VLA

December 5, 2017

ACUTE AND CHRONIC RENAL FAILURE

EXTRACELLULAR VESICLES

- Extracellular vesicles are cell-derived membrane particles ranging from 30 to 5,000 nm in size, including exosomes, microvesicles, and apoptotic bodies.
- They are released under physiological conditions, but also upon cellular activation, senescence, and apoptosis.
- They play an important role in intercellular communication. Their release may also maintain cellular integrity by ridding the cell of damaging substances.
- They can modify mechanisms important in the pathophysiology of kidney diseases, such as thrombosis, angiogenesis, tissue regeneration, immune modulation, and inflammation.
- In kidney diseases, extracellular vesicles may be utilized as biomarkers, as they are detected in both blood and urine.
- They may contribute to the pathophysiology of renal disease while also having beneficial effects associated with tissue repair. Because of their role in the promotion of thrombosis, inflammation, and immune-mediated disease, they could be the target of drug therapy, whereas their favorable effects could be utilized therapeutically in acute and chronic kidney injury.

Pediatr Nephrol. 2017 Nov 27. doi: 10.1007/s00467-017-3816-z.

Table 1 Main characteristics of exosomes, microvesicles, and apoptotic bodies

	Exosomes	Microvesicles	Apoptotic bodies
Size	30–100 nm	100–1,000 nm	1–5 μm
Origin	Intraluminal vesicles within multivesicular bodies	Plasma membrane and cellular content	Plasma membrane, cellular fragments
Mechanism of formation	Fusion of multivesicular bodies with the plasma membrane	Outward blebbing of the plasma membrane	Cell shrinkage and programmed cell death
Release	Constitutive and/or cellular activation	Constitutive and/or cellular activation	Apoptosis
Time of release	Ten minutes or more	Few seconds	–
Pathways	ESCRT-dependent Tetraspanin-dependent Ceramide-dependent Stimuli-dependent	Ca^{2+}-dependent Stimuli- and cell-dependent	Apoptosis-related
Lipid membrane composition	Enriched in cholesterol and ceramide, expose phosphatidylserine, contain lipid rafts	Expose phosphatidylserine, enriched in cholesterol and diacylglycerol, contain lipid rafts	–
Content	Proteins, mRNA, miRNA, lipids	Proteins, mRNA, miRNA, lipids	Cell organelles, proteins, nuclear fractions, DNA, coding and noncoding RNA, lipids

ESCRT – endosomal sorting complex required for transport

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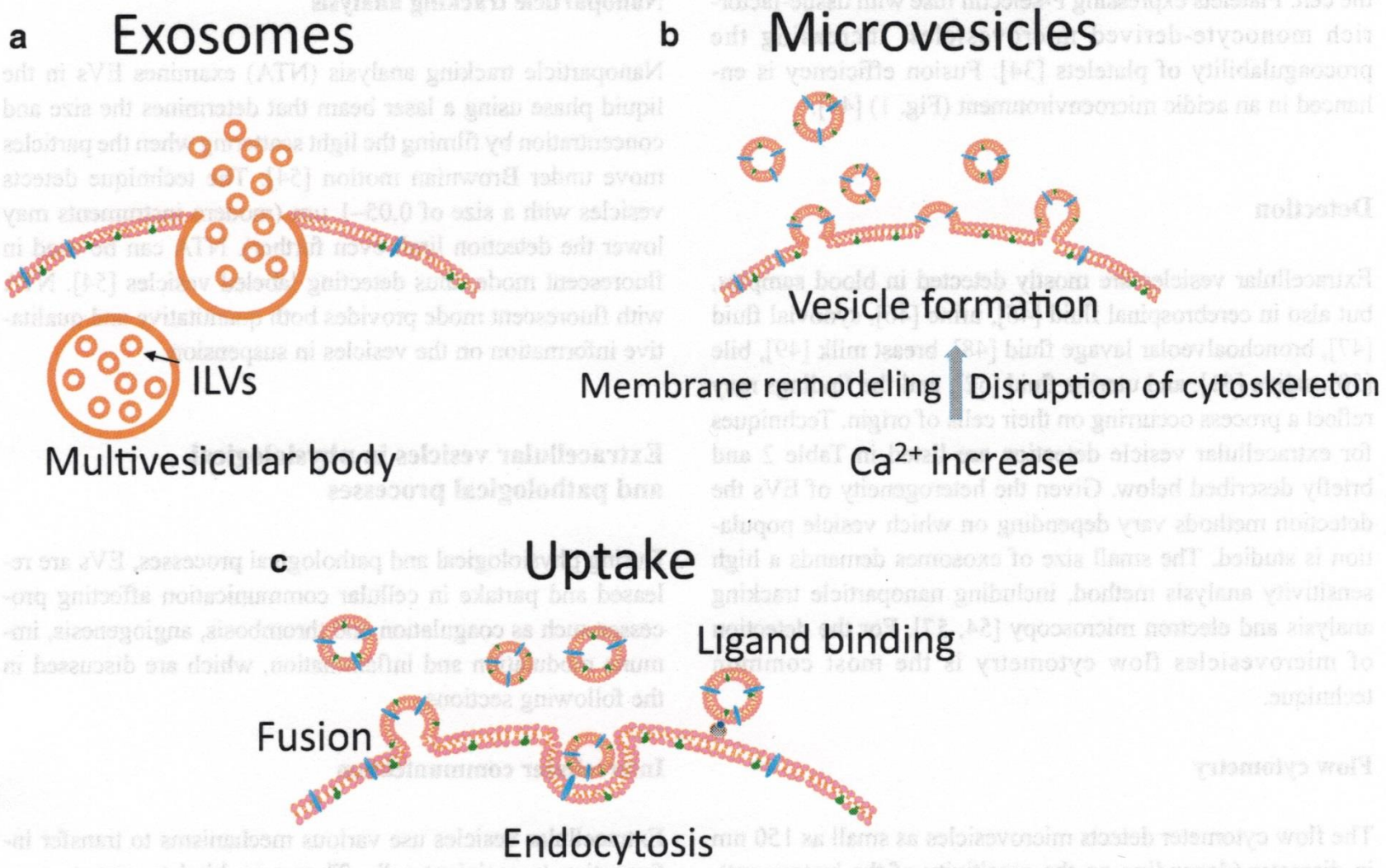

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EXTRACELLULAR VESICLES- FUNCTION

- During physiological and pathological processes, EVs are released and partake in cellular communication affecting processes such as coagulation and thrombosis, angiogenesis, immune modulation and inflammation.
- Glomerular endothelial cell-derived microvesicles exposing the kinin B1 receptor and interleukin 8 (IL-8) on their surface attracted neutrophils.
- Proximal tubular cells cultured in the presence of fenoldopam (a dopamine receptor agonist) released exosomes that reduced the production of reactive oxygen species in distal tubule and collecting duct cells, indicating the transfer of an anti-inflammatory response.

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EVS

- The prothrombotic, proinflammatory, and immunomodulatory properties associated with EVs, described above, may all contribute to and maintain tissue damage in the kidney and urinary tract during the development of AKI, glomerular and tubular diseases, infections, and chronic renal failure in addition to numerous other conditions affecting the kidney.
- Studies on the role of EVs in AKI have mostly been carried out in patients with sepsis, burns or other forms of acute tubular injury .

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EVS

- Their contribution to the induction and progression of renal diseases may lead to the development of treatments geared toward temporary reduction of EVs systemically in the circulation, or locally in the kidney and urinary tract. Treatments that reduce the release or uptake of EVs need to take into account the notion that EVs may also be cytoprotective, as their release and the removal of unwanted or damaging substances from their parent cells may maintain cellular integrity. EVs may have potentially beneficial properties associated with tubular regeneration and the induction of angiogenesis. The therapeutic potential and nephroprotective effects of EVs, owing to their capacity to shuttle proteins, lipids, and genetic cargo to recipient cells, are being explored in preclinical studies, which may lead to clinical trials in the future.

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RENAL FAILURE

- is a situation in which the kidneys fail to function adequately. It is divided in acute and chronic forms; either form may be due to a large number of other medical problems.
- Biochemically, it is typically detected by an decreased creatinine clearance
- Pathophysiologically, it is decrease in the glomerular filtration rate.
- When the kidneys malfunction, problems frequently encountered are abnormal fluid levels in the body, deranged acid levels, abnormal levels of potassium, calcium, phosphate, and (in the longer term) anemia.
- Long-term kidney problems have significant repercussions on other diseases, such as cardiovascular disease.

ACUTE RENAL FAILURE: ETIOLOGY

- Prerenal:
  - CV and volume depletion
  - Drug-induced or related (NSAIDs, ACEIs, diuretics)
- Intrarenal:
  - Inflammatory disease: Vasculitis, glomerulo-nephritis, drug-induced
  - Acute tubular necrosis
- Postrenal: Obstruction, Cancer, congenital abnormalities

ACUTE RENAL FAILURE

Pre-renal (causes in the blood supply):

- hypovolemia (decreased blood volume), usually from shock or dehydration and fluid loss or excessive diuretics use.
- hepatorenal syndrome in which renal perfusion is compromised in liver failure
- vascular problems, such as atheroembolic disease and renal vein thrombosis (which can occur as a complication of the nephrotic syndrome)

ACUTE RENAL FAILURE

Renal (damage to the kidney itself):

- infection usually sepsis (systemic inflammation due to infection),rarely of the kidney itself, termed pyelonephritis
- toxins or medication (e.g. some NSAIDs, aminoglycoside antibiotics, iodinated contrast, lithium)
- rhabdomyolysis (breakdown of muscle tissue) - the resultant release of myoglobin in the blood affects the kidney; it can be caused by injury (especially crush injury and extensive blunt trauma), drugs
- hemolysis - the hemoglobin damages the tubules; it may be caused by various conditions such as sickle-cell disease, and lupus erythematosus
- multiple myeloma, either due to hypercalcemia or "cast nephropathy" (multiple myeloma can also cause chronic renal failure by a different mechanism)
- acute glomerulonephritis which may be due to a variety of causes, such as anti glomerular basement membrane disease/Goodpasture's syndrome, Wegener's granulomatosis or acute lupus nephritis with systemic lupus erythematosus

ACUTE RENAL FAILURE

Post-renal (obstructive causes in the urinary tract) due to:

- medication interfering with normal bladder emptying.
- benign prostatic hypertrophy or prostate cancer.
- kidney stones.
- due to abdominal malignancy (e.g. ovarian cancer, colorectal cancer).
- obstructed urinary catheter.

ACUTE RENAL FAILURE: PATHOGENESIS

- Acute tubular necrosis (ATN):
  - Tubular cell sloughing
  - Reversibility/Irreversibility: dependent on time of intervention
- ATN Pathogenesis
  - Tubular occlusion theory and cast formation
  - Vascular hypoperfusion theory: Afferent vasoconstriction with efferent vasodilation
  - Role of renal mediators?

ACUTE RENAL FAILURE: CLINICAL PRESENTATION

- Heterogeneous group of disorders characterized by rapid deterioration in renal function (decreased GFR)
- Rapid elevation of urea in blood and serum creatinine
- Oliguria: variable
- Other: hematuria, proteinuria, edema, hypertension

ACUTE RENAL FAILURE: EARLY CLINICAL MANIFESTATIONS

- Symptoms depend on degree and cause of renal failure
- Initial Symptoms: Fatigue and malaise:
  - Loss of excretory capacity and accumulation of water, electrolytes and nitrogenous wastes
  - Prerenal azotemia: Elevated BUN/SrCr (20-30:1) with normal SrCr
  - Urinalysis: No casts detected
  - Maximal urinary concentration: 1500 mosm/L
  - Fractional Na excretion (99%)
  - May progress to ATN without proper treatment

ACUTE RENAL FAILURE: LATER CLINICAL MANIFESTATIONS

- Later Symptoms (frank ATN): dyspnea, orthopnea, heart (sound S3), edema
  - Normal BUN/SrCr, progressive elevation of SrCr
  - Casts (protein, RBC, epithelial cells)
  - Urine osmolality
  - Fractional excretion of Na (as low as 1%)

CHRONIC RENAL FAILURE-ETIOLOGY

- Diabetes mellitus (28%)
- Hypertension (25%)
- Glomerulonephritis (21%)
- Polycystic kidney disease (4%)
- Other (23%): Obstruction, infection, etc.

PATHOGENESIS OF CHRONIC RENAL FAILURE

- Chronic vs Acute renal failure pathogenesis:
  - Acute: tubular cell death and regeneration (reversible)
  - Chronic: Irreversible nephron loss
- Glomerular Hyperfiltration:
  - Compensatory mechanism with increased nephron GFR:
  - Pre-disposition to glomerular sclerosis
- Azotemia at 30-35% GFR
- Uremia: <20% normal excretory capacity

CHRONIC KIDNEY DISEASE

- is a progressive loss of renal function over a period of months or years through five stages. Each stage is a progression through an abnormally low and progressively worse glomerular filtration rate, which is usually determined indirectly by the creatinine level in blood serum.
- Stage 1 CKD is mildly diminished renal function, with few overt symptoms.
- Stage 5 CKD is a severe illness and requires some form of renal replacement therapy (dialysis or renal transplant). Stage 5 CKD is also called **end-stage renal disease (ESRD)**.

PATHOGENESIS OF UREMIA

- Retention of nitrogenous wastes
- Increased intracellular Na and water
- Decreased intracellular K
- Increased levels of bioactive substances normally cleared by kidneys (hormones)
- Decreased levels of hormones and other mediators produced by the kidney
- Decreased basal body temperature
- Diminished lipoprotein lipase activity

CHRONIC RENAL FAILURE: CLINICAL MANIFESTATIONS

- Sodium and water retention
- Hyperkalemia
- Metabolic Acidosis
- Mineral and Bone metabolism Disorders
- Cardiovascular and Pulmonary Disorders
- Hematologic Abnormalities
- Neuromuscular Abnormalities
- Gastrointestinal Abnormalities
- Endocrine Abnormalities
- Dermatologic Abnormalities

CHRONIC RENAL FAILURE: SODIUM AND VOLUME BALANCE

- Sodium and water retention:
  - CHF, Hypertension, ascites, edema
- Enhanced sensitivity to extra-renal sodium and water loss
  - vomiting, diarrhea, fever, sweating
  - Symptoms: dry mouth, dizziness, tachycardia, etc.

CHRONIC RENAL FAILURE: POTASSIUM BALANCE

- Hyperkalemia (GFR below 5 mL/min)
  - GFRs >5 mL/min: compensatory aldosterone-mediated K+ transport in the DTCs
  - K-sparing diuretics, ACEis, beta-blockers impair Aldosterone-mediated actions
  - Exacerbation of hyperkalemia:
    - Exogenous factors: K-rich diet, etc.
    - Endogenous factors: infection, trauma, etc.

CHRONIC RENAL FAILURE: POTASSIUM BALANCE AND DIABETES

- Diabetics (major cause of CRF):
  - Hyporeninemic hypoaldosteronism
  - Lack of renin - decreased angiotensin II - impaired aldosterone secretion - loss of compensation for low GFR

CHRONIC RENAL FAILURE: METABOLIC ACIDOSIS

Decreased acid excretion and ability to maintain physiologic buffering capacity:

- GFR > 20 mL/min: transient moderate acidosis
- Increased susceptibility to acidosis

CHRONIC RENAL FAILURE: MINERAL AND BONE DISEASES

Bone disease from:

- Decreased Ca++ absorption from the gut (decreased calcitriol- osteomalacia in adults)
- Over-production of PTH (decreased plasmatic calcium) –renal osteodystrophy
- Chronic metabolic acidosis (increased ionised calcium fraction)

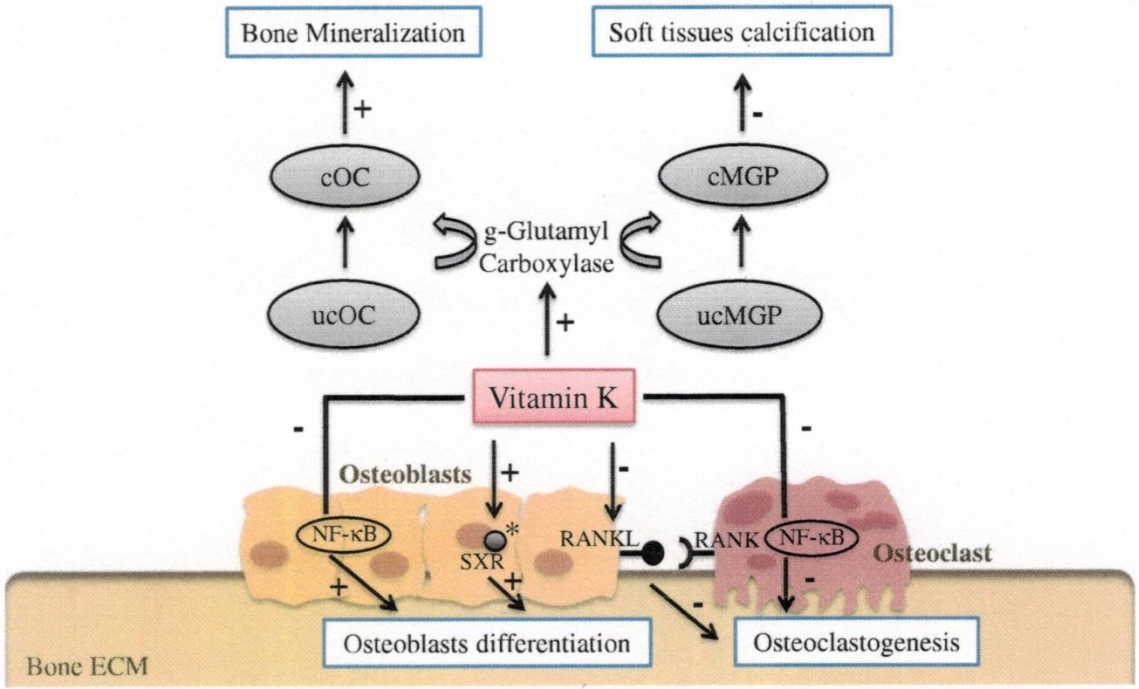


Fig. 1 – Mechanisms of action in bone. *: Evidence in animal models; ucOC: undercarboxylated Osteocalcin; cOC: carboxylated Osteocalcin; ucMGP: undercarboxylated Matrix Gla Protein; cMGP: carboxylated Matrix Gla Protein; NF-κB: nuclear factor κB; SXR: Steroid and Xenobiotic Receptor; RANKL: Receptor Activator of Nuclear factor Kappa B Ligand; RANK: Receptor Activator of Nuclear factor Kappa B; ECM: Extracellular matrix.

CHRONIC RENAL FAILURE:
CARDIOVASCULAR AND PULMONARY ABNORMALITIES

- **Volume and salt overload**
  - CHF and pulmonary edema
  - Hypertension
- **Hyperreninemia**: Hypertension
- **Pericarditis**: Remic toxin accumulation
- **Accelerated atherosclerosis**: linked to factors above and metabolic abnormalities (Ca alterations, hyperlipidemia)

CHRONIC RENAL FAILURE: HEMATOLOGICAL ABNORMALITIES

- **Anemia**: lack of erythropoietin production
- **Bone marrow suppression**:
  - uremic poisons: leukocyte suppression - infection
  - bone marrow fibrosis: elevated PTH an aluminum toxicity from dialysis
- **Increased bruising, blood loss (surgery) and hemorrhage**
- Lab Abnormalities: Prolonged bleeding time, abnormal platelet aggregation

CHRONIC RENAL FAILURE: NEUROMUSCULAR ABNORMALITES

- CNS Abnormalities:
  - Mild-Moderate: Sleep disorders, impaired concentration and memory, irritability
  - Severe: Asterixis, myoclonus, stupor, seizures and coma
- Peripheral neuropathies:
  - "restless legs" syndrome
- Hemodialysis-related neuropathies

CHRONIC RENAL FAILURE: GASTROINTESTINAL ABNORMALITIES

- **Peptic ulcer disease**: secondary hyperparathyrodism?
- **Uremic gastroenteritis**: mucosal alterations
- **Uremic fetor**: bad breath (ammonia)
- **Non-Specific abnormalities**:
  - anorexia, nausea, vomiting, diverticulosis, hiccoughs

CHRONIC RENAL FAILURE: ENDOCRINE ABNORMALITIES

- **Insulin**: Prolonged half-life due to reduced clearance (metabolism)
- **Amenorrhea and pregnancy failure**: low estrogen levels
- **Impotence, oligospermia and germinal cell dysplasia**: Low testosterone levels

CHRONIC RENAL FAILURE: DERMATOLOGIC ABNORMALITIES

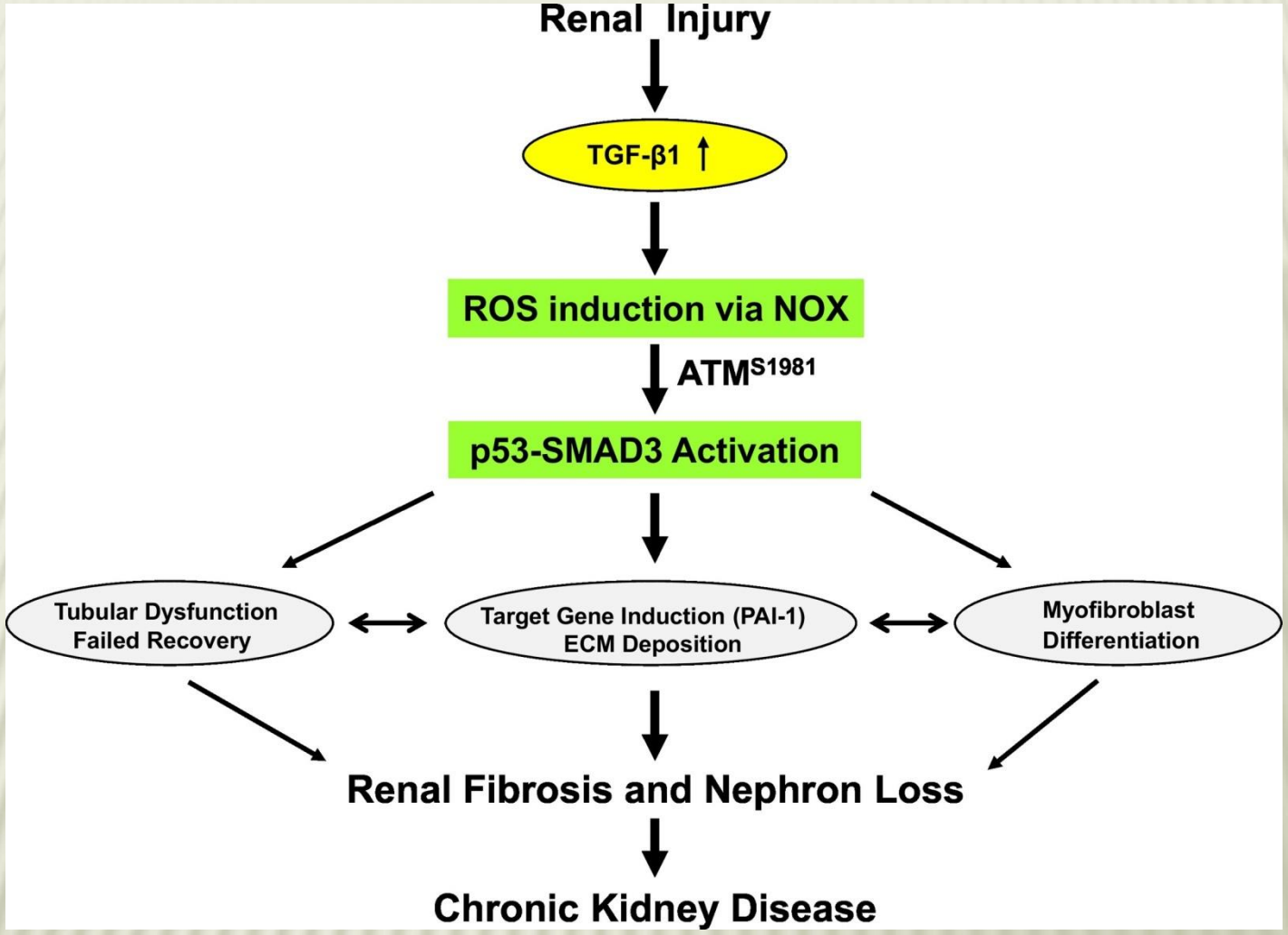
- **Pallor:** anemia
- **Skin color changes:** accumulation of pigments
- **Ecchymoses and hematomas:** clotting abnormalities
- **Pruritus and Excoriations:** Ca deposits from secondary hyperparathyroidism

FIBROSIS OF THE KIDNEY

- Sustained inflammation and repeated cycles of kidney injury/repair (or incomplete recovery) leads to tubular atrophy, progressive fibrosis, functional decline and, ultimately, organ failure.
- Episodic acute injury (AKI) to the proximal tubular epithelium is a major factor in the transition to chronic kidney disease (CKD) patients who survive AKI have an increased risk of development of CKD.
- Excessive accumulation of extracellular matrix (ECM; e.g., the fibrillar collagens, fibronectin) in the glomerular, interstitial and vascular compartments is accompanied by a significant decline in glomerular filtration rate and impaired epithelial regeneration.

FIBROSIS OF THE KIDNEY

- Interstitial fibrosis is both a pathophysiologic hallmark feature and prognostic biomarker of end-stage renal disease (ESRD).
- The primary sources of ECM synthesis during interstitial fibrogenesis are activated fibroblasts or myofibroblasts. Although controversial in origin, recent biomarker analysis and lineage-tracing studies suggest that this cell type-predictor of disease progression likely derives from FoxD1^{+} mesenchymal precursors (i.e., vascular pericytes and tissue-resident fibroblasts) with perhaps minor varying contributions from endothelial cells, completely or partially transdifferentiated tubular epithelia, and bone marrow fibrocytes.
- The persistence of such activated fibroblasts is a critical factor in the initiation and development of renal disease where they likely participate in the silent scarring phase prior to development of significant organ dysfunction.


Renal Injury
TGF-β1 ↑
ROS induction via NOX
ATM S1981
p53-SMAD3 Activation
Tubular Dysfunction
Failed Recovery
Target Gene Induction (PAI-1)
ECM Deposition
Myofibroblast
Differentiation
Renal Fibrosis and Nephron Loss
Chronic Kidney Disease

SCHEMATIC PRESENTATION OF THE RELEASE AND UPTAKE OF EXTRACELLULAR VESICLES

- **a** Exosomes are released from late endosomes termed multivesicular bodies bearing intraluminal vesicles (*ILVs*) intracellularly. When the multivesicular bodies fuse with the plasma membrane and empty their contents, ILVs are released and are termed exosomes once they are extracellular. Exosomes are the smallest extracellular vesicles.
- **b** Microvesicles are shed directly from the plasma membrane, thereby carrying membrane markers of the parent cell. Microvesicle formation is calcium-dependent and associated with loss of membrane asymmetry and disruption of the cellular cytoskeleton.
- **c** Extracellular vesicle uptake by target cells may occur via fusion of the vesicle membrane with the cell membrane or by endocytosis. The vesicle may also transduce an intracellular signal by ligand binding to a receptor on the recipient cell.

THANK YOU FOR YOUR ATTENTION