CNI NEPHROTOXICITY

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CNI

inhibition of calcineurin, a calcium- and calmodulin-dependent phosphatase .

these molecules bind to cyclophylin and FKBP12 for cyclosporine and tacrolimus.

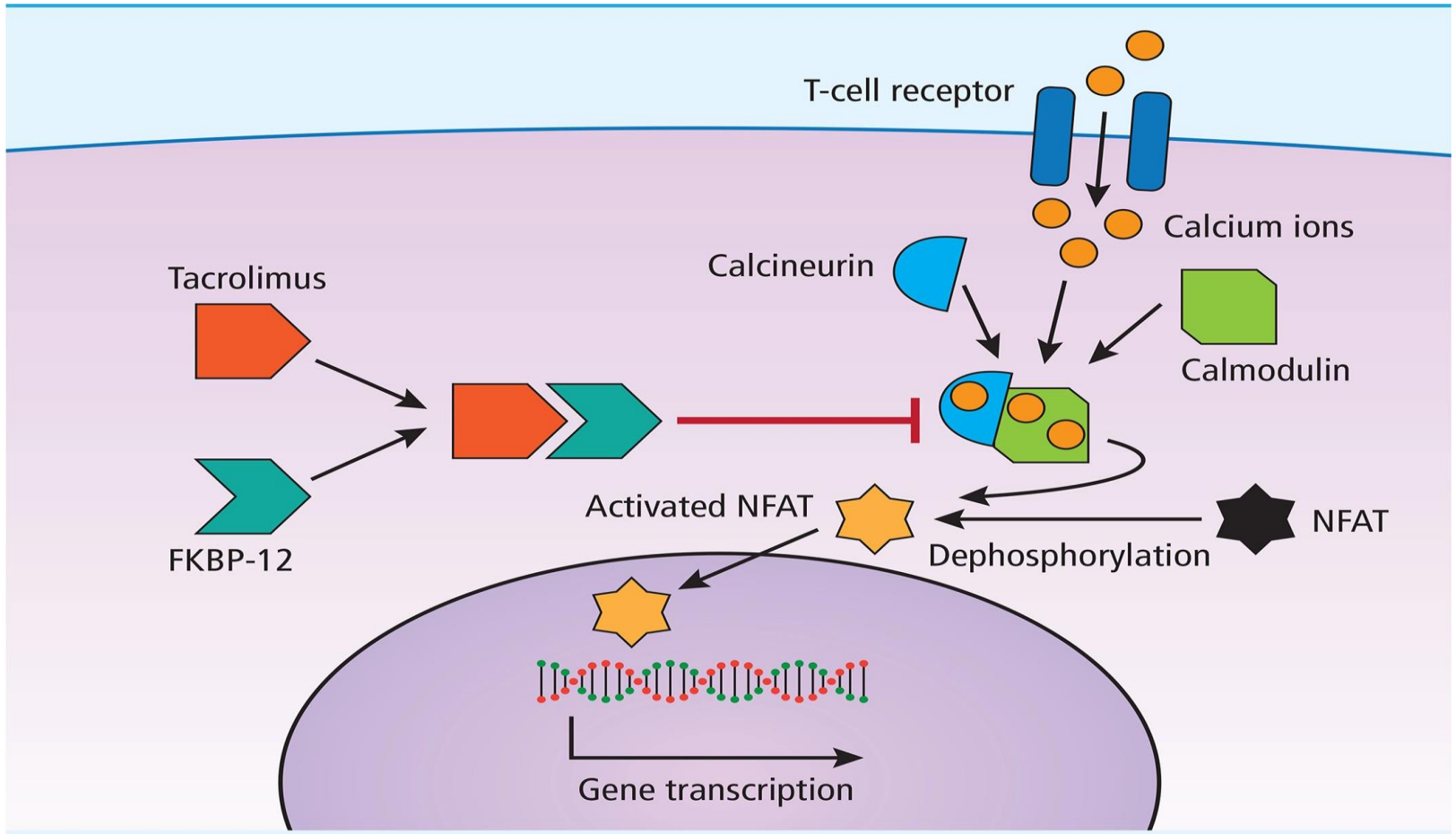
binding of cyclosporine-cyclophylin & tacrolimus-FKBP12 complexes to calcineurin

inhibits phosphatase activity of calcineurin

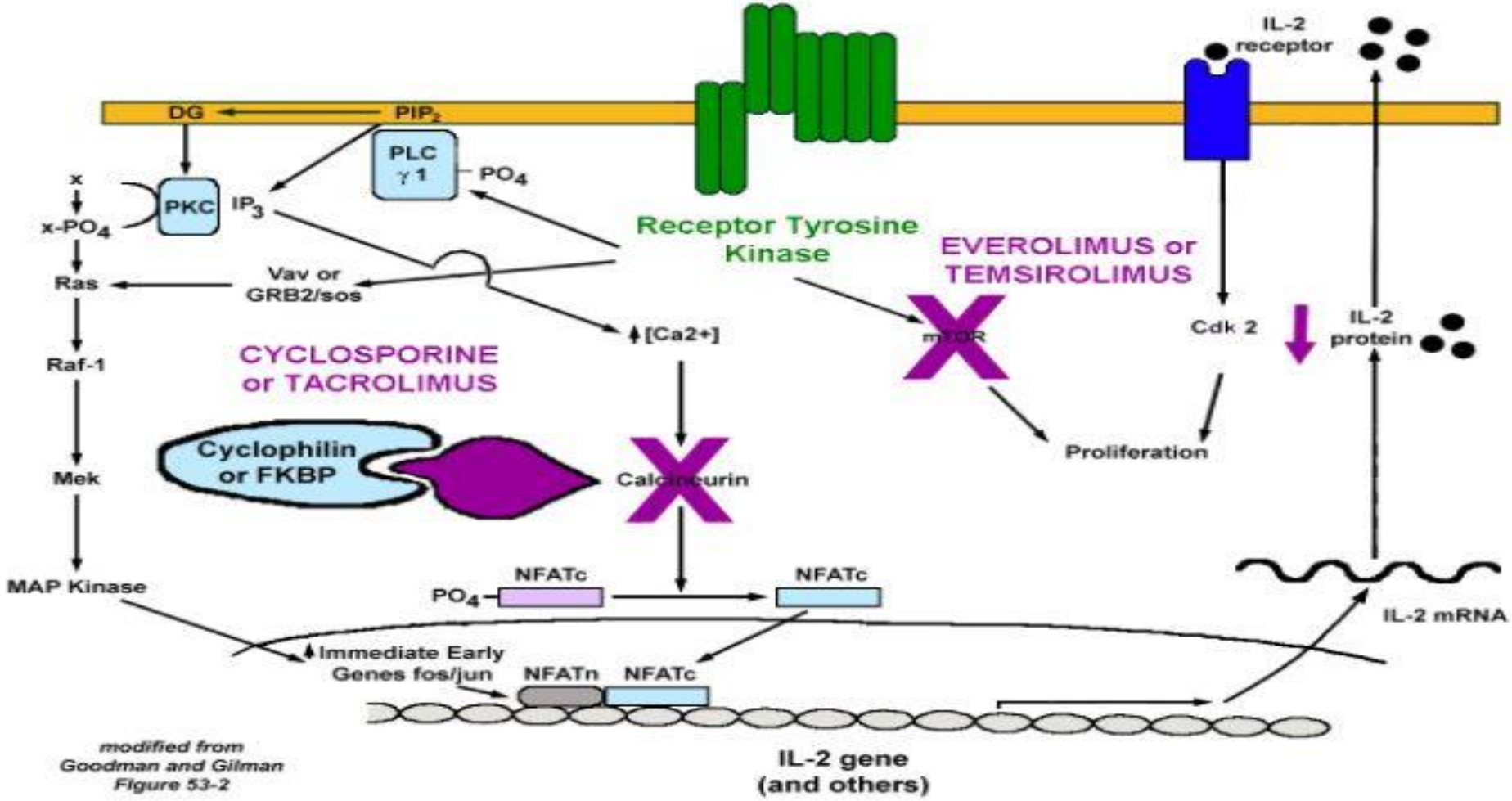
inhibition of the dephosphorylation (NFAT)

suppresses the transcription of IL-2

regulates IL-2 transcription & T cell activation.



NOTES. Tacrolimus binds to the immunophilin FKBP-12, inhibiting the phosphorylation activity of calcineurin and preventing the translocation of nuclear factor of activated T cells (NFAT) into the nucleus and the transcription of NFAT dependent genes. Inhibition of NFAT activation suppresses T-cell stimulation and prevents cell-mediated rejection.


IL-2 receptor
DG
PIP2
PLC γ1
PO4
x
x-PO4
PKC
IP3
Receptor Tyrosine Kinase
EVEROLIMUS or TEMSIROLIMUS
Ras
Vav or GRB2/sos
[Ca2+]
mTOR
Cdk 2
IL-2 protein
Raf-1
CYCLOSPORINE or TACROLIMUS
Cyclophilin or FKBP
Calcineurin
Proliferation
Mek
MAP Kinase
NFATc
PO4
NFATc
IL-2 mRNA
Immediate Early Genes fos/jun
NFATn
NFATc
IL-2 gene (and others)
modified from Goodman and Gilman Figure 53-2

Patients treated with the calcineurin inhibitors (CNIs) , high risk of developing kidney injury .

manifested as :

- **Acute kidney injury (AKI)**
- **Chronic kidney disease(CKD)**
- **Tubular dysfunction**
- **TMA**

INCIDENCE

a high incidence of oliguric acute kidney injury (AKI) and primary nonfunction.

the risk was greatest with prolonged ischemia time of the donated kidney prior to transplantation .

Subsequent trials showed that these problems were dose related.

Acute CNI nephrotoxicity

- Acute arteriolopathy
- Tubular vacuolization(isometric)
- Thrombotic microangiopathy(TMA)

Chronic CNI nephrotoxicity

- Interstitial fibrosis and tubular atrophy(striped)
- Medial arteriolar hyalinosis
- Glomerular capsular fibrosis
- Global glomerulosclerosis
- FSGS
- Juxtaglomerular apparatus hyperplasia
- Tubular microcalcifications

Cyclosporine versus tacrolimus :

Acute and chronic nephrotoxicity are generally similar .

- **tacrolimus has less nephrotoxicity with lower doses without compromising overall outcomes.**

RISK FACTORS

- High doses of cyclosporine or tacrolimus
- Older age of donated kidney
- Concomitant use of nephrotoxic drugs, (NSAIDs)
- Salt depletion and diuretic use
- Drugs that inhibit cytochrome P-450 3A4/5 (CYP3A4/5)
- Drugs that inhibit P-glycoprotein
- Genetic polymorphisms in the genes encoding CYP3A4/5 (CYP3A4/5) and P-glycoprotein (ABCB1)
- Genetic polymorphisms of other genes (e.g., TGF-B , ACE)

PATHOGENESIS AND PATHOLOGY

Acute calcineurin inhibitor nephrotoxicity

- vasoconstriction of the afferent and efferent glomerular arterioles.
- reductions in renal blood flow and glomerular filtration rate (GFR).
- impairment of endothelial cell function.
- reduced production of vasodilators & enhanced release of vasoconstrictors.
- Increased sympathetic tone.
- production of transforming growth factor (TGF)-beta-1, endothelin-1.
- production of reactive oxygen and nitrogen species.

Administration of a calcium channel blocker :

prevent renal vasoconstriction,
not the rise in endothelin excretion .

- ✓ **the use of calcium channel blockers to treat hypertension CNI treated transplant recipients.**

Acute CNI Nephrotoxicity

Vascular Effects: “Acute Arteriolopathy.”

- **vasoconstriction of the afferent arterioles**
- **increase in vasoconstrictor factors**
- **reduction of vasodilator factors**
- **free radical formation**

Cyclosporine leads to activation of the renin–angiotensin system (RAS) by :

- **direct effects of cyclosporine on juxtaglomerular cells.**
- **indirect effects from the renal vasculature hemodynamic changes.**

RAS activation:

- **reduces renal blood flow through the action of angiotensin II.**
- **augments the vasoconstrictory effects of angiotensin II in smooth muscle cells.**
- **Effect on intracellular calcium stores, smooth muscle cell phenotypic and contractility.**

Angiotensin II has pleiotropic effects including:

- **aldosterone release.**
- **stimulation of tubular transport.**
- **proinflammatory effects.**
- **profibrogenic and growth stimulatory actions.**

which are mainly mediated by AT1 receptors and induction of TGF-B.

cyclosporine induces imbalances in the vasodilator/ vasoconstrictor ratio of arachidonic acid metabolites (eicosanoids), which ultimately promotes renal vasoconstriction.

endothelial dysfunction as an essential factor in the pathogenesis of acute CNI nephrotoxicity. CNI inhibit NO synthesis and endothelium-dependent NO-mediated renal vasodilatation. Cyclosporine increase free radical formation and superoxide production, likely through vasoconstriction-associated hypoxia.

Endothelin was linked to acute CNI nephrotoxicity.
cyclosporine stimulates endothelin release from cultured renal epithelial cells.

Tubular Effects: “Toxic Tubulopathy.”

isometric tubular epithelial cell vacuolization is commonly seen in the context of acute CNI nephrotoxicity after kidney transplantation.

sublethal cyclosporine exposure induces :

- **heat shock protein expression ,**
- **decreased NO production in cultured tubular epithelial cells ,**
- **alterations in calcium influx and free cytosolic calcium concentration.**

Thrombotic Microangiopathy

- **the use of the CNIs is an important risk factor for post-transplant TMA attributed to the endothelial injury secondary to vasoconstriction-associated ischemia.**

- **cyclosporine and tacrolimus can increase platelet aggregation and activate prothrombotic factors.**

Chronic CNI Nephrotoxicity

Vascular Effects:

Nodular hyaline deposits in the media of afferent arterioles (arteriolar hyalinosis) is regarded as a hallmark of CNI nephrotoxicity and is characterized by the replacement of necrotic smooth muscle cells by focal or circular lumpy protein (hyaline) deposits at the periphery of the wall of afferent arterioles.

Tubular-Interstitial Effects:

Local hypoxia or ischemia of the tubulo-interstitial compartment, resulting from renal vasoconstriction induced by cyclosporine or tacrolimus, lead to the formation of free radicals or reactive oxygen species.

upregulation of TGF-B is considered an important etiologic factor in chronic CNI nephrotoxicity. TGF-B induces epithelial mesenchymal transition (EMT).

Glomerular Effects

calcineurin inhibition may cause focal segmental glomerulosclerosis lesions, possibly caused by hyperfiltration injury associated with either arteriolar hyalinosis or global glomerulosclerosis.

Kidney biopsy reveals:

- **an obliterative arteriolopathy (suggesting primary endothelial damage)**
- **ischemic collapse or scarring of the glomeruli**
- **vacuolization of the tubules.**
- **global and focal segmental glomerulosclerosis.**
- **focal areas of tubular atrophy and interstitial fibrosis (producing a picture of "striped fibrosis.”**

The factors responsible for chronic CNI nephrotoxicity:

- **increased expression of osteopontin.**
- **chemokines**
- **(TGF)-beta**
- **decreased expression of P-glycoprotein**
- **Increased apoptosis**

Electrolyte Disturbances

- Hyperkalemia
- Hypomagnesemia
- Hypophosphatemia
- Hyperchloremic metabolic acidosis
- Hyperuricemia
- Hypercalciuria

CLINICAL PRESENTATIONS

Acute cyclosporine and tacrolimus nephrotoxicity typically presents as an acute increase in plasma creatinine concentration, which is dose related and largely reversible after dose reduction or cessation of therapy.

The onset of acute CNI nephrotoxicity can occur anytime within hours to days to even years after CNI initiation.

In kidney transplant recipients, acute CNI nephrotoxicity can also manifest as delayed recovery of function of a newly transplanted but malfunctioning allograft.

In kidney transplant recipients, acute CNI nephrotoxicity may be difficult to differentiate from acute rejection. The only definitive diagnostic test is biopsy of the renal allograft.

Chronic CNI nephrotoxicity commonly presents as a chronic and progressive renal insufficiency due to glomerular and vascular disease, abnormalities in tubular function, and an increase in blood pressure . It is usually irreversible.

The use of CNIs has been associated with the development of de novo TMA after kidney transplantation.

present with :

- **schistocytes on the blood smear**
- **microangiopathic hemolytic anemia**
- **thrombocytopenia**
- **acute kidney injury (AKI).**

➢ **Concurrent use of cyclosporine with (mTOR) inhibitors increase the risk of TMA**

Prevention and Treatment of CNI Nephrotoxicity

-CNI Avoidance, Withdrawal, and Minimization

-Calcium Antagonists.

-RAS Inhibition.

-Vasodilatatory Prostanoids.

other therapeutic approaches are promising for the prevention of CNI nephrotoxicity:

anti-TGF antibodies, antioxidants , statins , and magnesium supplementation .

However, no human studies with these approaches are available.

Therapies with unclear benefit

Fish oil

Calcium channel blockers

Renin-angiotensin system inhibitors

Therapies with no benefit

Pentoxifylline

Thromboxane synthesis inhibitor

frontiers in Pharmacology

ORIGINAL RESEARCH
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Nephrotoxicity of Calcineurin Inhibitors in Kidney Epithelial Cells is Independent of NFAT Signaling

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Background: Calcineurin inhibitors (CNIs) such as cyclosporine A and tacrolimus are commonly used after renal transplantation to suppress the immune system. In lymphoid cells, cyclosporine A acts *via* the calcineurin/nuclear factor of activated T-cell (NFAT) axis. In non-lymphoid cells, such as kidney epithelial cells, cyclosporine A induces calcineurin inhibitor toxicity. It is unknown *via* which off-targets cyclosporine A induces calcineurin inhibitor toxicity in kidney epithelial cells.

Methods: To measure a compound's potential to induce nephrotoxicity, the expression of the surrogate marker Fn14 was measured by flow cytometry. Compounds were tested for their potential to induce Fn14 either chemically or plasmid-mediated. Mice were injected with various compounds, and changes in nephrotoxic gene expression levels of the kidney epithelial cells were then analyzed.

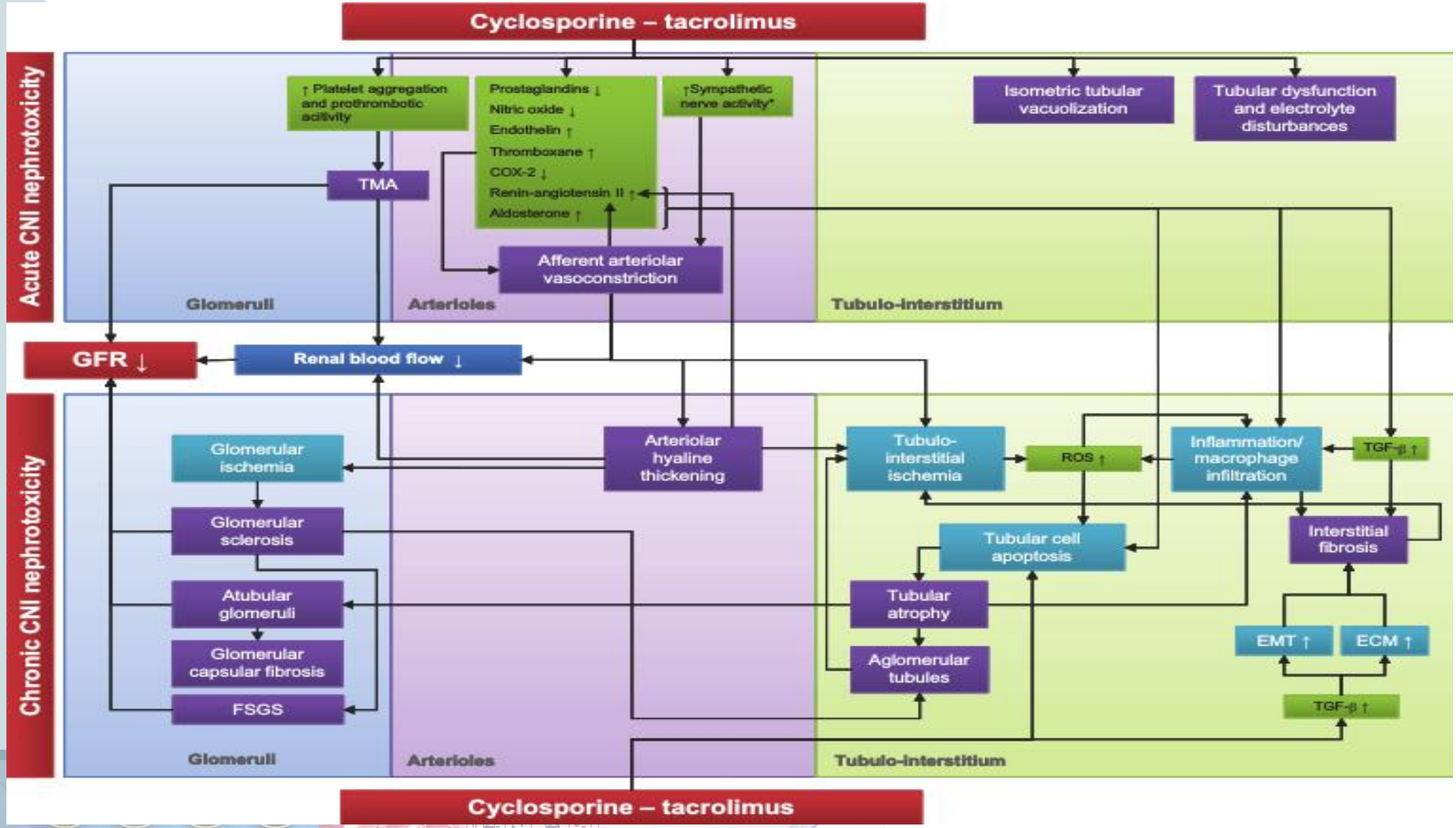
OPEN ACCESS

Edited by:

These findings show that cyclosporine A acts independently of NFAT on kidney epithelial cells.

inhibition of serine/threonine protein kinases mimics cyclosporine A's activity on kidney epithelial cells.

contributes likely to the development and progression of calcineurin inhibitor toxicity.


Cyclosporine – tacrolimus
Acute CNI nephrotoxicity
↑ Platelet aggregation and prothrombotic activity
Prostaglandins ↓
Nitric oxide ↓
Endothelin ↑
Thromboxane ↑
COX-2 ↓
Renin-angiotensin II ↑
Aldosterone ↑
↑Sympathetic nerve activity*
Isometric tubular vacuolization
Tubular dysfunction and electrolyte disturbances
TMA
Afferent arteriolar vasoconstriction
Glomeruli
Arterioles
Tubulo-interstitium
GFR ↓
Renal blood flow ↓
Chronic CNI nephrotoxicity
Glomerular ischemia
Glomerular sclerosis
Atubular glomeruli
Glomerular capsular fibrosis
FSGS
Arteriolar hyaline thickening
Tubulo-interstitial ischemia
ROS ↑
Inflammation/ macrophage infiltration
TGF-β ↑
Tubular cell apoptosis
Interstitial fibrosis
Tubular atrophy
Aglomerular tubules
EMT ↑
ECM ↑
TGF-β ↑
Glomeruli
Arterioles
Tubulo-interstitium
Cyclosporine – tacrolimus


Thanks for Attention