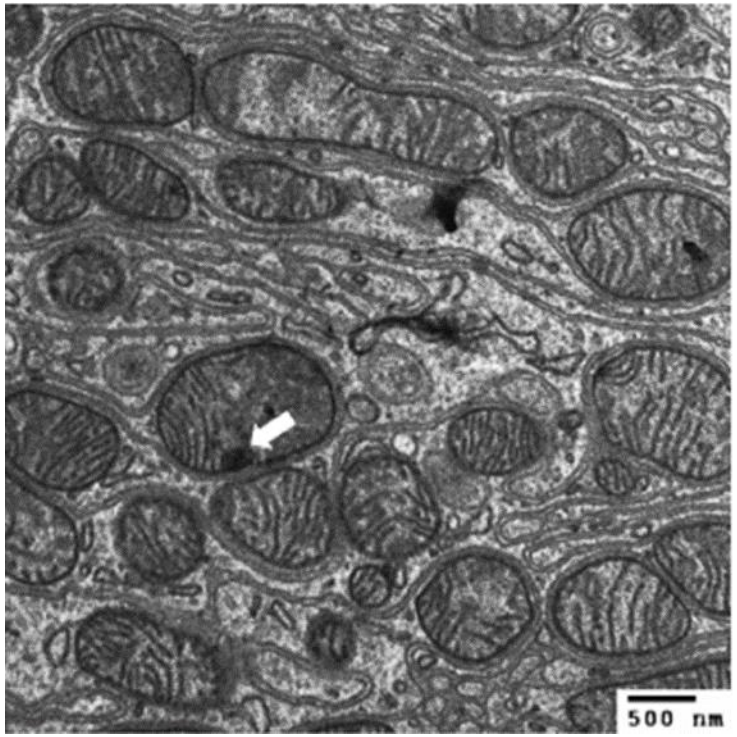
By :farhad khoshjou

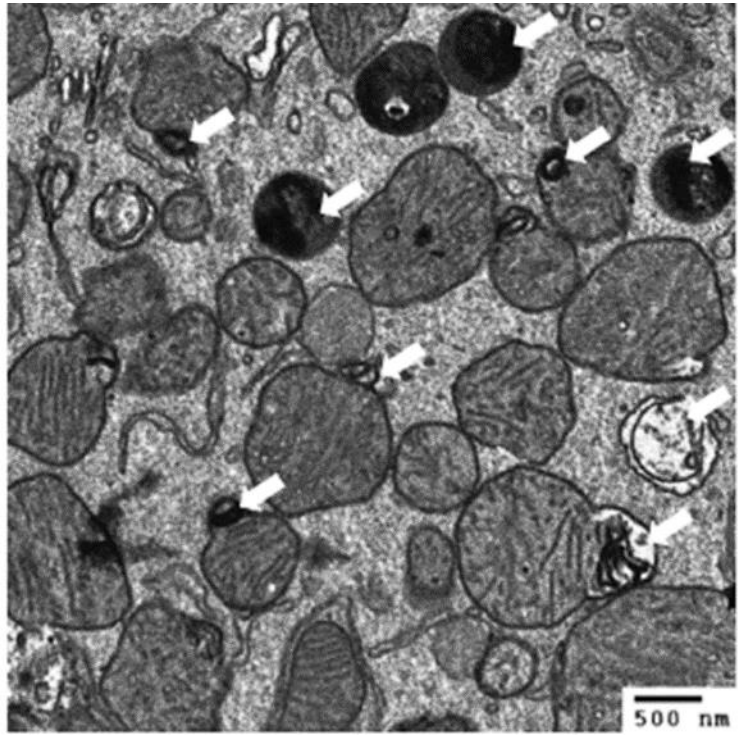
nephrologist

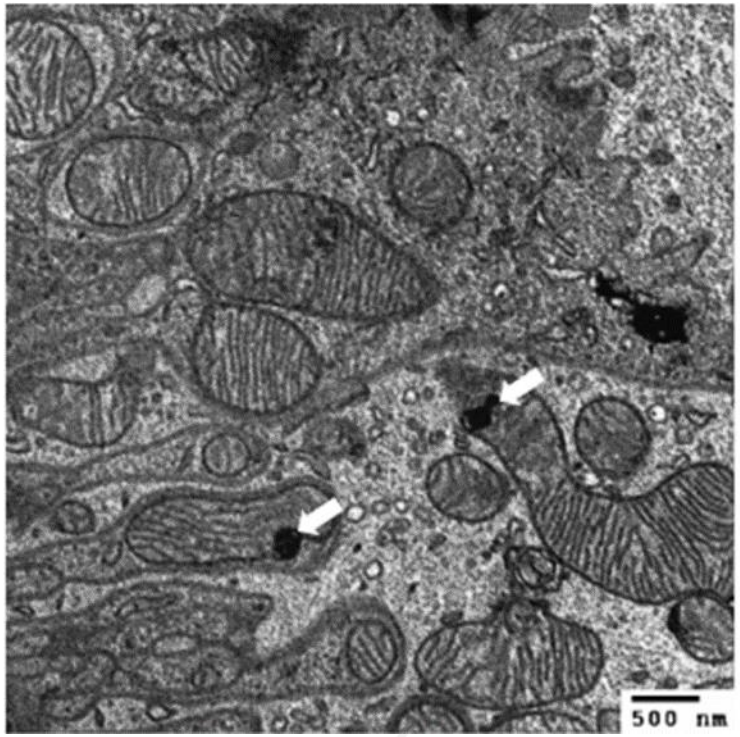
TEHRAN 2023


Inherited mitochondrial cytopathies
• mtDNA mutations
• mtDNA deletions
• mtDNA duplication
• nDNA mutations
Acquired
• Oxidative stress
• RAAS activation
• High glucose
• Hyperuricemia
• Proteinuria
• Uremic toxins
• TGF-β
• Ischemia/hypoxia
Mitochondrial dysfunction
• Decreased cellular function
• Sublethal injury
Podocyte
• Foot process effacement
• Detachment
• Apoptosis
Tubular epithelial cell
• Apoptosis/necrosis
• Epithelial-mesenchymal transition
Endothelial cell
• Apoptosis/necrosis
• Endothelial-mesenchymal transition
Renal diseases


mtDNA
normal mitochondria
decrease in number
crest lost
autophagy lysosome becomes larger
produce more ROS
mtDNA leaking
injured mitochondria
decrease
increase


500 nm


500 nm

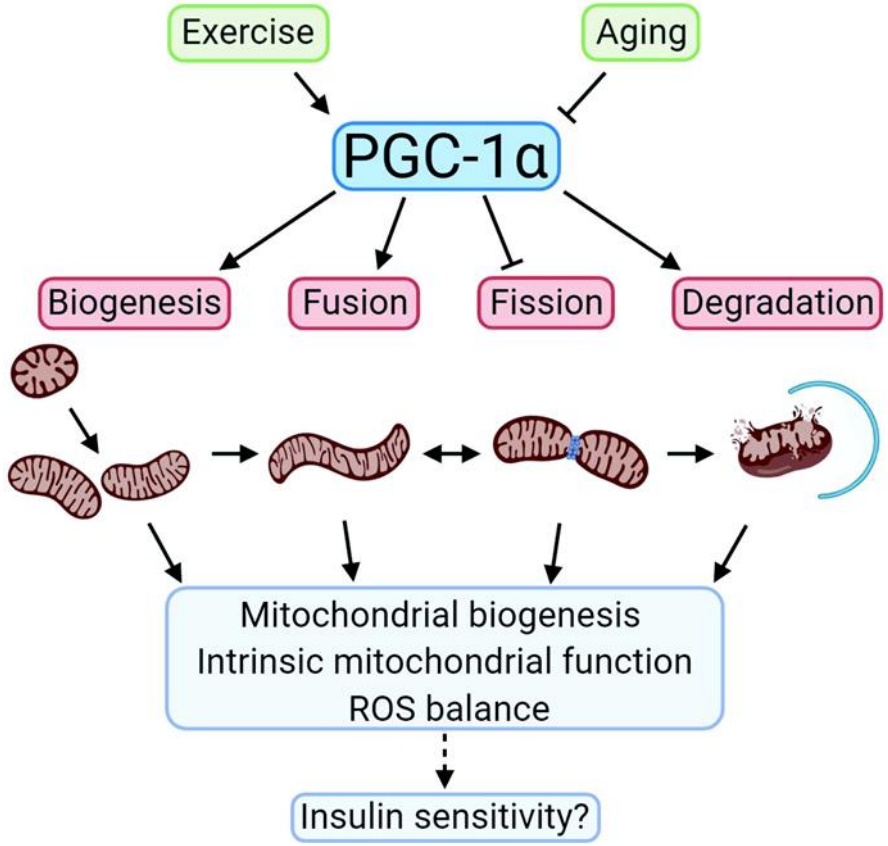

500 nm

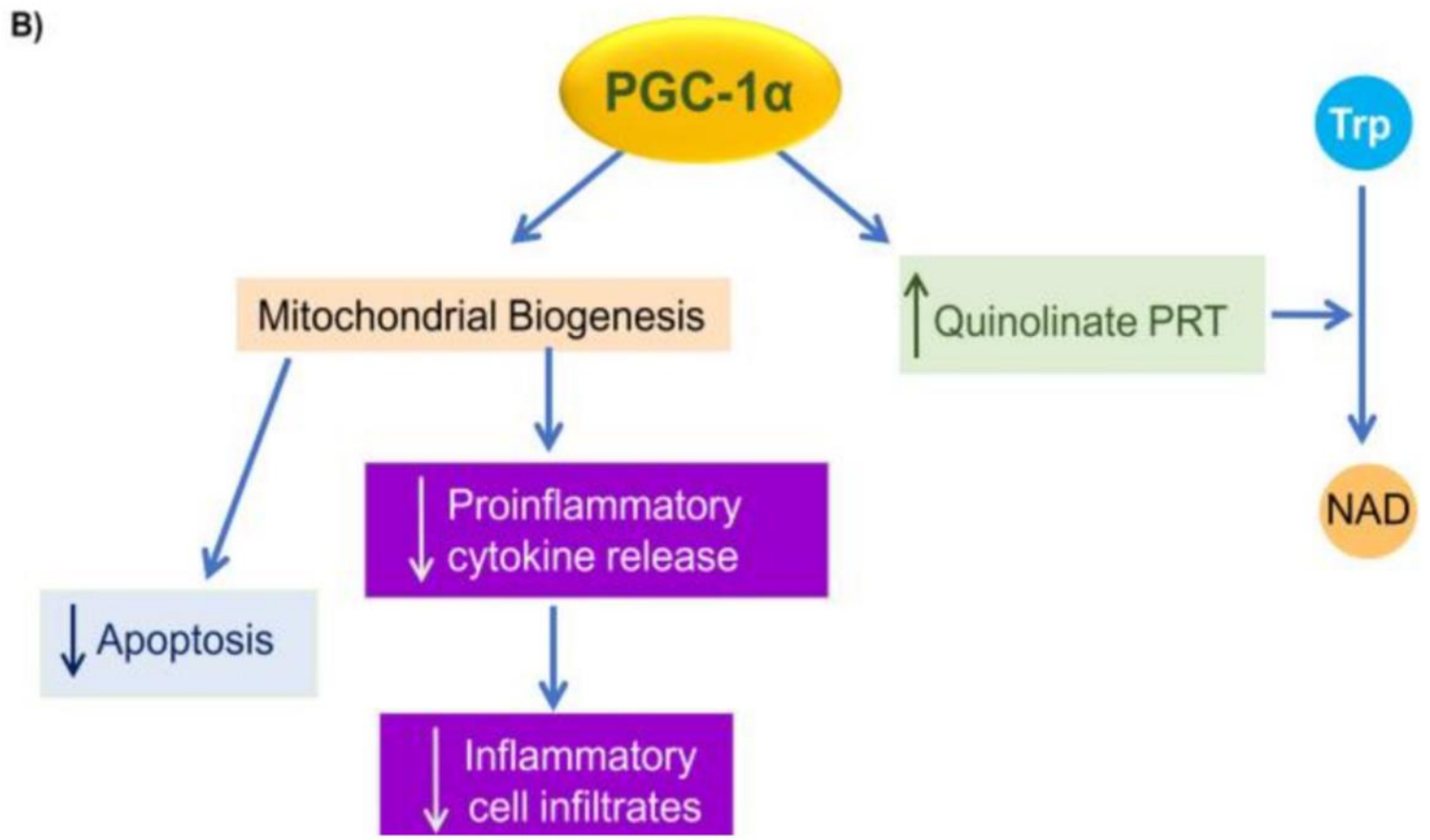
Important factors in mitochondria biogenesis

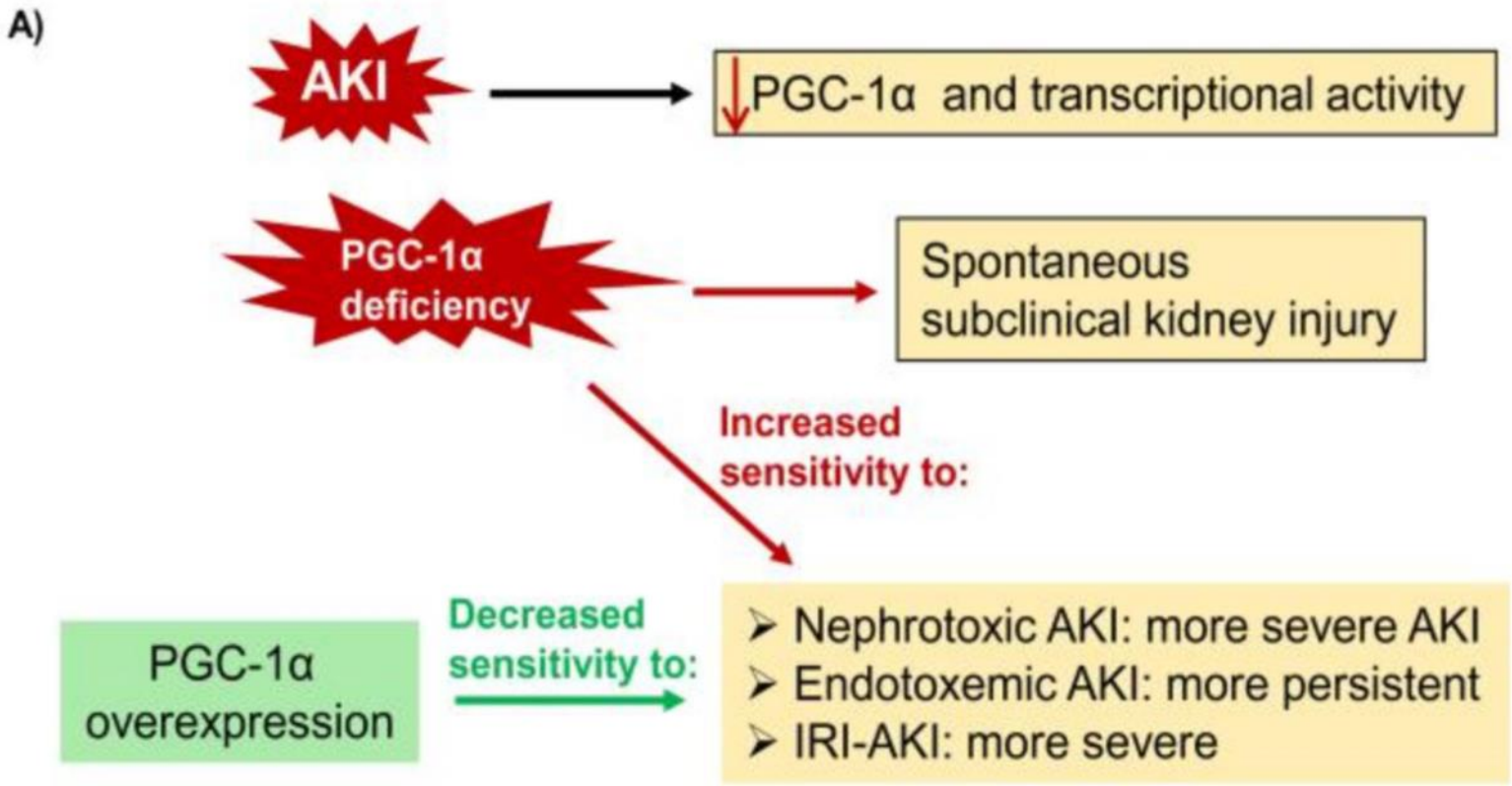
1) Peroxisome proliferator-activated receptor gamma coactivator 1-alpha(PGC-1α)

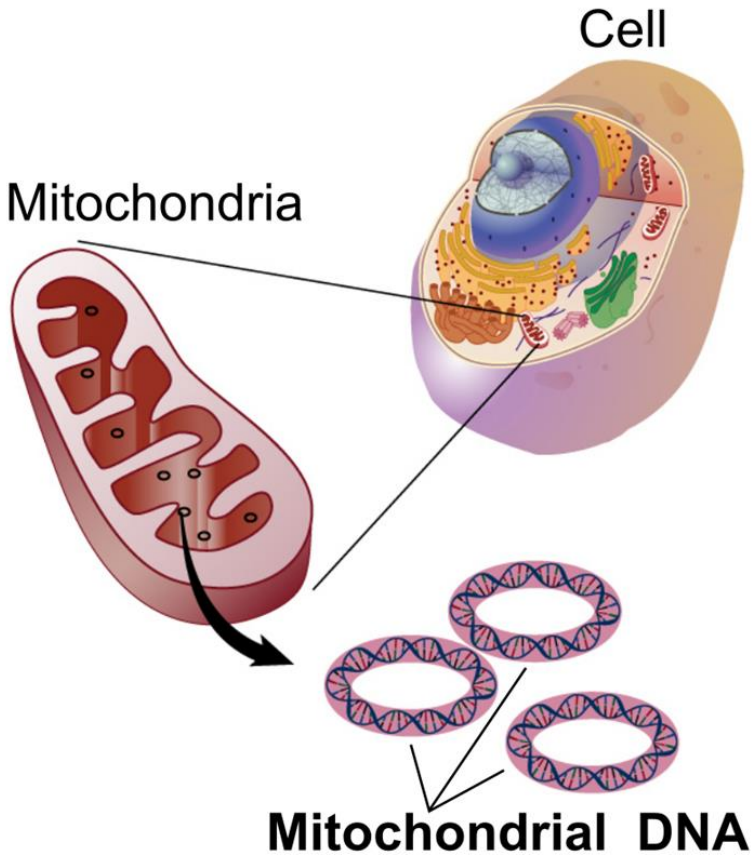
2) Mitochondria DNA(mtDNA)

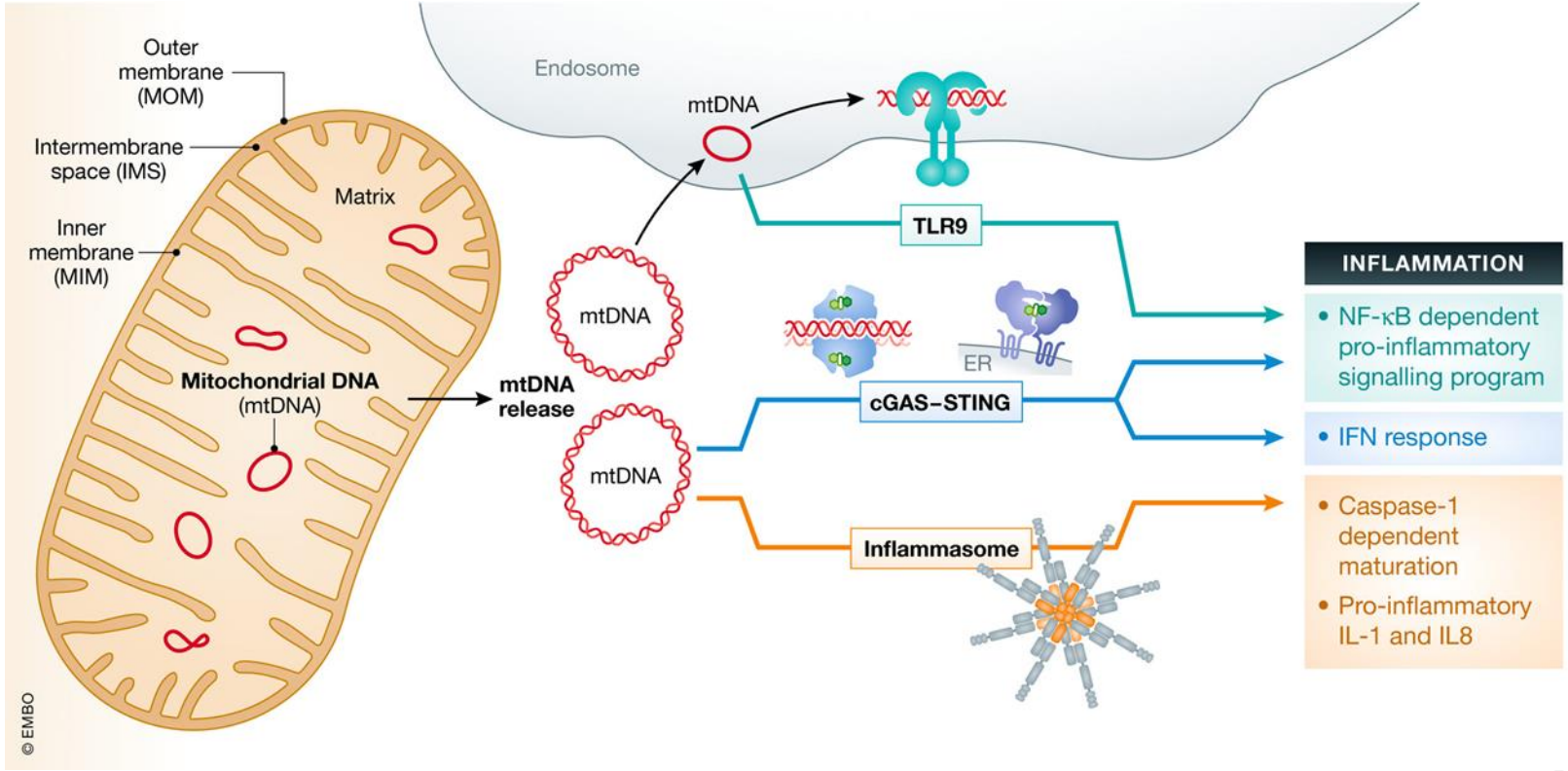
3) Transcription factor A of mitochondria(TFAM)

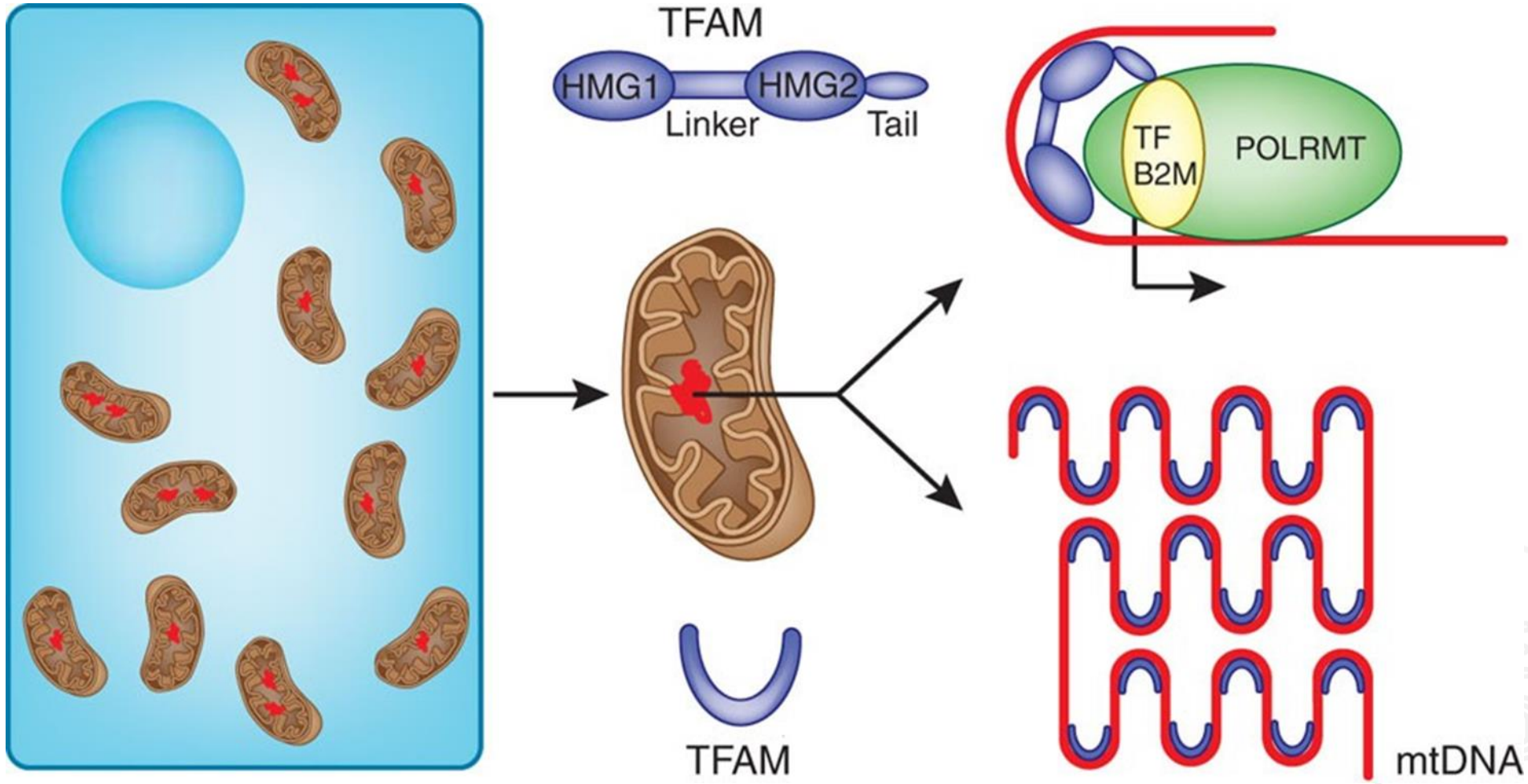

Exercise
Aging
PGC-1α
Biogenesis
Fusion
Fission
Degradation
Mitochondrial biogenesis
Intrinsic mitochondrial function
ROS balance
Insulin sensitivity?

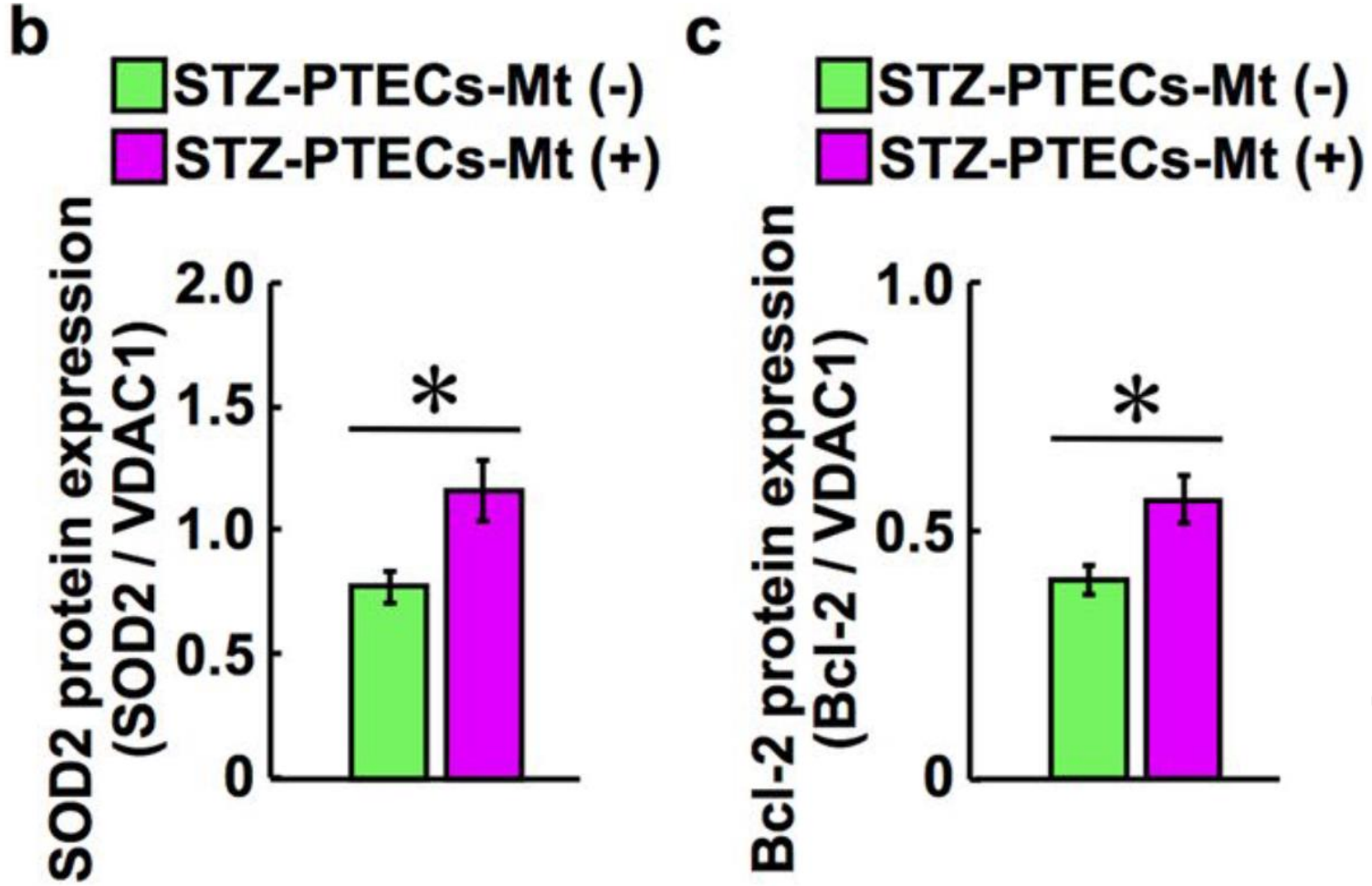

B)
PGC-1α
Trp
Mitochondrial Biogenesis
Quinolinate PRT
Proinflammatory cytokine release
NAD
Apoptosis
Inflammatory cell infiltrates

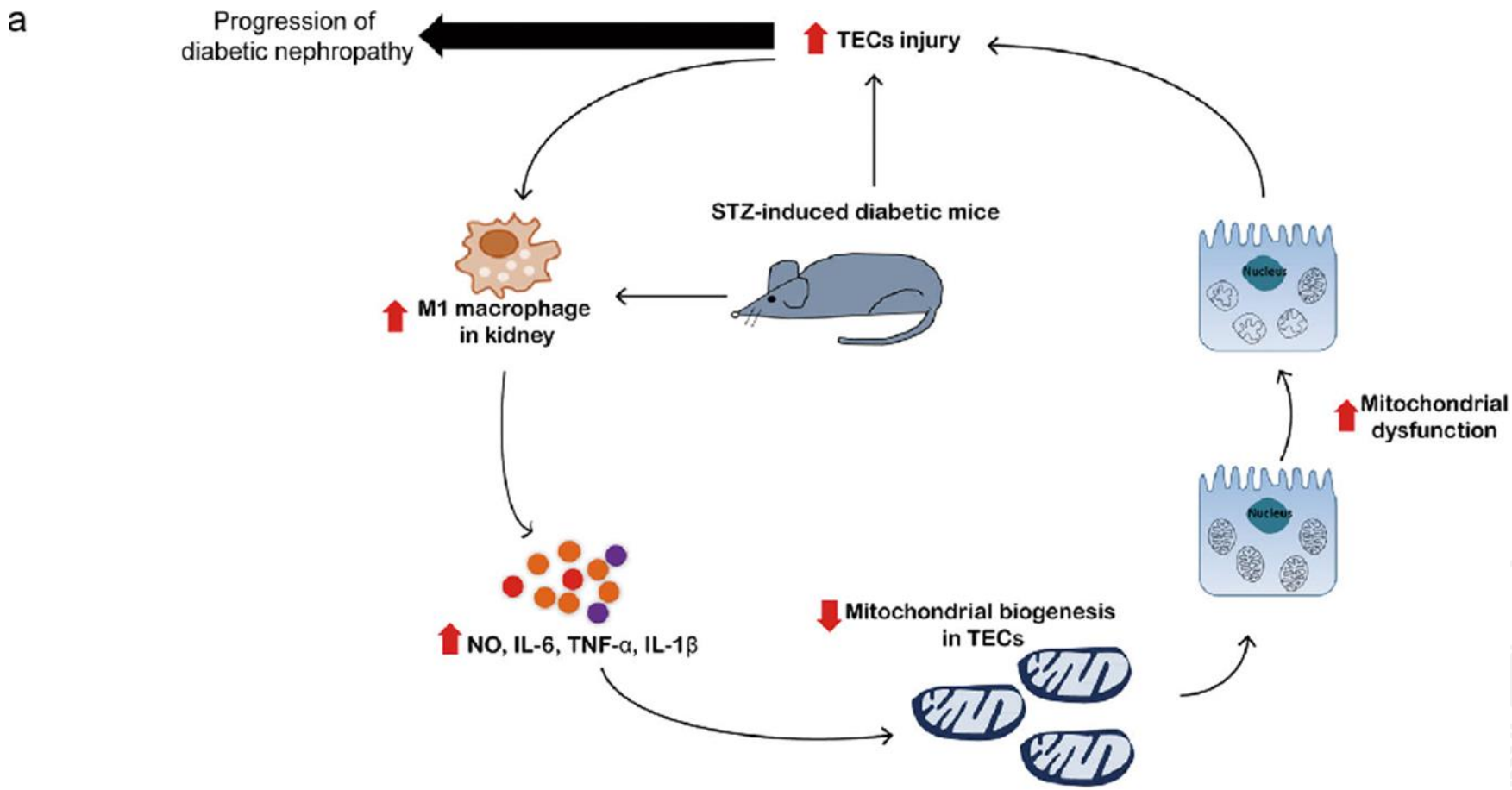

A)
AKI
PGC-1α and transcriptional activity
PGC-1α deficiency
Spontaneous subclinical kidney injury
Increased sensitivity to:
PGC-1α overexpression
Decreased sensitivity to:
Nephrotoxic AKI: more severe AKI
Endotoxemic AKI: more persistent
IRI-AKI: more severe

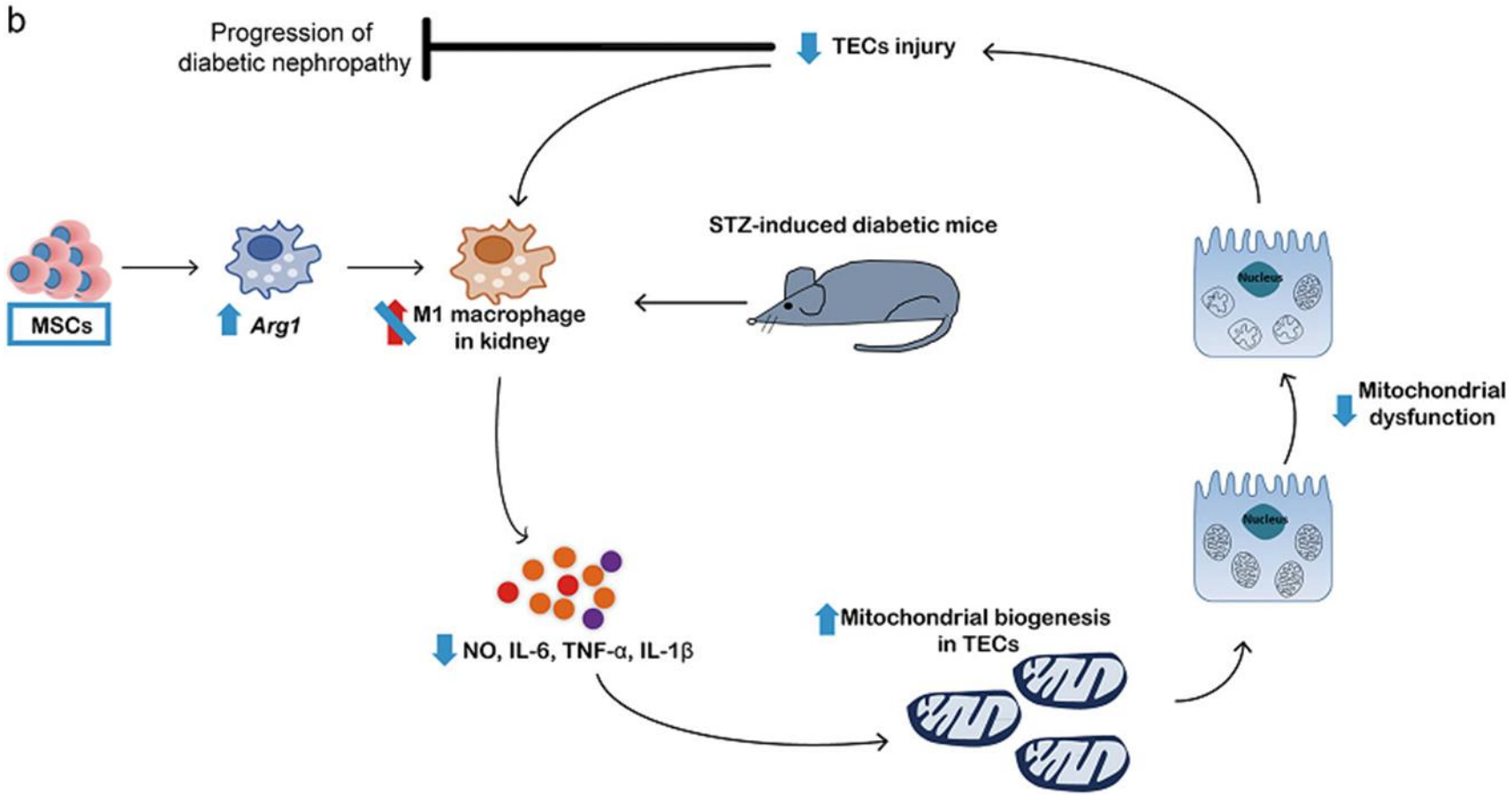

Cell
Mitochondria
Mitochondrial DNA

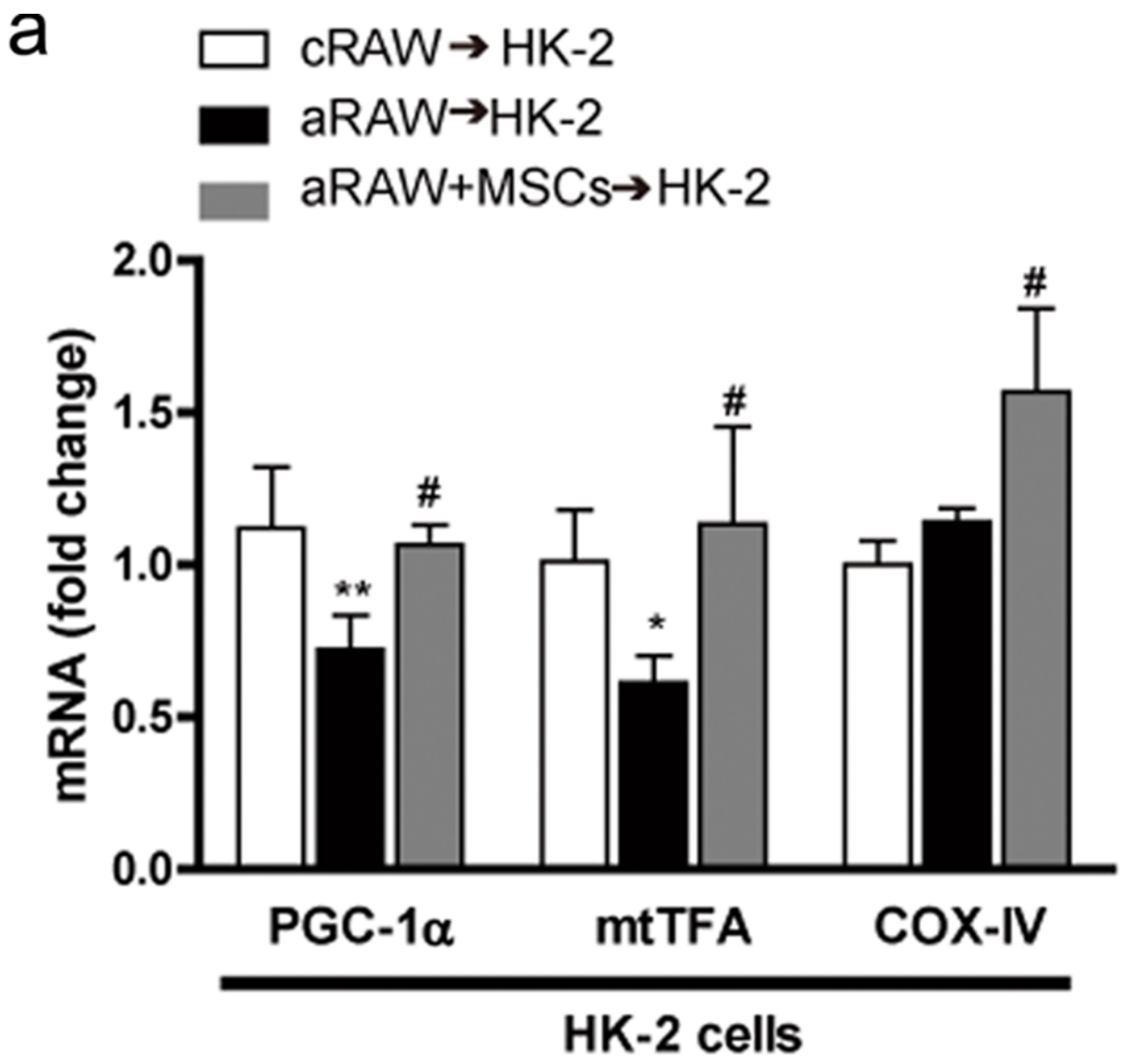

Outer membrane (MOM)
Intermembrane space (IMS)
Inner membrane (MIM)
Matrix
Mitochondrial DNA (mtDNA)
mtDNA release
Endosome
mtDNA
TLR9
cGAS–STING
ER
Inflammasome
INFLAMMATION
• NF-κB dependent pro-inflammatory signalling program
• IFN response
• Caspase-1 dependent maturation
• Pro-inflammatory IL-1 and IL8
© EMBO


TFAM
HMG1
HMG2
Linker
Tail
TF
B2M
POLRMT
TFAM
mtDNA


b
STZ-PTECs-Mt (-)
STZ-PTECs-Mt (+)
SOD2 protein expression
(SOD2 / VDAC1)
2.0
1.5
1.0
0.5
0
*
c
STZ-PTECs-Mt (-)
STZ-PTECs-Mt (+)
Bcl-2 protein expression
(Bcl-2 / VDAC1)
1.0
0.5
0
*

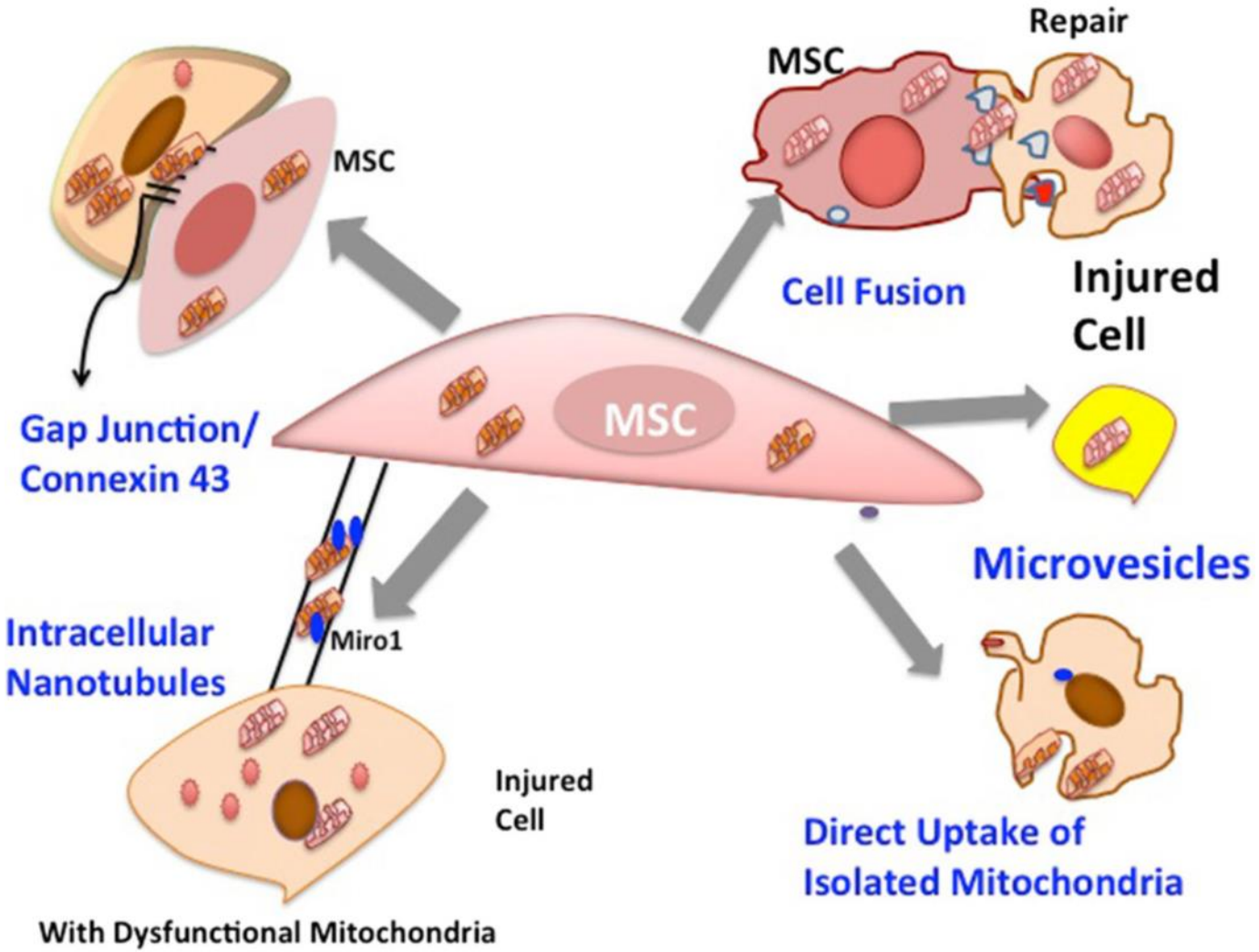

a
Progression of diabetic nephropathy
TECs injury
STZ-induced diabetic mice
M1 macrophage in kidney
Nucleus
Mitochondrial dysfunction
Nucleus
NO, IL-6, TNF-α, IL-1β
Mitochondrial biogenesis in TECs


b
Progression of diabetic nephropathy
TECs injury
STZ-induced diabetic mice
MSCs
Arg1
M1 macrophage in kidney
Nucleus
Mitochondrial dysfunction
Nucleus
NO, IL-6, TNF-α, IL-1β
Mitochondrial biogenesis in TECs

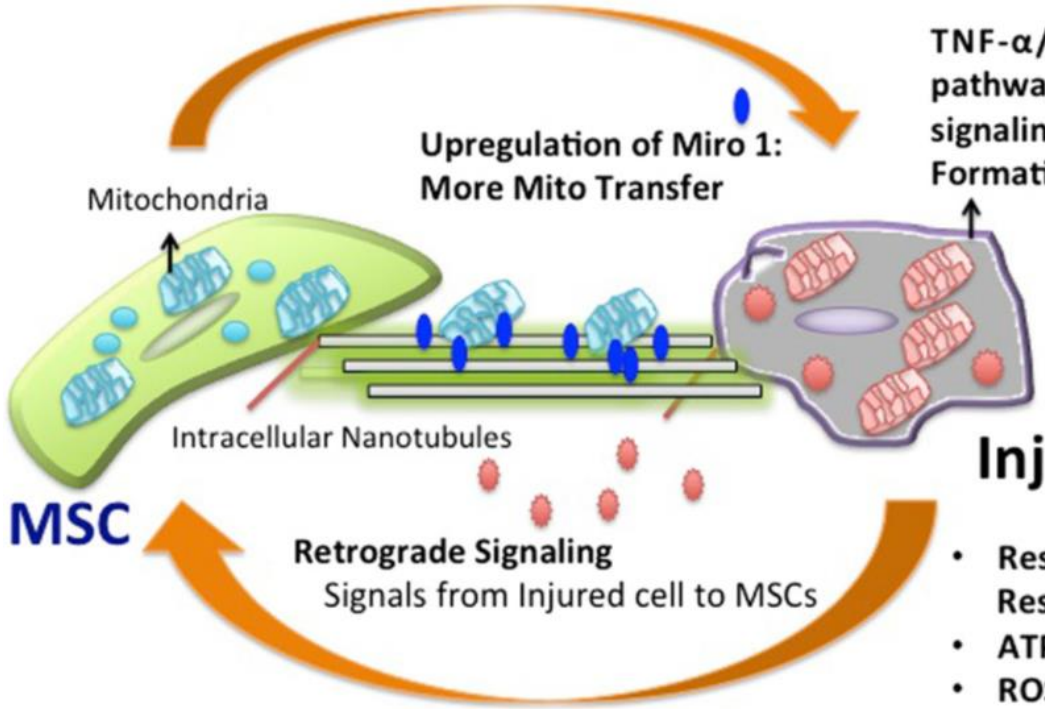

a
cRAW→HK-2
aRAW→HK-2
aRAW+MSCs→HK-2
mRNA (fold change)
2.0
1.5
1.0
0.5
0.0
**
*
#
#
#
PGC-1α
mtTFA
COX-IV
HK-2 cells


MITOCHONDRIAL TRANSFER

Different Modes of Mitochondria Transfer

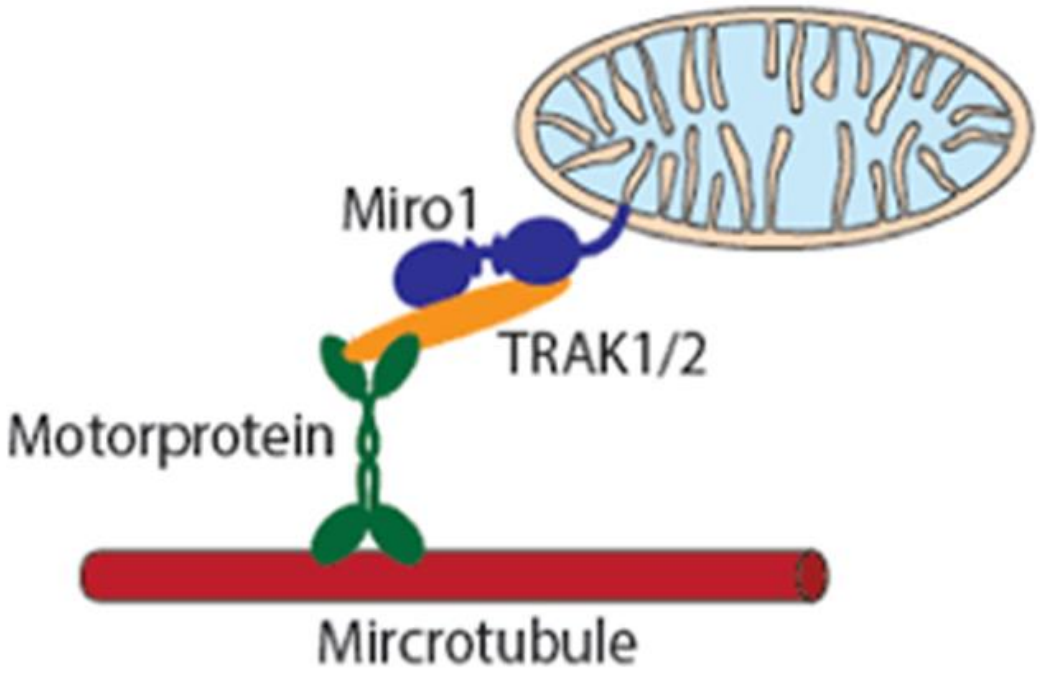


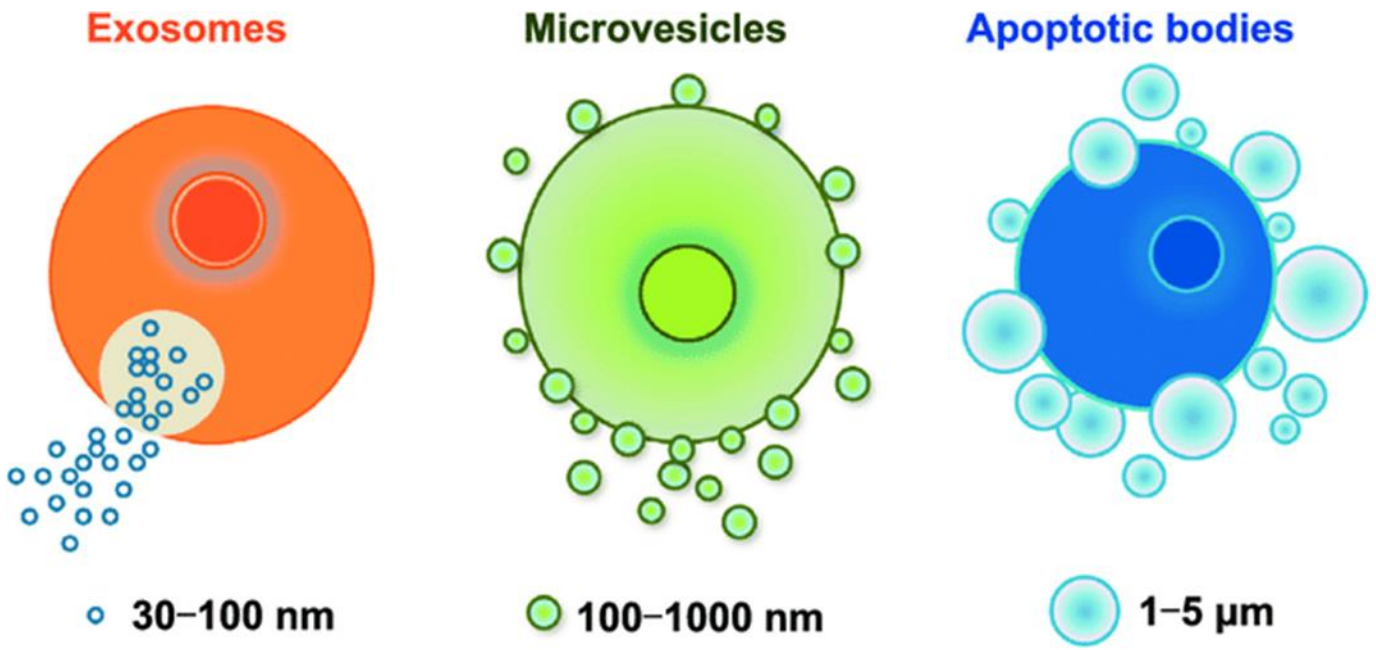
Mechanisms of Mitochondria Transfer

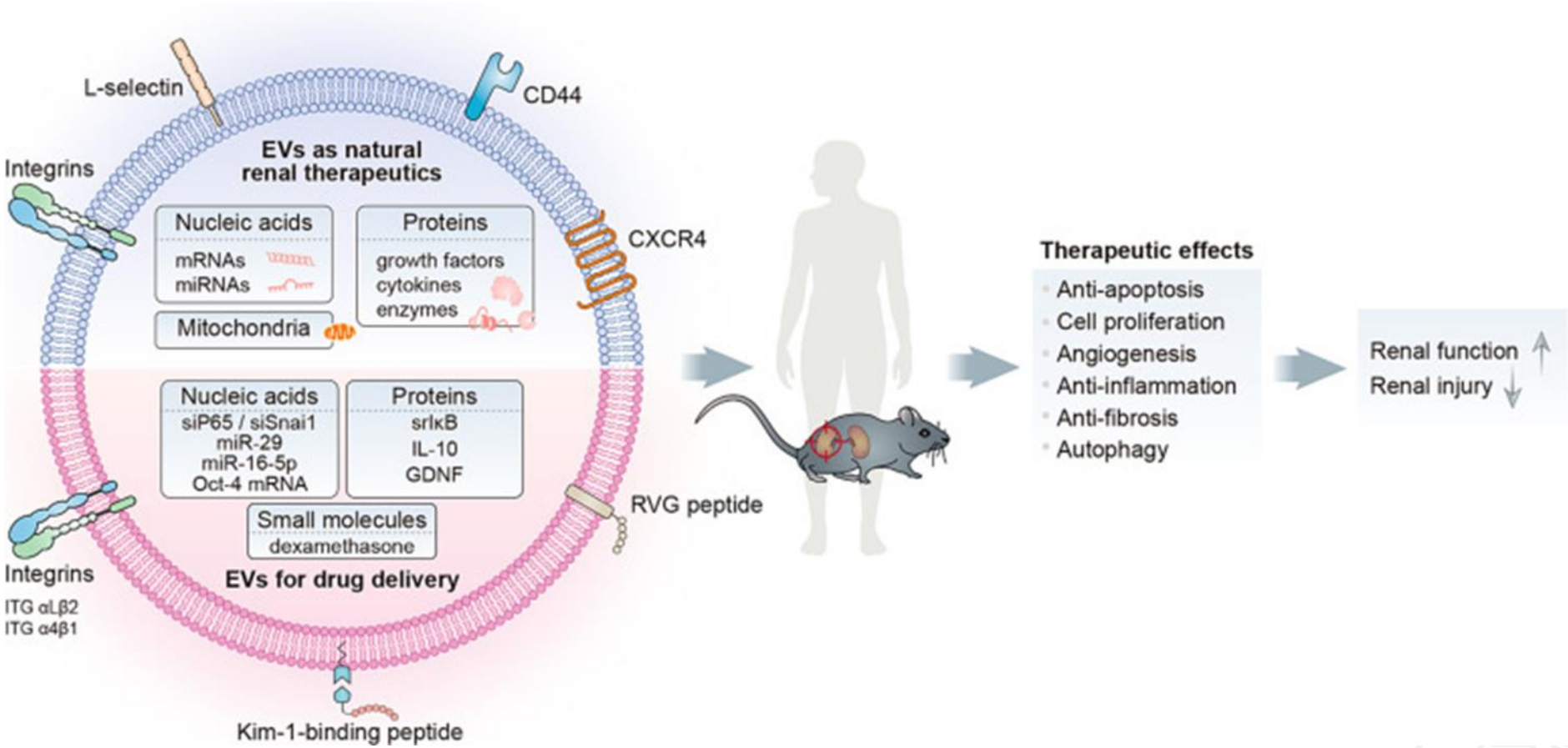


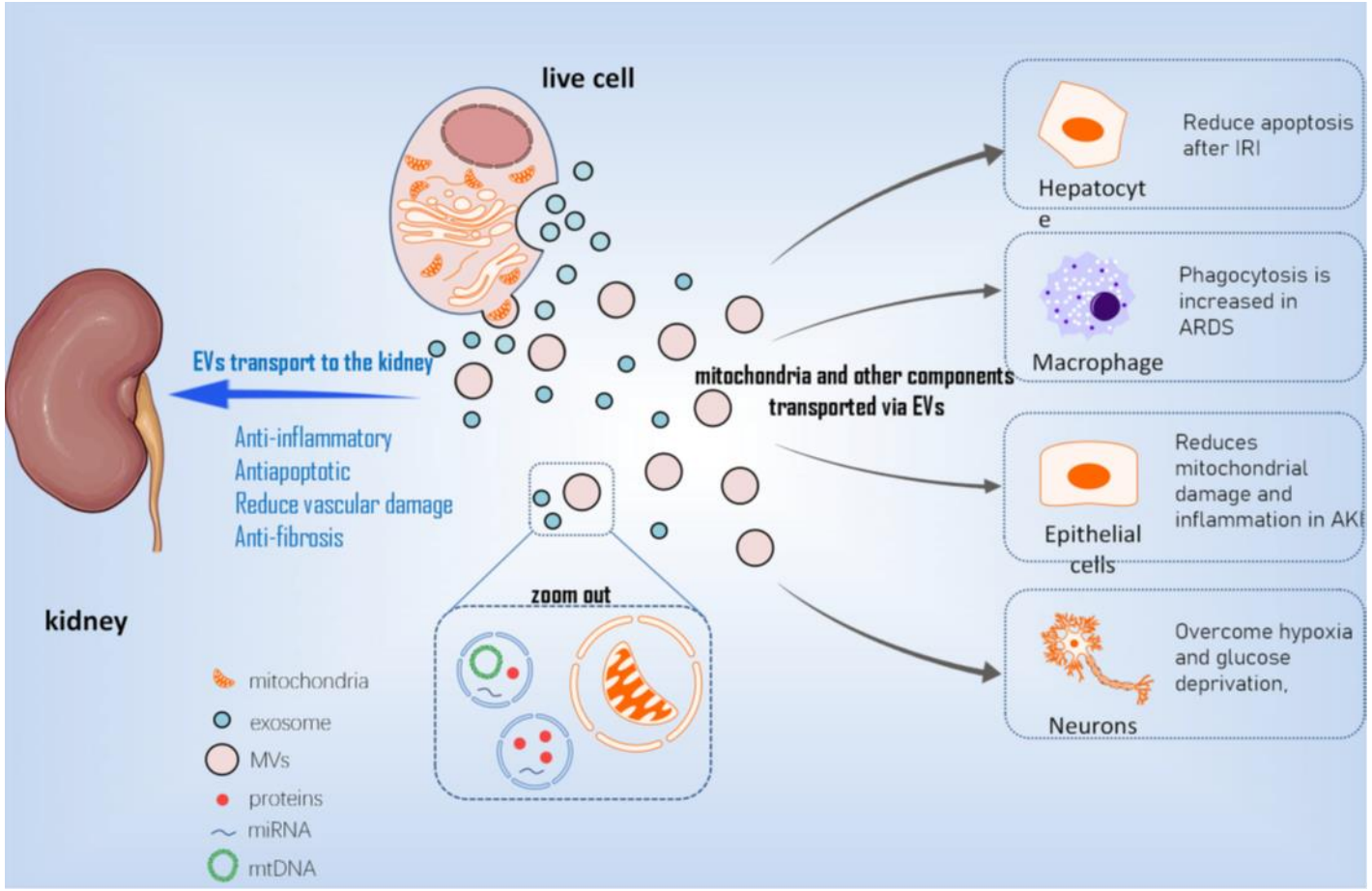
Injured Cell

- Restoration of Respiration
- ATP Levels Increases
- ROS Levels Reduced
- Increase in Mitochondrial Bioenergetics/ PGC-1 α upregulation


Miro1
TRAK1/2
Motorprotein
Mircrotubule


Exosomes
Microvesicles
Apoptotic bodies
30–100 nm
100–1000 nm
1–5 µm


L-selectin
CD44
Integrins
EVs as natural renal therapeutics
Nucleic acids
mRNAs
miRNAs
Proteins
growth factors
cytokines
enzymes
Mitochondria
CXCR4
Nucleic acids
siP65 / siSnai1
miR-29
miR-16-5p
Oct-4 mRNA
Proteins
srIκB
IL-10
GDNF
Small molecules
dexamethasone
RVG peptide
Integrins
ITG αLβ2
ITG α4β1
EVs for drug delivery
Kim-1-binding peptide
Therapeutic effects
Anti-apoptosis
Cell proliferation
Angiogenesis
Anti-inflammation
Anti-fibrosis
Autophagy
Renal function
Renal injury

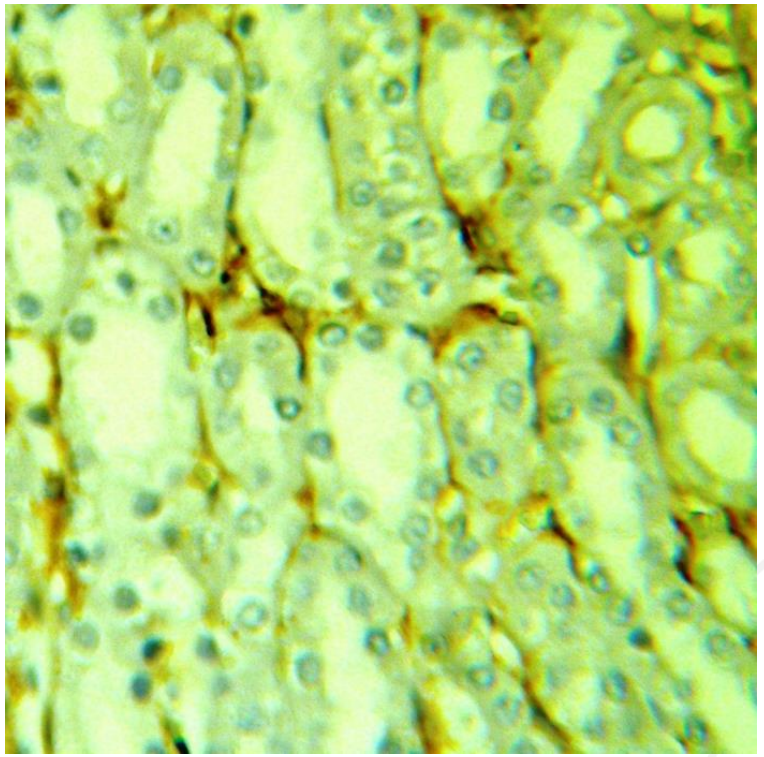

live cell
EVs transport to the kidney
Anti-inflammatory
Antiapoptotic
Reduce vascular damage
Anti-fibrosis
kidney
zoom out
mitochondria
exosome
MVs
proteins
miRNA
mtDNA
mitochondria and other components transported via EVs
Hepatocyte
Reduce apoptosis after IRI
Macrophage
Phagocytosis is increased in ARDS
Epithelial cells
Reduces mitochondrial damage and inflammation in AKI
Neurons
Overcome hypoxia and glucose deprivation.

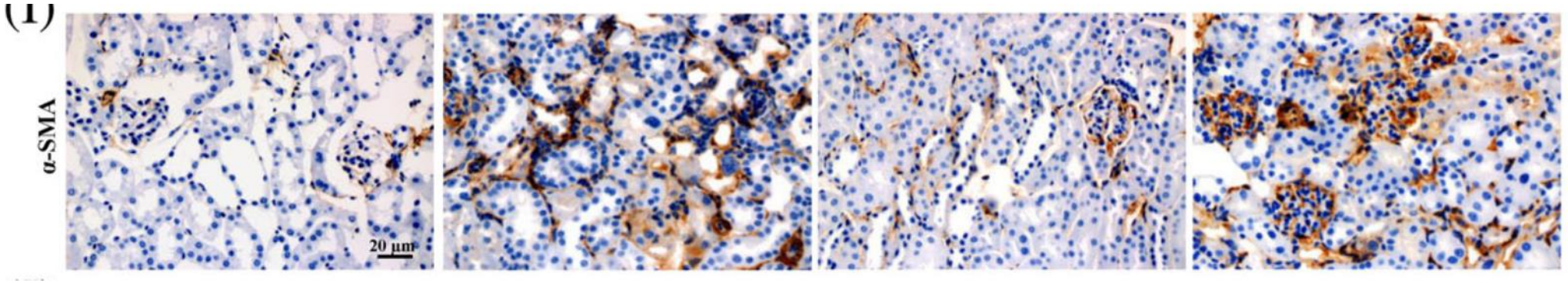
J Nephropathol. 2017;6(1): 1-4.

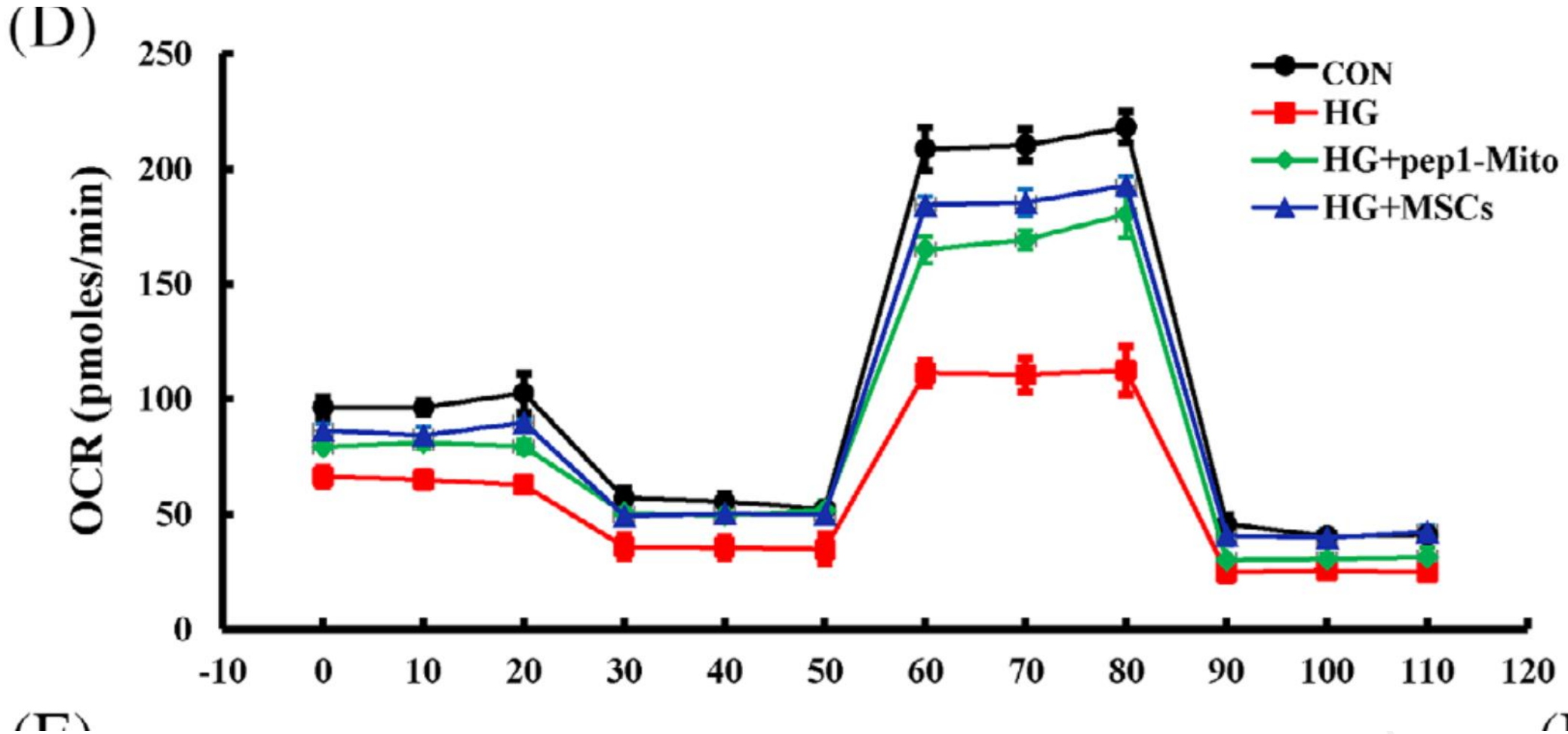
Tempol effect on epithelial-mesenchymal transition induced by hyperglycemia

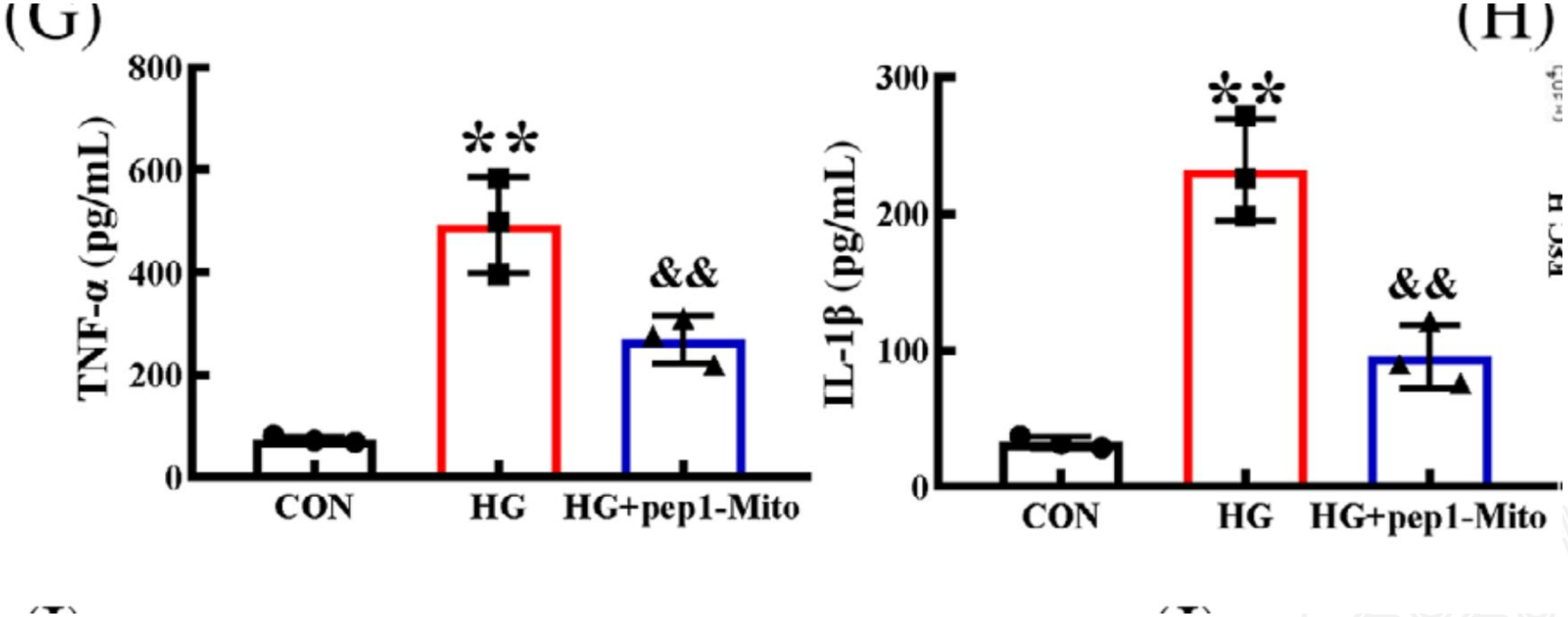
Mohammad Jafari 1, Farahnaz Dadras 2, Hamid Reza Ghadimipour 1, Mohamad Ali Seif Rabiei 3, Farhad Khoshjou 4*


b




(I)
α-SMA
20 μm


(D)
OCR (pmoles/min)
250
200
150
100
50
0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
CON
HG
HG+pep1-Mito
HG+MSCs
(E)
(E)


(G)
TNF-α (pg/mL)
800
600
400
200
0
**
&&
CON
HG
HG+pep1-Mito
(H)
IL-1β (pg/mL)
300
200
100
0
**
&&
CON
HG
HG+pep1-Mito

Mitochondrial Transfer into Human Oocytes Improved Embryo Quality and Clinical Outcomes in Recurrent Pregnancy Failure Cases

Yoshiharu Morimoto 1,* , Udayanga Sanath Kankanam Gamage 2, Takayuki Yamochi 3, Noriatsu Saeki 4,Naoharu Morimoto 5, Masaya Yamanaka 6, Akiko Koike 7, Yuki Miyamoto 7, Kumiko Tanaka 8, Aisaku Fukuda 9, Shu Hashimoto 3 and Ryuzo Yanagimachi 10

Conclusion: Mitochondrial transfer into human oocytes is an effective clinical option to enhance embryo quality in recurrent in vitro fertilization failure cases.


Thank you for
your attention