CHRONIC ALLOGRAFT FAILURE

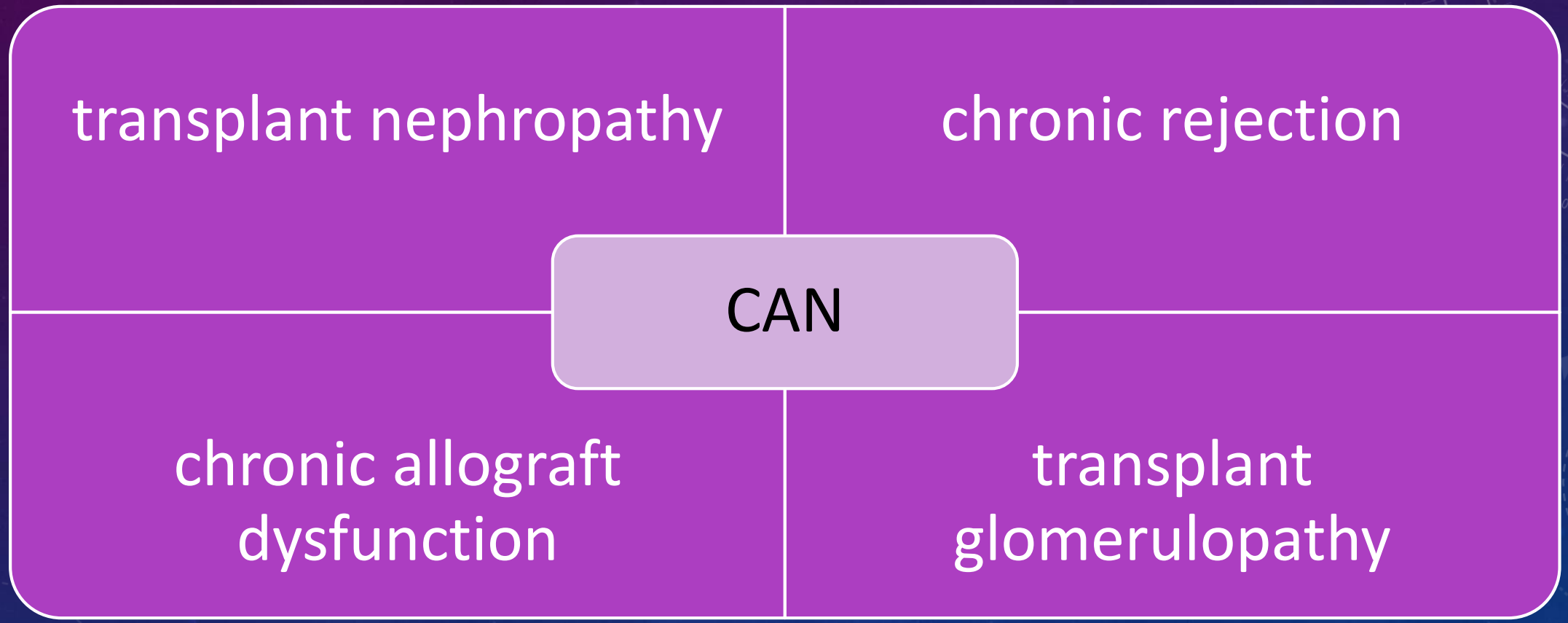
- Kidney allograft failure is one of the most common causes of end-stage kidney disease (ESKD), accounting for 25 to 30 percent of patients awaiting kidney transplantation.
- over 15-20 percent of kidney transplantations performed in the United States go to patients who have failed one of more kidney allografts.

- Graft failure :

1. morbidity
2. cost of returning to dialysis
3. higher risk of death
4. increasing demand on transplantable organ

1991

- CAN is a histopathologic description that refers to the features of chronic interstitial fibrosis and tubular atrophy within the kidney allograft.
- The term can was introduced to replace CHRONIC REJECTION
- The intention was to reverse the misconception that all late scarring of the allograft was caused by alloimmune injury/rejection.


transplant nephropathy
chronic rejection
CAN
chronic allograft dysfunction
transplant glomerulopathy

2005

- The revised Banff 2005 classification system replaced CAN with "**interstitial fibrosis and tubular atrophy (IF/TA), without evidence of any specific etiology**" .
- This was done to differentiate specific diagnostic entities (such as chronic active antibody-mediated rejection [ABMR], chronic active T cell-mediated rejection [TCMR], calcineurin inhibitor [CNI] toxicity, and BK polyomavirus [BKPyV]-associated nephropathy) from a nonspecific fibrotic subtype of CAN.

- CAN is a histopathological description, rather than a specific disease entity, that refers to the features of chronic interstitial fibrosis and tubular atrophy within the kidney allograft without specifying the etiology.

CHRONIC ALLOGRAFT DYSFUNCTION –

- Chronic allograft dysfunction is defined as a clinical condition characterized by a slow (over a period of months to years), progressive decrease in kidney function, usually associated with hypertension and worsening proteinuria.

Chronic allograft dysfunction may result from

- CAN
- recurrent and de novo glomerulonephritis
- BKPyV-associated nephropathy
- late or recurrent acute rejection
- renal artery stenosis
- ureteric obstruction.

- The recognition that **IFTA** is final common pathway for many injury led to :

1. Improve allograft surveillance
2. Biomarkers
3. Obtaining a biopsy before chronic injury
4. Recognition that the changes in slope of GFR is a late finding

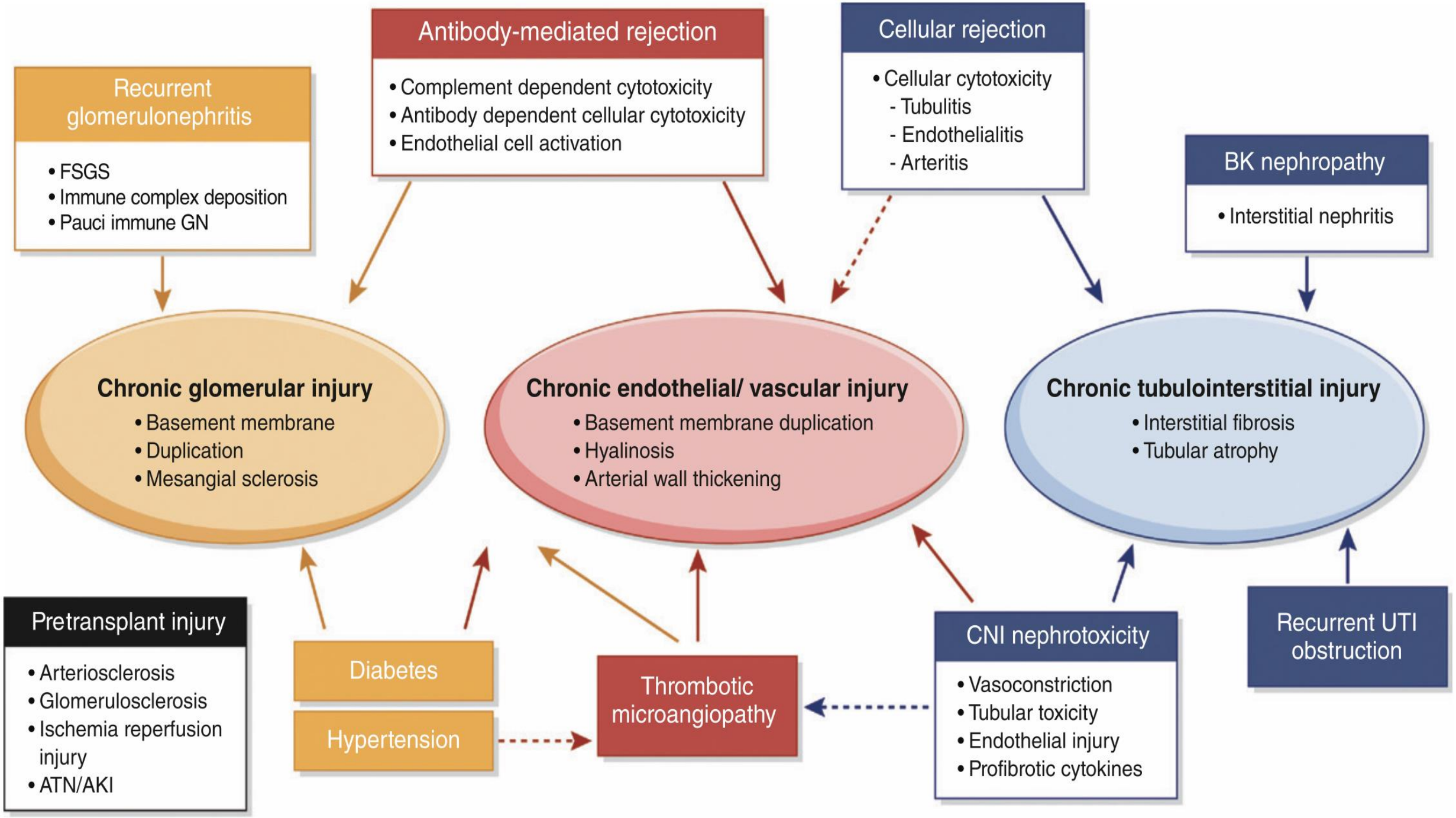
RISK FACTORS FOR CHRONIC ALLOGRAFT INJURY

Alloantigen-dependent factors

- Cellular and antibody mediated rejection
- Immunosuppressive regimens
- Infection such as Bk nephropathy and recurrent UTI

Alloantigen-independent factors

- Hypertension
- Glomerular hyperfiltration and hypertrophy
- Superimposed recurrent or de novo kidney parenchymal disease
- Delayed graft function
- Hyperlipidemia
- Diabetic nephropathy


Recurrent glomerulonephritis
• FSGS
• Immune complex deposition
• Pauci immune GN
Antibody-mediated rejection
• Complement dependent cytotoxicity
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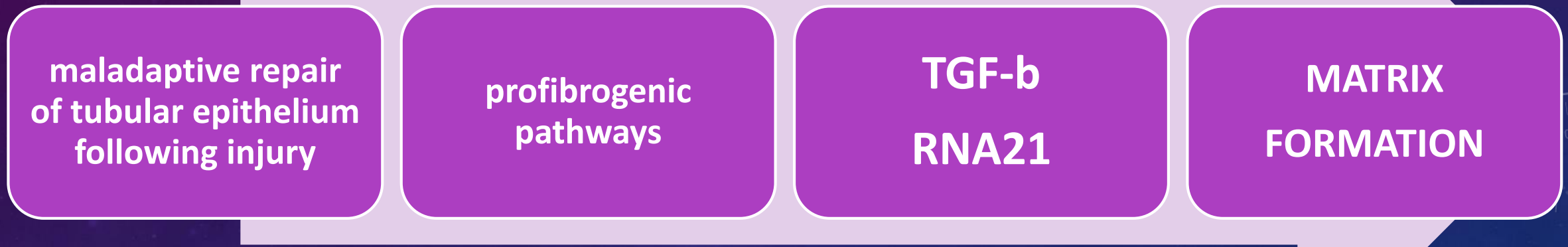
• Glomerulosclerosis
• Ischemia reperfusion injury
• ATN/AKI
Diabetes
Hypertension
Thrombotic microangiopathy
CNI nephrotoxicity
• Vasoconstriction
• Tubular toxicity
• Endothelial injury
• Profibrotic cytokines
Recurrent UTI obstruction

SUBOPTIMAL DONOR

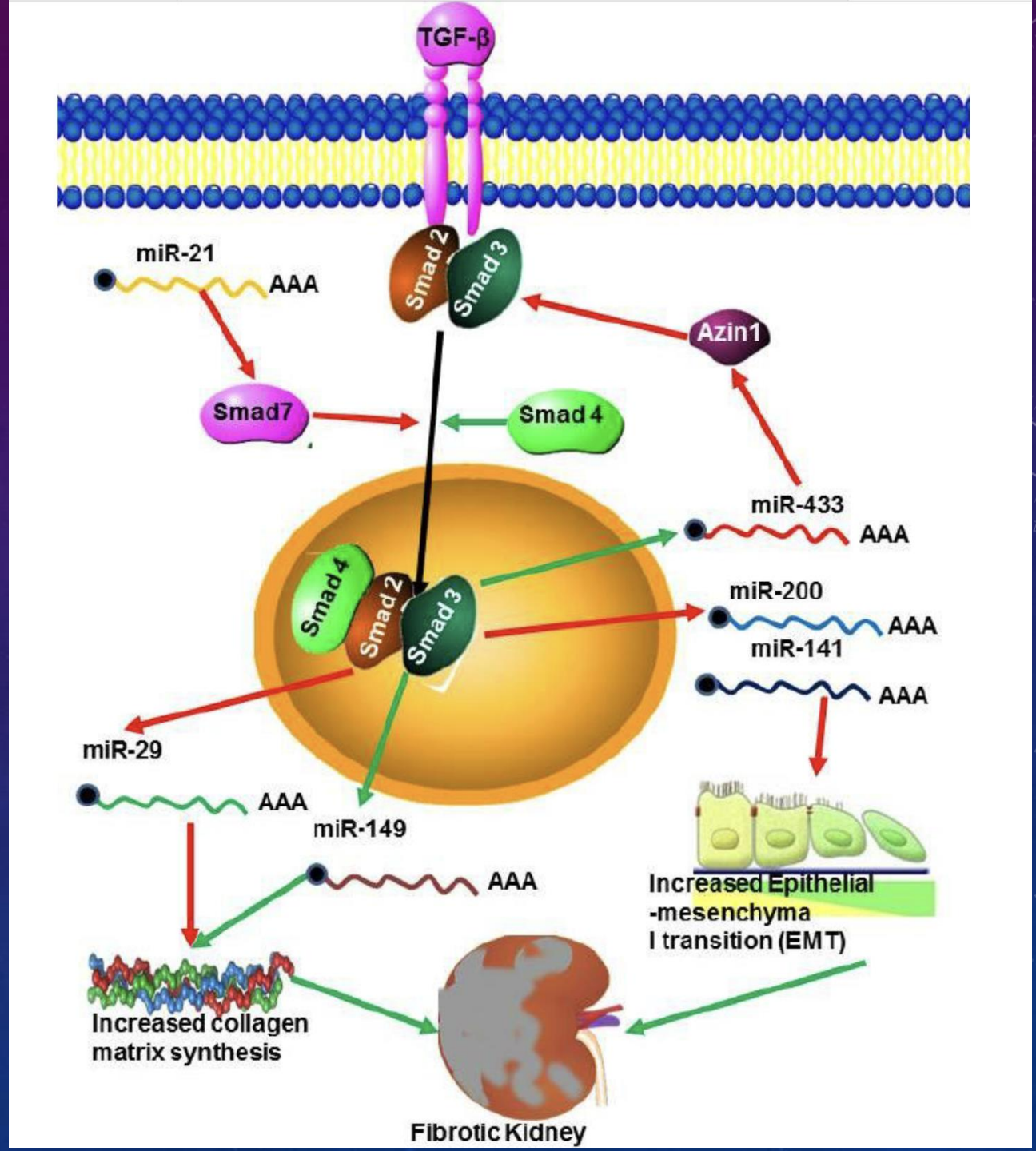
- We must consider “fixed deficit” on the basis of reduced nephron mass so the reduced capacity to respond the injury
- higher Kidney Donor Risk Index ,older age , size mismatch , brain death and ischemia- reperfusion injury
- Hyperfiltration , proinflammatory environment

TARGETS OF INJURY: THE INTERSTITIUM

- **maladaptive repair of tubular epithelium following injury**
- **profibrogenic pathways**
- within the environment of repeated stress, injury, or under duress of calcineurin inhibitors , tubular epithelial cells, as well as T cells and macrophages, express profibrotic growth factors
- This results in downstream activation of mesenchymal cells, including pericytes, fibroblasts, and fibrocytes, which themselves may now produce matrix.


maladaptive repair of tubular epithelium following injury
profibrogenic pathways
TGF-b
RNA21
MATRIX FORMATION

TGF-B
ENHANCED EXPRESSION OF MICRO- RNA21 THE KEY IN PROFIBROGENIC PATHWAY



- gene expression studies in human kidney allografts shows IF/TA with upregulation of connective tissue growth factor and TGF-b, matrix metalloproteinases, collagens, and a-smooth muscle actin
- progressive fibrosis detected in the early course of transplantation that are predictive of later injury .(the importance of IF/TA)

- “failed-repair proximal tubule cell state,”
- dynamic nature of the repair response may be a new target for mitigating graft failure.

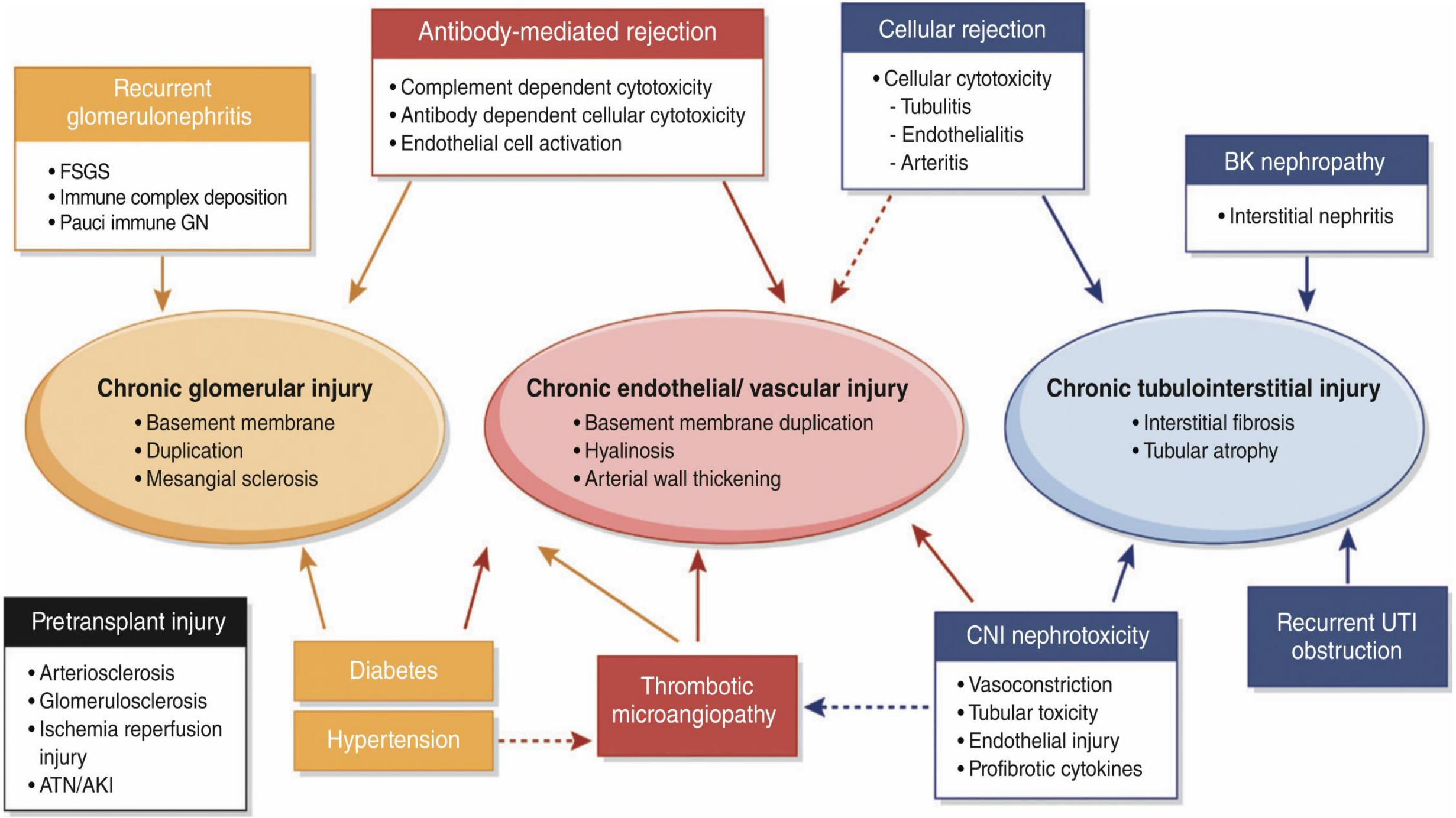
- More recent studies indicate that only 17% of transplants instead of 66% in later study have moderate to severe IFTA (5 year)
- more effective immunosuppression with tacrolimus, with less subclinical and clinical inflammation as well as the notion that tacrolimus may be “less fibrogenic” compared with the use of cyclosporin

ALLOGRAFT INFLAMMATION IS AN IMPORTANT MEDIATOR OF CHRONIC GRAFT INJURY

- Surveillance biopsy studies associated subclinical cellular rejection and under- immunosuppression with progression of IF/TA
- Total inflammation including inflammation in both scarred and unscarred tissue was identified as an independent risk factor for graft failure
- Interestingly, gene expression of allografts with i-IFTA lesions was more frequently associated with antibody-mediated rejection gene transcripts and eventual graft loss

- i-IFTA is not specific and may be seen :

1. in BK virus nephropathy
2. recurrent glomerular disease
3. antibody-mediated rejection
4. pyelonephritis.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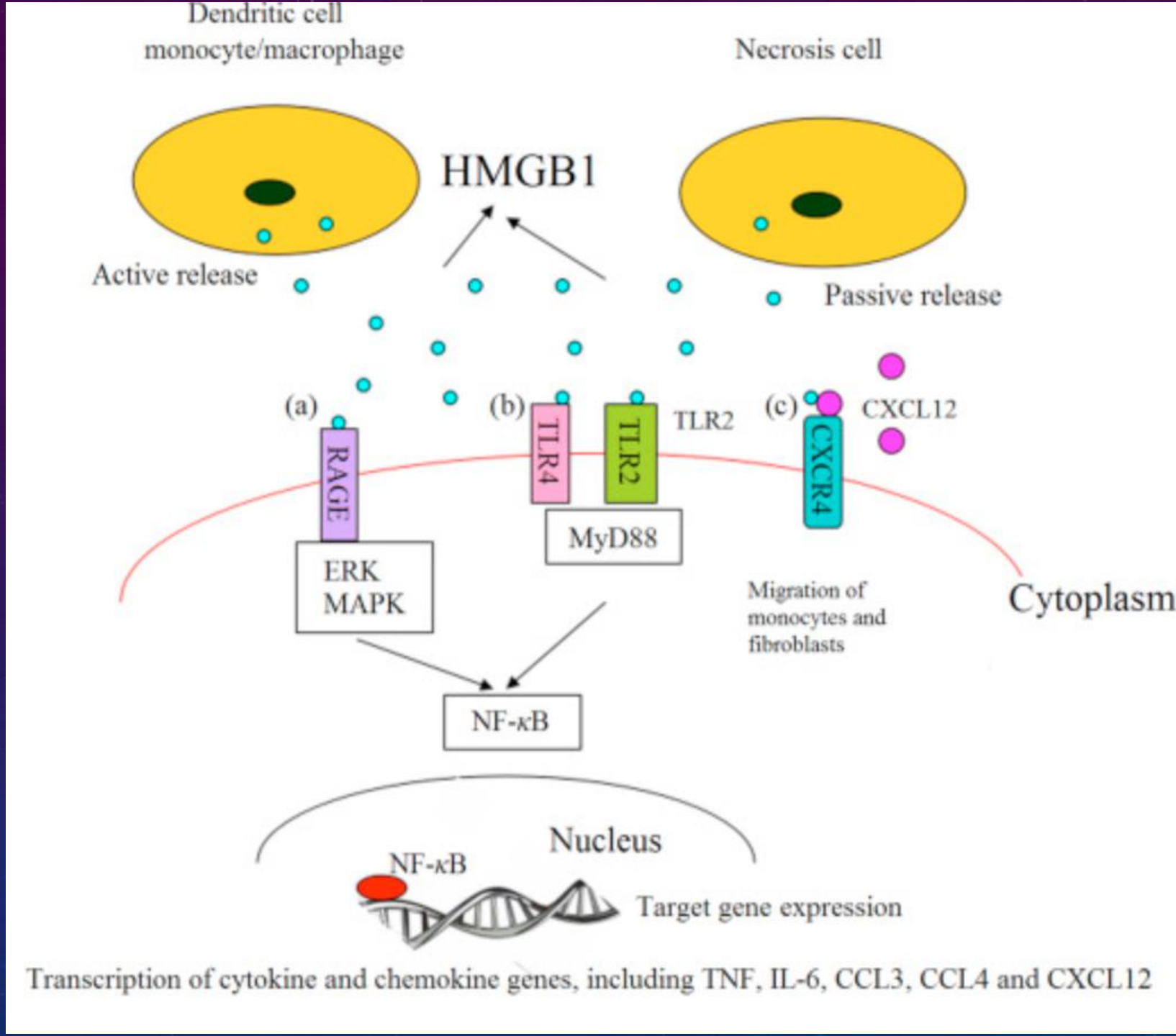
Recurrent UTI obstruction

CALCINEURIN INHIBITORS NEPHROTOXICITY

- vascular (arteriolar), tubular, and glomerular dysfunction
- activation of the renin- angiotensin system, with effects on kidney vasculature as well as on juxtaglomerular cells
- direct effects on the epithelium and interstitium , with release of reactive oxygen species , mitochondrial dysfunction and HMGB1 release by tubular epithelial cells, and apoptosis
- loss of epithelial phenotype with endoplasmic reticulum stress
- High mobility group box 1 (HMGB1)



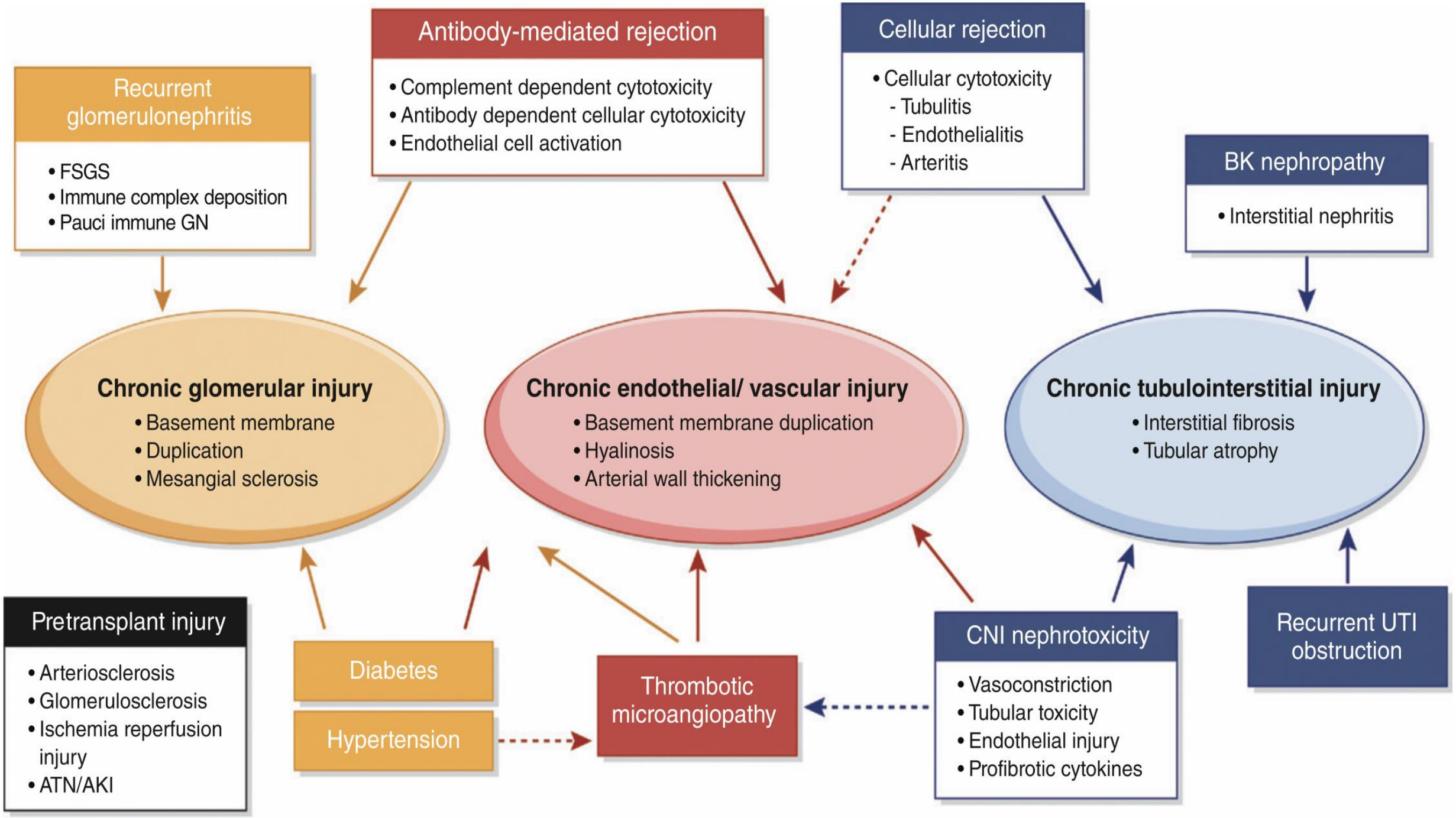
Transcription of cytokine and chemokine genes, including TNF, IL-6, CCL3, CCL4 and CXCL12

- no specific therapies that ameliorate calcineurin inhibitor nephrotoxicity.
- minimization or avoidance of these agents has resulted in cellular and antibody-mediated rejection .
- minimization of these agents to avoid toxicity may provoke subclinical and clinical alloimmune activation .
- Effective management strategies that limit calcineurin inhibitor injury while facilitating therapeutic levels are an unmet need in the transplant recipient.

VIRAL NEPHROPATHY WITH BK VIRUS

- BK virus, with a **tropism for uroepithelium**, undergoes replication under the immunosuppressive milieu resulting in a marked inflammatory response, leading to tubular epithelial cell injury and, ultimately, IF/TA
- The mainstay of intervention includes proactive monitoring for viral DNA with immunosuppressive reduction upon detection of BK viremia and/or viruria.

- molecular analysis of allograft biopsies with BK nephropathy indicated similar gene expression to that of acute T cell–mediated rejection
- BK virus nephropathy was associated with a profibrogenic milieu, although whether this was due directly to viral invasion or related to the antiviral immune response is not clear
- NanoString 800-gene panel to detect immune response and BK viral genes have also demonstrated an overlap of transcripts in BK virus nephropathy and T cell–mediated rejection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TARGETS OF INJURY: THE ENDOTHELIUM

- The injured endothelium responds by increased vasoconstriction, inflammation, and hypercoagulation , as well as upregulation of adhesion molecules and class 2 MHC expression, increasing graft immunogenicity.
- endothelial cell apoptotic death may release apoptotic exosome-like vesicles, which, in turn, promote further endothelial dysfunction, autoantibody production, and complement deposition .
- endothelial cell activation leads to recruitment of inflammatory cells and proliferation of vascular smooth muscle cells, resulting in neointima formation.


injured endothelium
increased vasoconstriction
inflammation
hypercoagulation
upregulation of adhesion molecules
class 2 MHC expression
increasing graft immunogenicity
release apoptotic exosome-like vesicles
recruitment of inflammatory cells
proliferation of vascular smooth muscle cells
neointima formation

- chronic antibody-mediated rejection may be characterized by peritubular capillary injury, ultimately resulting in basement membrane duplication or laminations.
- with no prescribed and effective therapy median graft survival is 3.25 years, with a three-fold higher risk of graft failure

- Risk factors for graft failure include

1. proteinuria
2. reduced allograft function
3. class 2 HLA donor-specific antibody (DSA) and de novo DSA compared with preformed/preexisting donor antibody

TREATMENT OF CHRONIC ACTIVE ANTIBODY-MEDIATED REJECTION

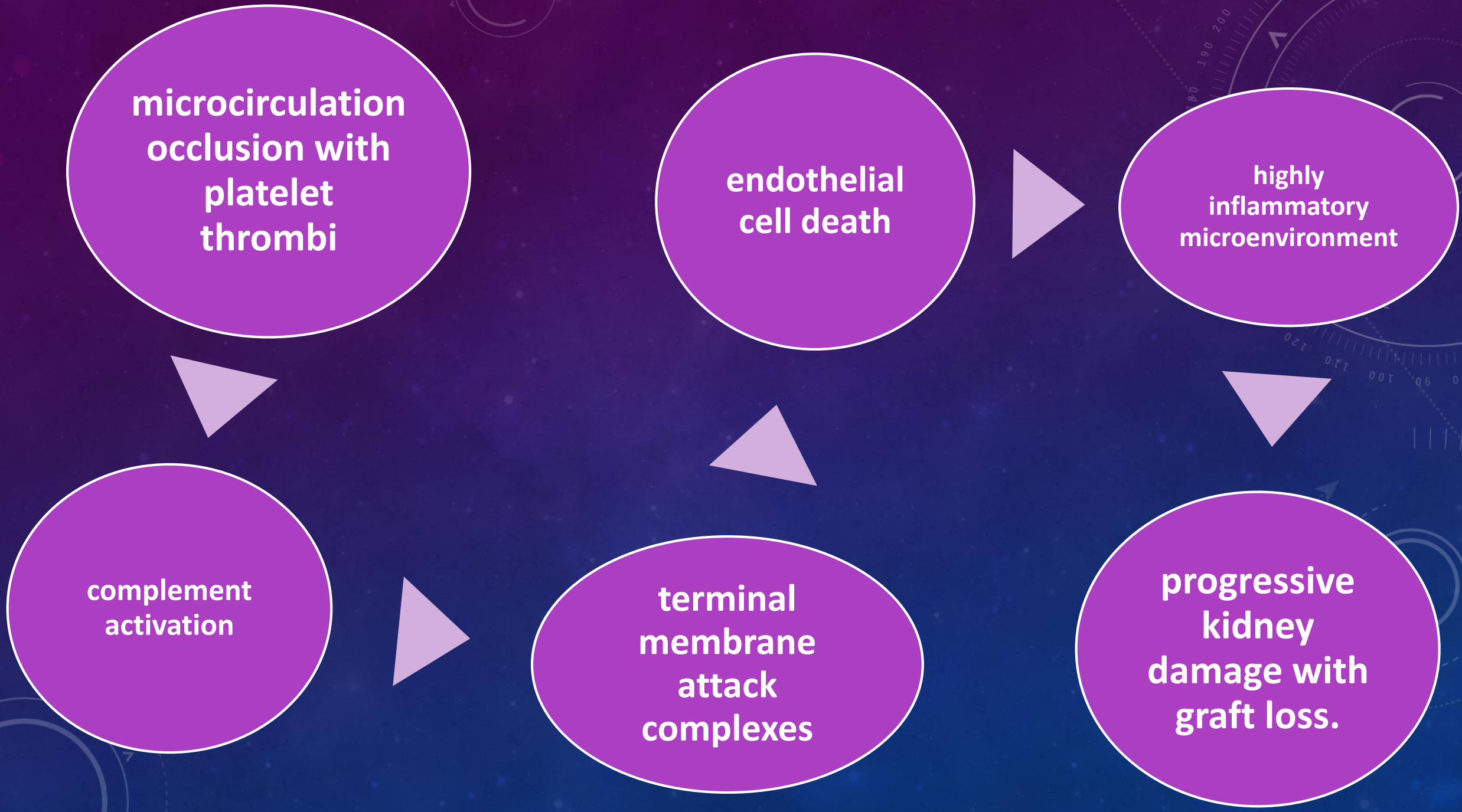
1. **optimizing immunosuppression** with supportive care, such as reintroduction of steroids (if on a steroid-free regimen), maintaining trough tacrolimus levels .5 ng/ml
2. **optimizing medical management** with a focus on BP, blood glucose, and dyslipidemia .

- Past studies with complement inhibition and proteasome inhibitors have had no effect on outcomes, and newer trials are underway, including the use of neutralizing IL-6 antibody, targeting natural killer and plasma cells

THROMBOTIC MICROANGIOPATHY OF THE GLOMERULUS

1. Etiologies include primary genetic syndromes with complement activation as well as
2. secondary causes, including antidonor HLA antibody, calcineurin inhibitor, and viral infections such as HIV, CMV, and parvovirus.

- Regardless of the cause, the presence of microcirculation occlusion with platelet thrombi, complement activation, and terminal membrane attack complexes causing endothelial cell death is a highly inflammatory microenvironment leading to progressive kidney damage with graft loss.


microcirculation occlusion with platelet thrombi
endothelial cell death
highly inflammatory microenvironment
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terminal membrane attack complexes
progressive kidney damage with graft loss.

TARGET OF INJURY: THE GLOMERULUS

- recurrent GN following kidney transplant may account for up to 15% of graft failures.

THE TIMING OF DETECTION OF CHRONIC INJURY

- Although serum creatinine is used to monitor allograft function and detect injury, it lacks specificity and sensitivity for early allograft injury.
- considerable nephron damage and loss can occur before a significant change in creatinine.
- biopsy reveals more advanced processes

- clear need for biomarkers to detect the onset and etiology of chronic allograft injury
- surveillance biopsies at specified time points post-transplant may detect “subclinical” rejection, but benefits of therapeutic implementation are not certain.
- the cost and time-consuming and invasive nature

- Gene expression profiles may be useful in terms of predicting graft failure and progression
- donor-derived cell free DNA to detect allograft injury

IBOX

- multicomposite measure called the integrated risk prediction score (iBOX) might provide risk prediction of graft failure.
- allograft function, proteinuria, the level of donor-specific HLA antibody, and the histopathologic variables of severity of IF/TA, microvascular injury, inflammation, and tubulitis

THERAPEUTIC MANAGEMENT

1. improved matching using molecular typing between donor and recipient ,
2. improved donor selection :donor quality, organ preservation methods that mitigate innate injury.
3. Preemptive approaches :detection and management of cellular and humoral rejection prior to clinical detection
4. tailoring of immunosuppressive therapies on the basis of immune risk profiles
5. addressing medication nonadherence.
6. The final aspect is antifibrotics, a topic that is worthy of an entire review
7. use of SGLT2 inhibitors in diabetic glucose management in kidney transplant recipients

THE DIFFERENTIAL DIAGNOSIS OF CHRONIC ALLOGRAFT NEPHROPATHY (CAN)

- **Chronic antibody-mediated rejection**
- **Diabetic kidney disease**
- **Recurrent or de novo glomerulonephritis**
- **BK polyomavirus-associated nephropathy**
- **Late or recurrent acute rejection**
- **Renal artery stenosis**
- **Membranoproliferative glomerulonephritis** : HCV

DIAGNOSTIC EVALUATION

- Chronic allograft nephropathy (CAN) should be suspected in any kidney transplant recipient who presents with chronic allograft dysfunction (ie, slow, progressive decrease in kidney function, usually associated with hypertension and worsening proteinuria).

DIAGNOSTIC EVALUATION

kidney ultrasound with Dopplers of the renal artery, exclude renal artery stenosis.

estimate proteinuria by determining a spot urine protein-to-creatinine ratio.

If urine pr>1 gr

perform a kidney allograft biopsy.

assess for the presence and strength/titers of (DSAs)

assess for the presence of BK

blood viral load

PREVENTION

- However, there is **no** effective therapy available for established CAN, and all patients inevitably progress to end-stage kidney disease (ESKD).

PREVENTION

- **In the first year**, for example, attention may generally be directed at the prevention of rejection
- **in subsequent years** among stable patients, management may focus upon limiting exposure to calcineurin inhibitors (CNIs).

PREVENTION OF REJECTION

- preventing these episodes, especially in the first year posttransplantation
- Despite the possible increased risk of CAN due to CNI therapy with this approach, the immunosuppressive benefits of this regimen outweigh its possible adverse effects.

ADDITIONAL PREVENTIVE MEASURES

1. optimizing human leukocyte antigen (HLA) matching,
2. reducing ischemic injury (which increases proinflammatory cytokines and others),
3. avoiding sensitization

MODIFICATION OF IMMUNOSUPPRESSION

- changes in immunosuppressive therapy have largely been ineffective in changing the prognosis for patients with established CAN.
-

REDUCING CALCINEURIN INHIBITOR EXPOSURE

- minimize CNI therapy by targeting lower trough levels (such as 3.5 to 5 ng/mL for tacrolimus and 75 to 125 ng/mL for cyclosporine).

NOT RECOMMENDED

- Withdrawal of the CNI has been shown to be associated with more acute rejection and the development of donor-specific antibodies (DSAs) and is **not** recommended
- **Withdrawal of glucocorticoids**
- switch cyclosporin to tacrolimus

- For patients with established CAN who are receiving azathioprine as part of their maintenance immunosuppression, we suggest switching to mycophenolate rather than continuing azathioprine.
- Benefits may also be observed in CNI minimization strategies in which MMF is used in combination with the CNI.

- aggressive control of blood pressure and hyperlipidemia.
- use of SGLT2 inhibitors in diabetic glucose management in kidney transplant recipients


Thank you

- HMGB1 is a position-dependent multifunctional protein. Inside the cell, nuclear HMGB1 regulates the structure and function of chromosomes, while cytoplasmic HMGB1 sustains autophagy. Outside the cell, HMGB1 is a mediator of inflammation, immunity, and the metabolic response. The release of HMGB1 is related to active or passive processes and can be adjusted at various levels. In particular, ROS and redox signals play a central role in driving the secretion and release of HMGB1 by coupling various posttranslational modifications. Targeting the release and activity of HMGB1 provides a strategy for the treatment of various diseases, especially infection and tissue damage.

- High mobility group box 1 (HMGB1) is a nuclear protein that can bind to DNA and act as a co-factor for gene transcription. When released into extracellular fluid, it plays a proinflammatory role by acting as a damage-associated molecular pattern molecule (DAMP) (also known as an alarmin) to initiate innate immune responses by activating multiple cell surface receptors such as the receptor for advanced glycation end-products (RAGE) and toll-like receptors (TLRs), TLR2, TLR4 or TLR9. This proinflammatory role is now considered to be important in the pathogenesis of a wide range of kidney diseaseswhether they result from hemodynamic changes, renal tubular epithelial cell apoptosis, kidney tissue fibrosis or inflammation.