Biology of urinary system treatment damage

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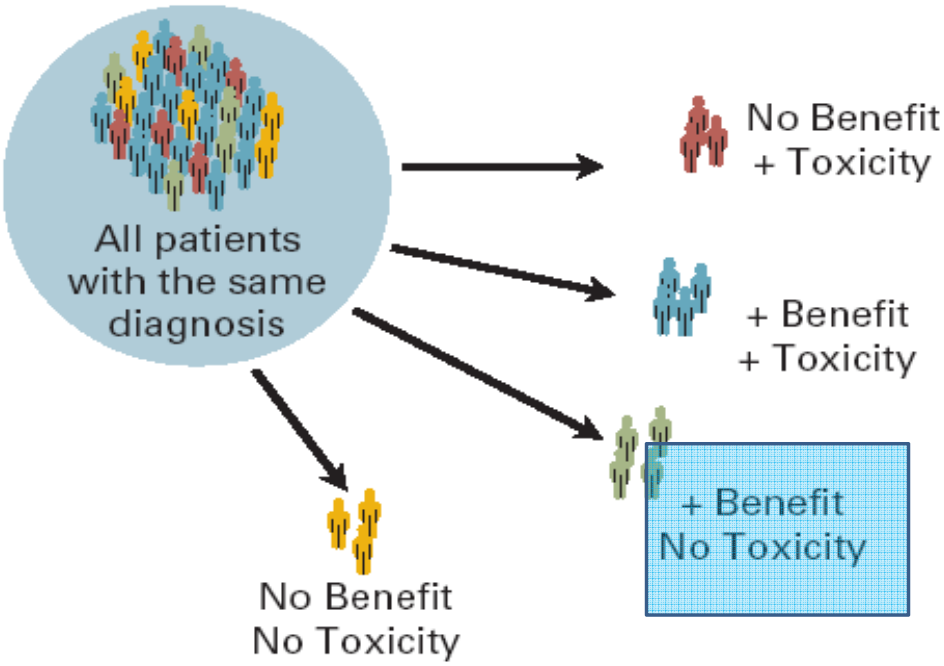
General concepts

•Despite positive advancement in oncological treatments for various malignancies, urinary toxicity remains a complication and sometimes limits life-saving therapies.

•Radiotherapy, chemotherapy and new biologic agents present a toxicity profile that is very different among them

•Their use requires in-depth knowledge of a large number of possible side-effects and drug interactions that have to be evaluated in light of patients' comorbidities and general health status.

General concepts:
BENEFIT – TOXICITES/RATIO



Walgren et al, JCO 2005

Roadmap

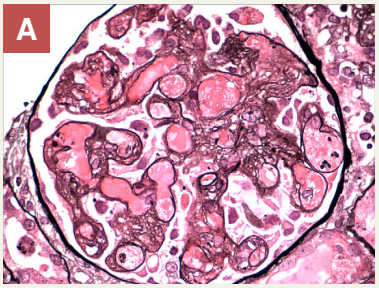
Chemotherapeutic agents and urinary system toxicity

Renal toxicity

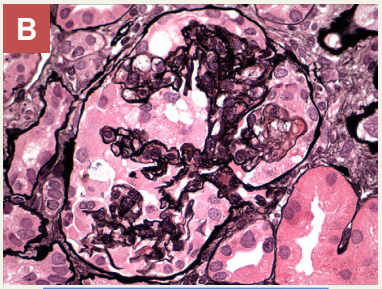
Classification of Chemotherapy-Associated Renal Lesions

Table 2. Kidney injury associated with chemotherapeutic agents

- Renal vasculature
  - hemodynamic AKI (capillary leak syndrome)
    - IL-2, denileukin diftitox
  - thrombotic microangiopathy
    - antiangiogenesis drugs (bevacizumab and tyrosine kinase inhibitors)
    - gemcitabine and cisplatin
    - mitomycin C and IFN
- Glomeruli
  - minimal change disease
    - IFN
    - pamidronate
  - focal segmental glomerulosclerosis
    - IFN
    - pamidronate
    - zoledronate (rare)
- Tubulointerstitium
  - acute tubular necrosis
    - platinums, zoledronate, ifosfamide, and mithramycin
    - pentostatin, imatinib, diaziquone, and pemetrexed
  - tubulopathies
    - Fanconi syndrome
      - cisplatin, ifosfamide, and azacitadine, diaziquone, imatinib, and pemetrexed
    - salt wasting
      - cisplatin and azacitadine
    - magnesium wasting
      - cisplatin, cetuximab, and panitumumab
    - nephrogenic diabetes insipidus
      - cisplatin, ifosfamide, and pemetrexed
    - syndrome of inappropriate antidiuresis
      - cyclophosphamide and vincristine
  - acute interstitial nephritis
    - sorafenib and sunitinib
  - crystal nephropathy
    - methotrexate



Thrombotic microangiopathy



Glomerulosclerosis

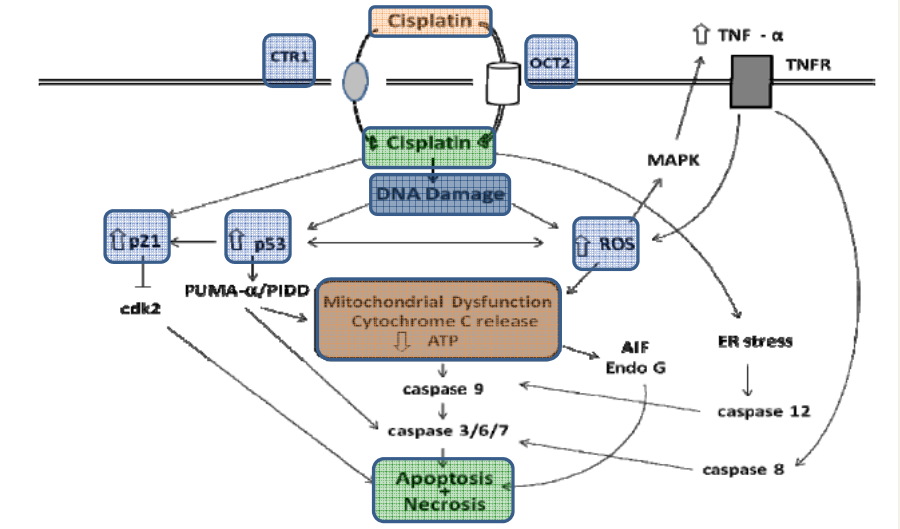
Renal manifestation and risk factors *of Cisplatin Nephropaty*

Renal manifestations of Cisplatin Treatment	
Acute kidney injury (20–30%)	[15,16]]
Hypomagnesemia (40–100%)	[17–21]
Fanconi-like syndrome	[22–26]
Distal renal tubular acidosis	[27]
Hypocalcemia	[28,29]
Renal salt wasting	[22,30–36]
Renal concentrating defect	[22,34,37–40]
Hyperuricemia	[41]
Transient proteinuria	[42]
Erythropoietin deficiency	[43]
Thrombotic microangiopathy	[44]
Chronic renal failure	[15,45,46]

Risk Factors for Cisplatin Nephropathy
Increased risk
Dose
Frequency
Cumulative dose
Older age
Female sex
Smoking
Hypoalbuminemia
Pre-existing renal insufficiency (limited data in humans)
Decreased risk
Diabetes (uncertain in humans)
OCT2 polymorphisms

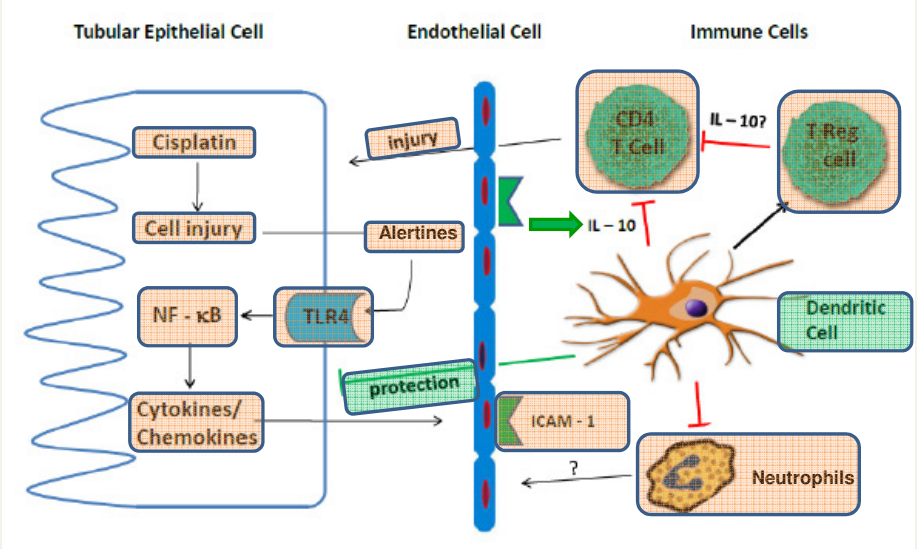
Classification of Chemotherapy-Associated Renal Lesions: *Tubules: Acute Tubular Injury*

Pathways of cisplatin-induced epithelial cell death



Classification of Chemotherapy-Associated Renal Lesions: *Tubules: Acute Tubular Injury*

Immune mechanisms of cisplatin nephrotoxicity

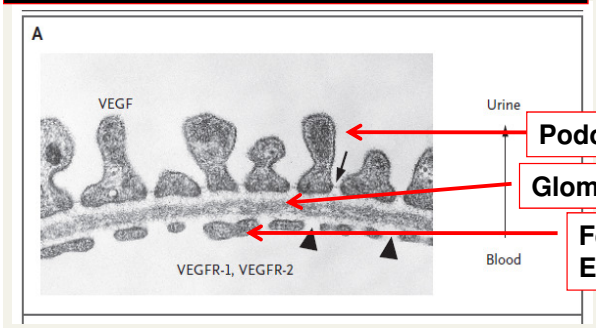


VEGF inhibition and Renal thrombotic microangiopathy

- The discovery that vascular endothelial growth factor (VEGF) is a critical factor in the growth of blood vessels led to the development of VEGF inhibitors
- The addition of bevacizumab to chemotherapeutic regimens improved survival rates among patients with cancers of the colon, lung, and breast
- Bevacizumab is also used as a single agent for renal-cell carcinoma
- Two of the most common adverse effects are proteinuria (in 21 to 64% of patients) and hypertension (in 3 to 36%).
- Direct experimental evidence indicates a mechanism of glomerular injury by VEGF inhibitors. Genetic ablation of VEGF production in the kidney recapitulates the glomerular injury found in humans

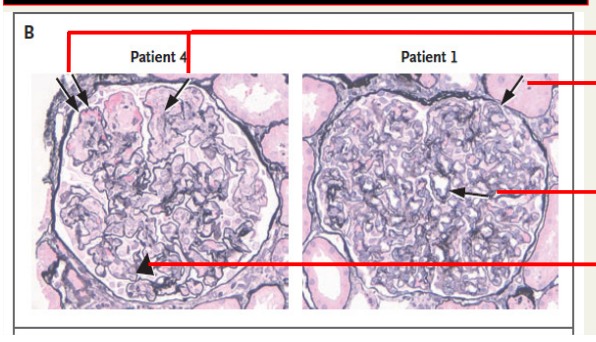
Bevacizumab and Renal thrombotic microangiopathy

Utrastructural glomerular filtration barrier



- Podocytes produce VEGF
- Glomerular basement membrane
- Fenestrated glomerular endothelial cells Expressing VEGFR

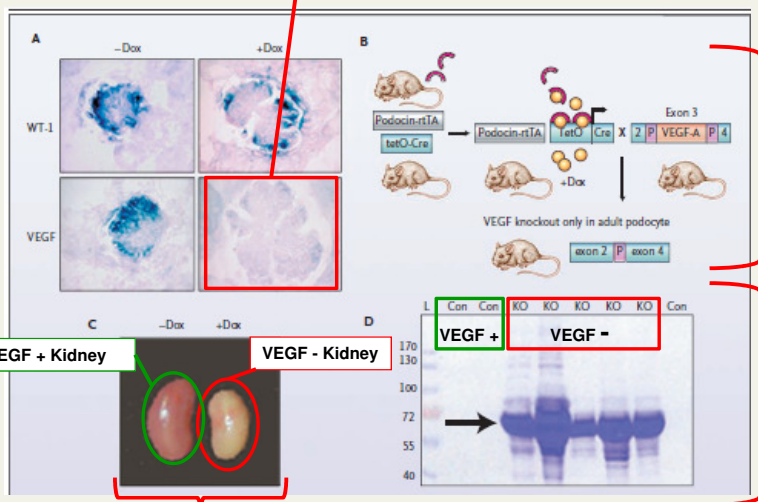
Bevacizumab induced microangiopathy



- Prominent endothelial swelling
- Mesangial cell loss
- Double contours of capillary basement membranes
- Red cell fragments

Bevacizumab and Renal thrombotic microangiopathy

The successful silencing of VEGF from podocytes confirmed by a lack of VEGF RNA expression after induction with doxycycline (+Dox), as compared with normal levels of Wilms' tumor suppressor 1 (WT-1) RNA, another gene expressed by podocytes.



VEGF + Kidney

VEGF - Kidney

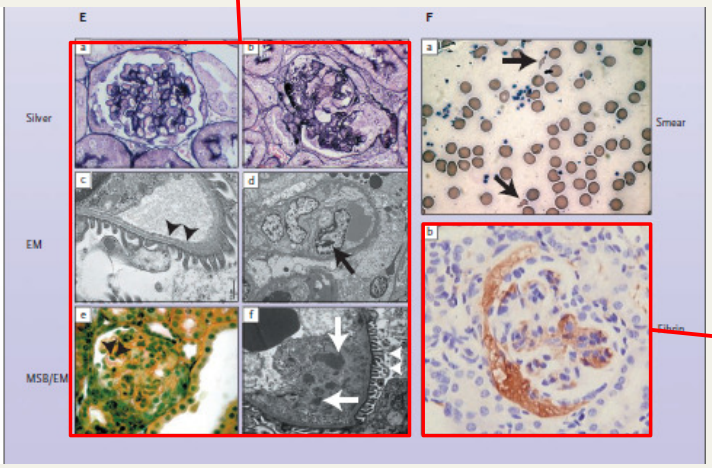
Breeding strategy used to generate a cell-specific knockout of VEGF in podocytes by using a Tet-On system

Albuminuria detected 4 weeks after VEGF knockdown in all mutant mice.

Kidney from a VEGF Knocked-down mouse after 9 weeks appears pale, small, and sclerotic. These findings are consistent with end-stage kidney failure, as compared with a normal kidney.

Bevacizumab and Renal thrombotic microangiopathy

Hystologically murine model closely resembles the human pathology



Immunohistochemical staining shows that glomeruli from VEGF defective mutants are highly positive for fibrin

Bladder

Bladder GAG Layer/Epithelial Permeability

- **It has been hypothesized that radiation cystitis is the result of some defect in the epithelial permeability barrier of the bladder surface glycosaminoglycans**
- Major classes of glycosaminoglycans (GAGs) include *hyaluronic acid, heparin sulfate, heparin*, chondroitin 4-sulfate and chondroitin 6-sulfate, dermatan sulfate, and keratan sulfate

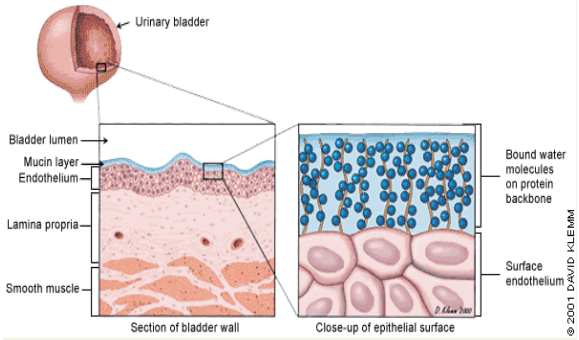
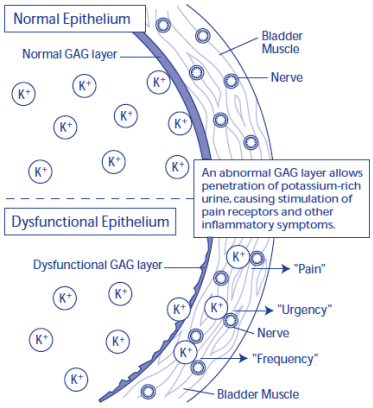


Figure 1. A Depiction of Normal and Abnormal Bladder Epithelium



Roadmap

Radiation therapy and urinary system toxicity

Renal toxicity
Clinical correlates

Radiation nephropathy
Diagnostic challenges

Long latency phase after exposure

Clinical signs become detectable after months or years.

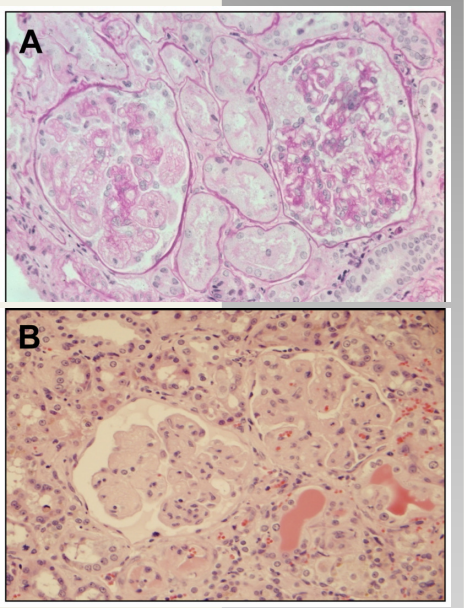
- ***Acute radiation nephropathy:*** 6-12 months
- ***Chronic radiation nephropathy:*** 2-10 years (with or without acute phase)

Diagnostic features are non-specific

Clinical: Hypertension, proteinuria, edema, urinary casts, reduced GFR

Histology: TMA like changes in glomeruli and arteries, acute and chronic tubular injury, glomerular scarring, intimal fibrosis, interstitial fibrosis might be due to many other types of injury

Radiation nephropathy appearance



Sieber F, et al Radiat Res. 2009; 171:368–73.

Roadmap

Radiation therapy and urinary system toxicity

Bladder toxicity
Clinical correlates

Clinical Definition of Radiation cystitis

- Histologic and clinical changes are time and dose dependent
- Early signs may appear 4-6 weeks after initiation of therapy
- Late reactions may appear between 3 months and 10 years (Am J Surg Pathol 1978;2:159)
- Toxicity enhanced if radiation is given with cyclophosphamide
- Similar changes with intravesical chemotherapy, which often affects superficial layer of urothelium and causes denuding cystitis

Clinical Definition of Radiation cystitis

Storage Symptoms	Voiding Symptoms	Post-Micturition Symptoms
▪ Urgency ▪ Frequency (≥8 micturitions/24 hrs) ▪ Incontinence ▪ Nocturia (Waking up ≥ 2 times at night to void)	▪ Poor flow ▪ Intermittency ▪ Straining ▪ Hesitancy ▪ Terminal dribble	▪ Post-void dribble ▪ Incomplete emptying

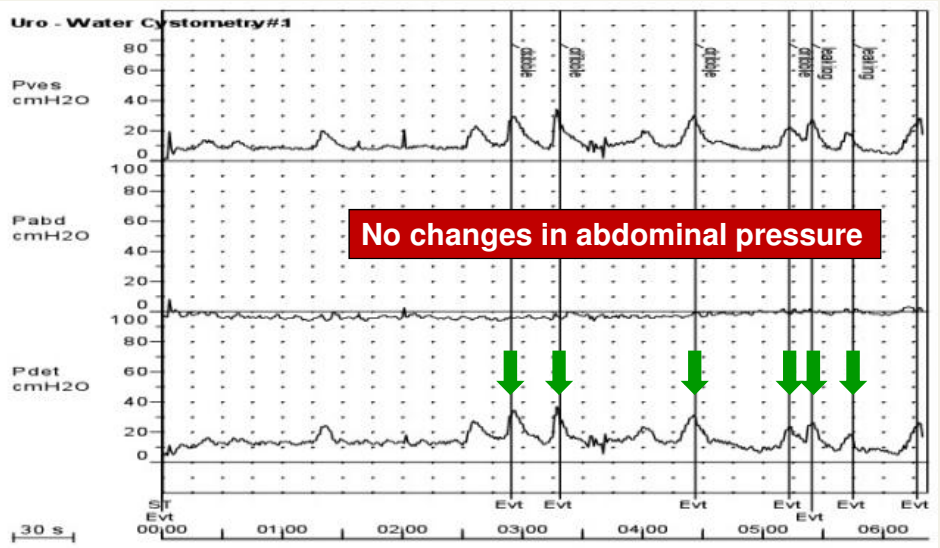
Suggestive of Radiation cystitis

Suggestive of radioinduced Bladder Outlet Obstruction

+

Voiding pain and Gross hematuria

Urodynamic findings of Radiation cystitis

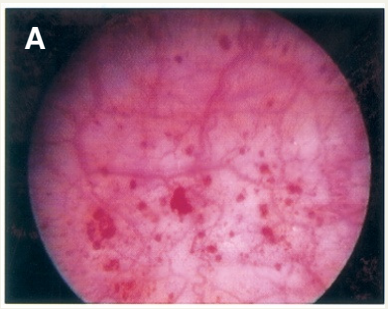


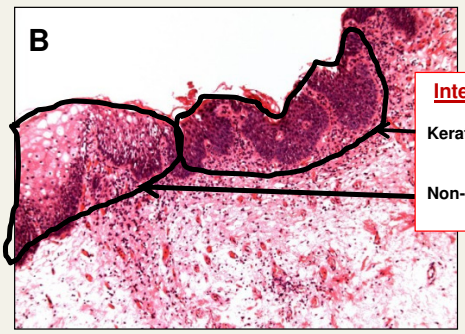
No changes in abdominal pressure

Cystometric Phase

Episodic contractions of bladder detrusor during filling

Cystoscopic and hystologic appearance of Radiation cystitis

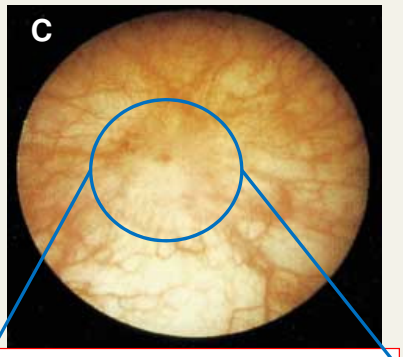




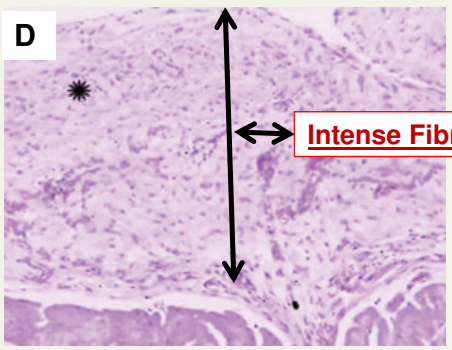
Intense mucosal inflammation:

Keratinising metaplasia

Non-keratinising metaplasia



Bladder scar with radiating vessels



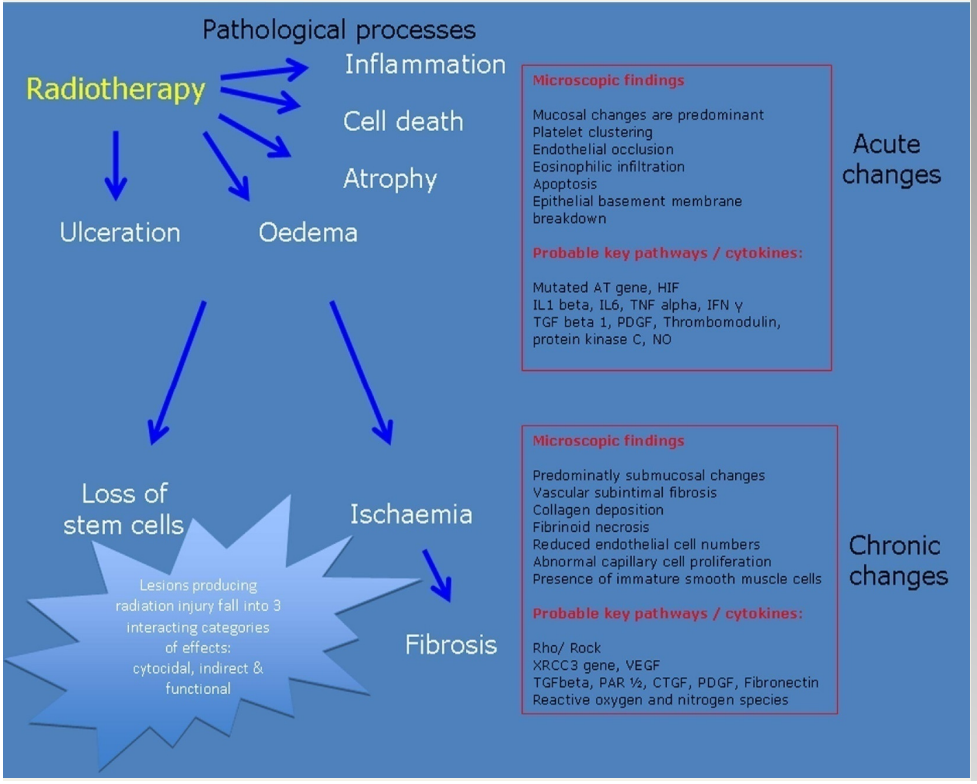
Intense Fibrosis

Roadmap

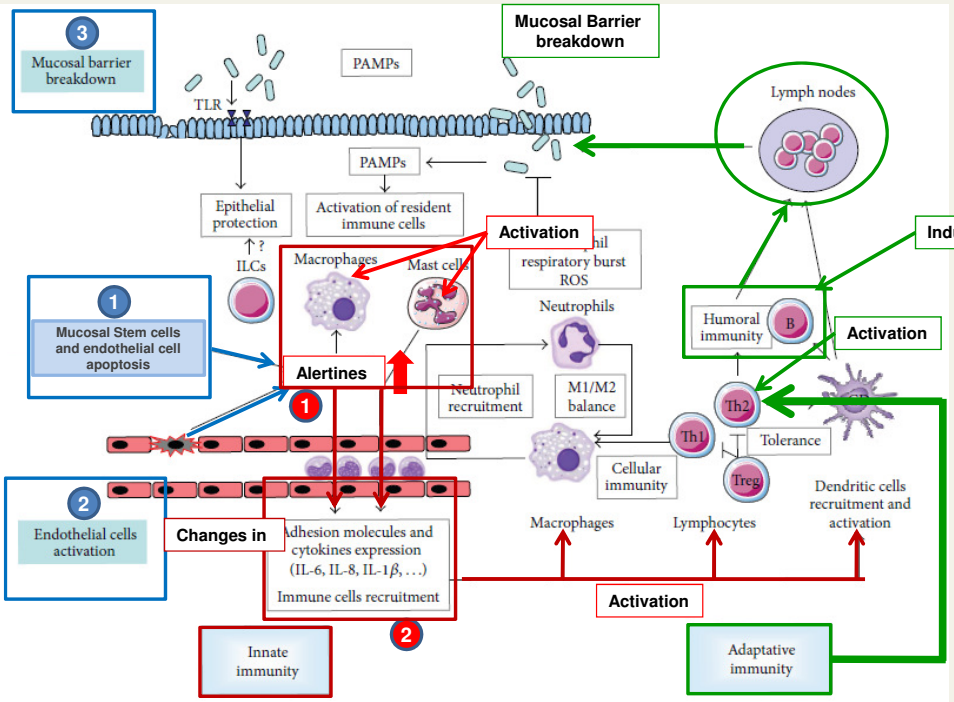
Radiation therapy and urinary system toxicity

Shared biological correlates

Cell and molecular pathways to radiation injury



Shared biological correlates
Radiation-induced Inflammation



Shared biological correlates
Radiation-Induced Vascular damage

Early endothelial effects

- Apoptosis
- Activation: increased expression of cell adhesion molecules and cytokine secretion
- Recruitment of inflammatory cells
- Pro-coagulant and pro-thrombotic phenotype
- Increased permeability
- ROS production

Late endothelial effects

- Microvessel collapse: rupture and dilatation of capillaries
- Thickening of the basal membrane Thrombosis
- Chronic pro-inflammatory phenotype
- Chronic production of ROS
- Senescence

Effects of irradiated endothelium on surrounding normal tissues

- Ischemia
- Necrosis
- Tissue fibrosis

Isabelle Corre et al *Int. J. Mol. Sci.* ***2013, 14, 22678-22696***

J Am Coll Cardiol. 2010;55(12):1237-1239. doi:10.1016/j.jacc.2009.11.053

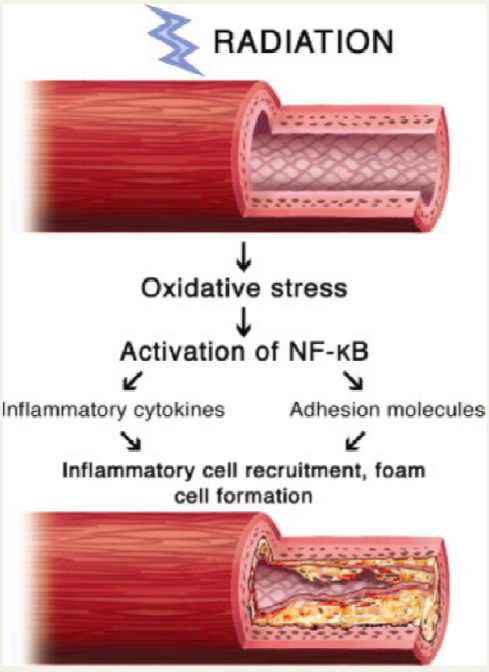
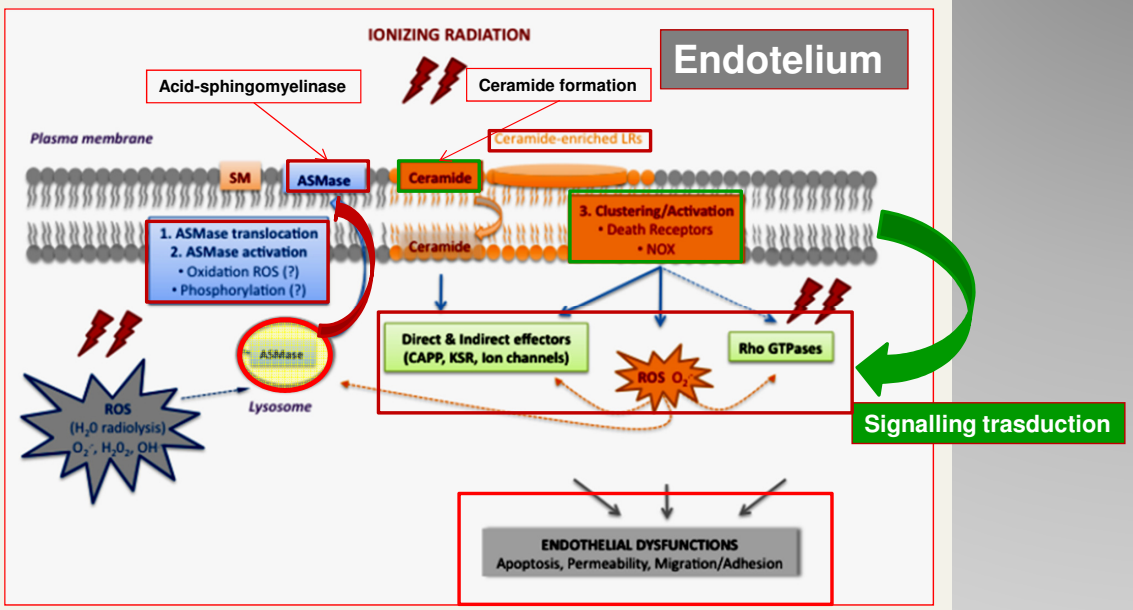


Figure Legend:

Proposed Mechanism of Involvement of NF-κB in Radiation-Induced Vascular DiseaseNF-κB = nuclear factor-kappa B.

Shared biological correlates
Radiation-Induced Vascular damage



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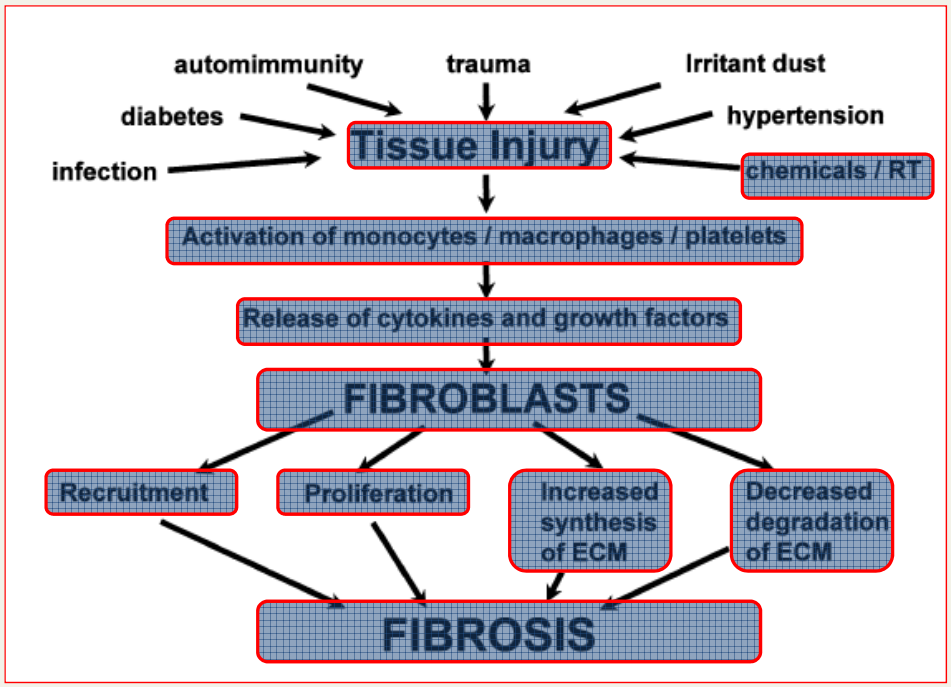
Shared biological correlates
Radiation-Induced FIBROSIS

Consolidate biological events



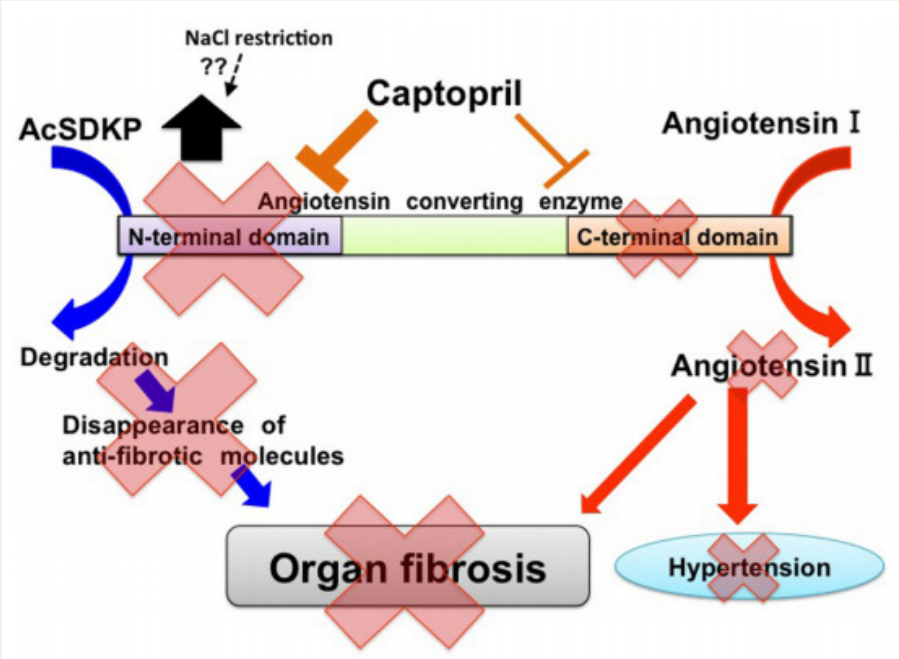
Roadmap

Radiation therapy renal fibrosis

Diversified biological correlates

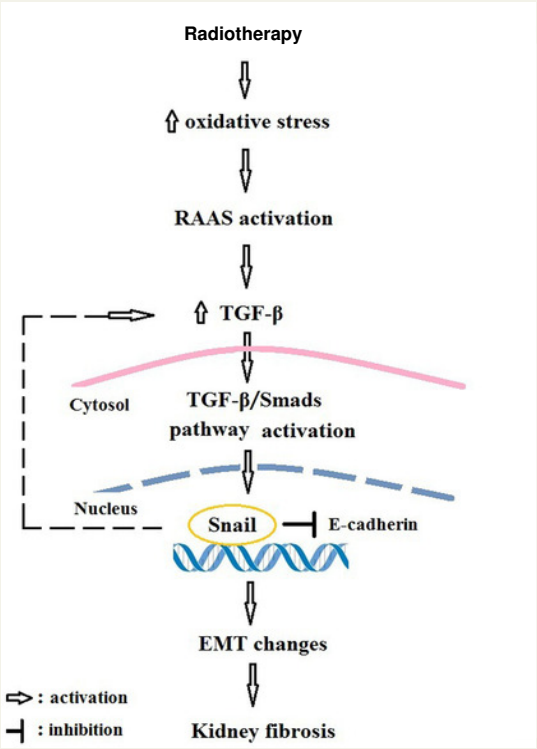
Renal fibrosis

Renin-Angiotensin system in radio-induced renal toxicity



Kidney

Renin-Angiotensin system in radio-induced renal toxicity



Conclusions

- Despite dramatic improvements in patient survival and drug tolerability, urinary system toxicity remains an important complication of oncological treatments.
- Common and diversified biological processes are responsible for urinary system toxicity after oncological treatments.
- All clinicians involved in the management of patients with tumor oncologists must be familiar with the toxicity of these treatments.
- Undoubtedly the knowledge of the biological processes responsible for acute and late toxicity may favor the development of biological tailored supportive treatments