IMMUNOLOGIC MECHANISMS IN THE KIDNEY INFLAMMATORY DISEASES

(Prof Dr Besim Prnjavorac
General Hospital Tešanj, BiH)

INFLAMMATION AS UBIQUITOUS PROCESS

- Inflammation is one of the primary defensive barriers of human body;
- It's body's innat immune response to foreign matters, or tissue damage;
- Inflammation can also occur when there is not a foreign substance to fend of.
- In this case, inflammation "turn on the body" and lead to disease, specially identified as autoimmune diseases.

INFLAMATION AND "SELF – NO-SELF" TISSUE RECOGNITION

- Tissue damage lead to change of structure, with or without possibility to change of immunologic patterns of tissue recognition. (horor autotoxicus)
- Damaged tissue should be alienated from the body, or repaired, if possible;
- Inflamamation is very well regulated, and "self-limited", with autoregulatory patterns.

REPARATION OF DAMAGED TISSUE

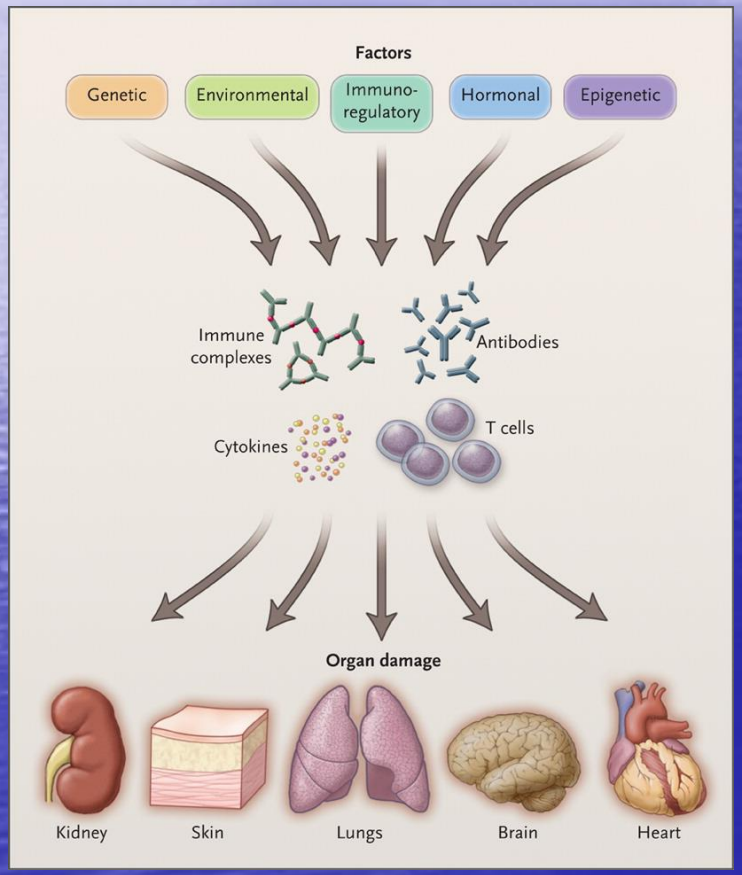
- Inflammation shoud be "self limited", in any case of appearance; If no, autoimmune process can and will proceed.
- Injury is "main point" of interest in any pattern of inflammation, as "body protection";
- Body cells (Leucocytes, lymphocytes, dendritic cells, macrophages) involved in immune respons work in both patterns, non-specific and specific, were "self-recognition" is obvious.

INFLAMMATION – CAUSE OR RESULT OF KIDNEY TISSUE DAMAGE

- **Apoptosis** of inflammatory cells is a necessary and effective process in inflammation, as a self-preserving action of inflammation;
- In chronic kidney disease, inflammation could appear as a cause or as result of disease;
- As chronic kidney disease (CKD) progresses, a commanding presence of inflammatory markers can be measured in the blood with increased concentration according to inflammatory patterns;

INFLAMMATORY AND IMMUNE PATTERNS AS CAUSE OF KIDNEY DISEASES

Autoimmune patterns – inadequate apoptosis function



- **Overview of pathogenesis of SLE;**

NEJM,2011; 365:2110-21

INFLAMATORY AND IMMUNE PATERNS AS CAUSE OF KIDNEY DISEASES (no the subject of this presentation)

- Immunocomplexes in basal membrane as pattern of damage;
  - Vasculitis (any case);
  - Goodpasture syndrome;
  - Poststreptococcus infection and ASTO sensibilisation
- Granuloma formation (Wegener);
- Precipitation of proteins and interstitial cellular infiltration (meny cases of glorulonephritis);

INFLAMATION AS RESULT OF KIDNEY INJURY (acute and CKD)

- Complemet function is necessaire for removal of immuncomplexes (Ag-AB);
- If Antigen for long time overcome AT concentration Ag-stimulation is permanent, and production of complexes can be faster than removal;
- As the chronic kidney disease progresses, commanding presence of inflammaory markers increses in the blood;
- C-reactive protein (CRP), IL16, IL-6, TNF;
- In prolonged inflammation transforming factor β (TGF-β) increase.

INFLAMMATION AS RESULT OF KIDNEY INJURY
(acute and CKD)

- Its known that anemia (any cause), with tissue hypoxia, speed up kidney injury;
- Drug toxicity is more harmful with anemia than without;
- Most drug related kidny injury appear as interstial disease, were are a lot of immune cells.

- It's known so, renal failure can start with increasing of clearance (hyperemia and hyperperfusion in acute phase in any inflammation);

- Inflamation go toward resolution, but when and how, that's the job of cytokines, as regulatory factors of inflammation;

FIBROGENESIS, BED OUTCOME OF INFLAMMATION

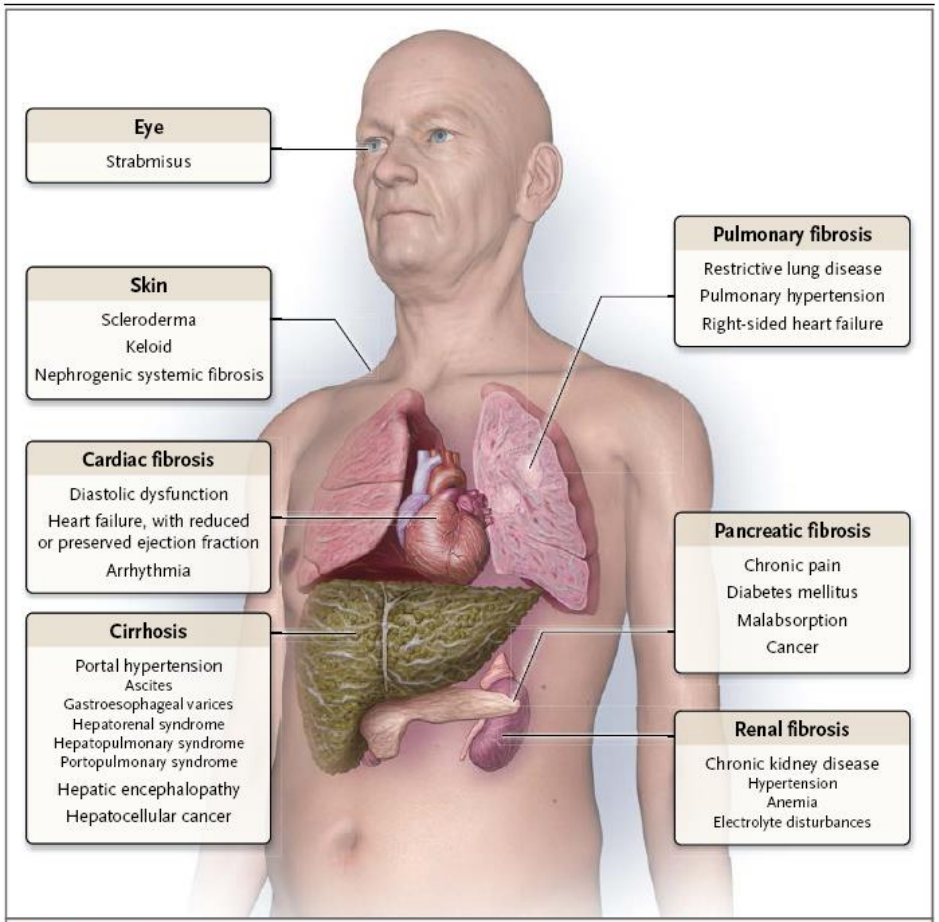
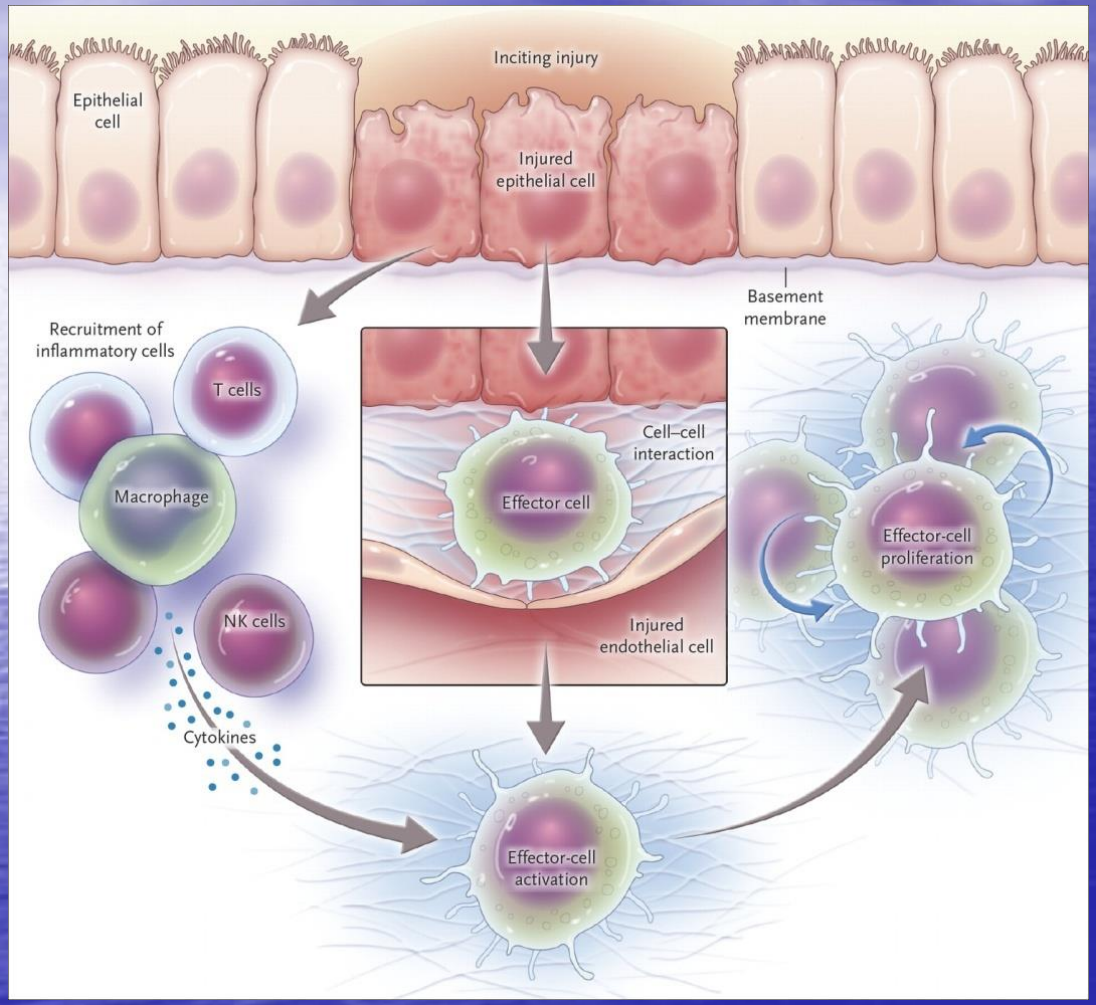


Figure 1. Fibrogenesis and Major Organ Systems.
Fibrosis is a pathologic feature of disease in virtually all organs. It has protean and often lethal consequences and accounts for substantial morbidity and mortality. Selected organs and associated diseases are highlighted.

- **Fibrosis can appeares as one of bed outcome of inflammation;**
- **If TGF-β is dominant in regulation of inflammation, fibrosis appears;**
- **Multiple organs – all mesenchimal tissue are the target**

NEJM, 2015; 372: 1138-46

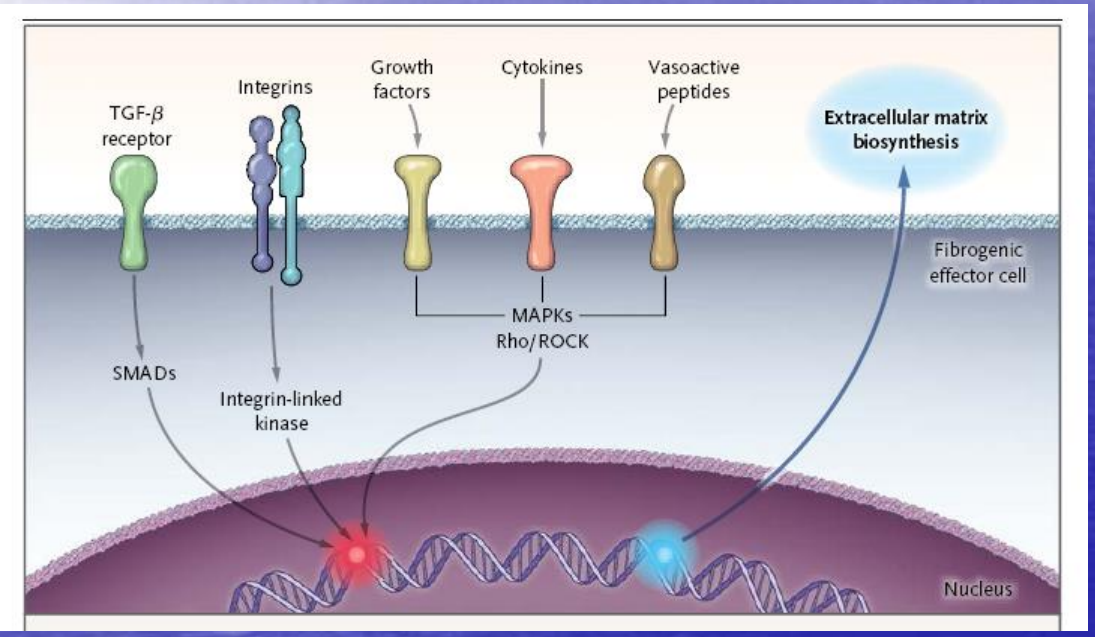
CELLULAR INJURY AND INFLAMMATION - FIBROGENESIS



- Epithelial cells injury provoke inflammation;
- Importante cytokines: VEGF-vascular endothel growth factor, TGF-β, IL-1,
- Importante cells: MF, T-ly, NK,
- Importante ubiquitous molecules TLR4-Toll-like receptor 4;

NEJM, 2015; 372: 1138-46

MOLECULAR PATHWAYS OF FIBROSIS



- TGF-β initiate process
- Protein synthesis of integrin – fibrose tissue fastener:
- Cytokines EGF
- Tissue matrix proteins sythesis

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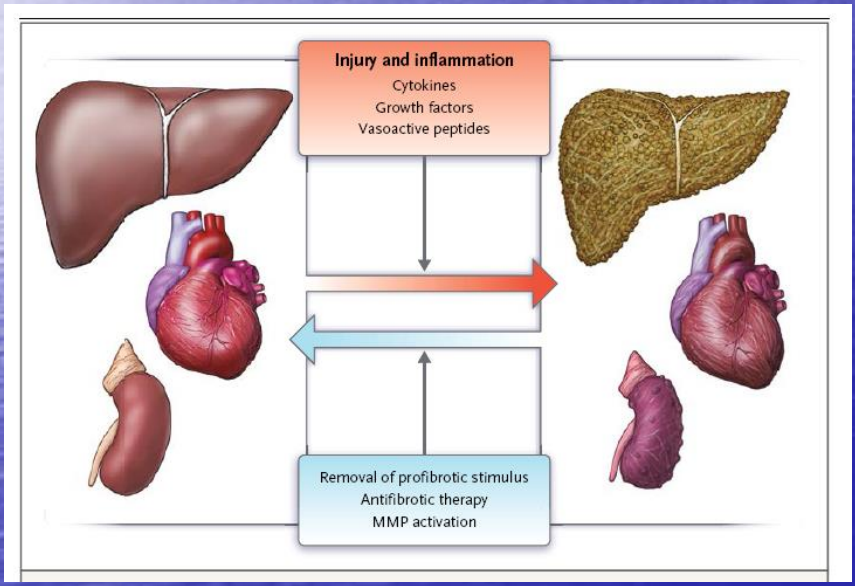
REVERSIBILITY OF FIBROSIS



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- Fibrosis is plastic process in which there is dynamic interplay between extracellur matrix, protein deposition and degradation.
- If degradation overtakes deposition fibrosis can be reversed.
- Therapeutuc intervention targeting the underlying disease process may help to reverse fibrogenic process.
- (Perfenidon- inhibits TGF–β and fibrosis formatioon
- MMP – Matrix metalloproteinase

POSSIBLE TH. INTERVENTION (Pentoxyphyllin)

Table 1. Pathways and Processes in Fibrogenesis and Current Treatments.*

Organ	Pathways and Processes	Diseases	Drugs	Summary of Effectiveness	Source of Data†
Heart	Aldosterone antagonism, TGF-β antagonism, RAS inhibition, cGMP inhibition, inhibition of cholesterol synthesis, inhibition of Na-K-Cl cotransporter	Heart failure, cardiomyopathy, hypertrophic cardiomyopathy, cardiomyopathy induced by type 2 diabetes, heart failure or cardiomyopathy induced by hypertension	Spironolactone, eplerenone, canrenone, pirfenidone, sildenafil, statins, ACE inhibitors, ARBs, torsemide, MRAs	ACE inhibitors, ARBs, and MRAs are associated with decreased fibrosis on MRI and decreased arrhythmogenesis (the latter suggests effects of drugs on fibrosis)	Kosmala et al.,[67] Giannetta et al.,[68] Antonopoulos et al.,[69] Roubille et al.,[70] TORAFIC Investigators Group[71]
Liver	RAS inhibition, inhibition of collagen synthesis, inhibition of effector-cell fibrogenesis, inhibition of oxidative stress, signaling of PPAR γ-agonists	Many diseases of the liver	ACE inhibitors, ARBs, colchicine, interferon γ-1b, vitamin E, pioglitazone, farglitazar	Specific antifibrotic agents listed have generally been ineffective in halting or reversing fibrosis	Sanyal et al.,[72] Kim et al.,[73] Kershenobich et al.,[74] Morgan et al.,[75] Muir et al.,[76] Pockros et al.,[77] McHutchison et al.[78]
Kidney	RAS inhibition, aldosterone antagonism, TGF-β antagonism, Nrf2 pathway	Primarily renal diseases related to hypertension or diabetes	ACE inhibitors, ARBs, spironolactone, pirfenidone, bardoxolone	ACE inhibitors and ARBs are moderately effective in slowing progression of diabetic nephropathy (indirectly suggesting effects on fibrosis)	Lambers Heerspink et al.,[79] Ruggenenti et al.,[80] Bonventre,[81] Guney et al.,[82] Sharma et al.,[83] de Zeeuw et al.[84]
Lung	TGF-β antagonism, direct inhibition of effector-cell fibrogenesis, multikinase inhibition, inhibition of oxidative stress	Primarily idiopathic pulmonary fibrosis	Pirfenidone, interferon γ-1b, bosentan, ambrisentan, macitentan, nintedanib, acetylcysteine	Pirfenidone and nintedanib led to improvements in clinical outcomes	Raghu et al.,[85-87] King et al.,[88] Richeldi et al.,[89] Martinez et al.[90]
Skin	Endothelin-receptor antagonism, multikinase inhibition	Scleroderma, nephrogenic systemic fibrosis	Bosentan, imatinib mesylate	Small studies show modest effects	Kuhn et al.,[91] Kay and High[92]

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CONNECTION BETWEEN INFLAMMATION AND COAGULATION

- Coagulation pathway starts with High Mollecular Weight Kininogen (HMWK – inflammation mediator);
- Inflammation is associated with a coagulation cascade and can lead to elevated procoagulant status;
- Specifically potent are: C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, and soluble adhesion molecules;
- In addition, IL-1 and tumor necrosis factor (TNF) lead to procoagulant status and elevated cardiovascular risk;
- Elevated levels of inflammatory markers add an increase in cardiovascular risk in patients with CKD.

CARDIOVASCULAR REPERCUSSION OF KIDNEY DISEASES AND "VICE VERSA"

- An association of renal dysfunction and cardiovascular risk has been demonstrated in recent studies.
- As shown in recent literature, use of statins, such as hypolipemic drugs, can reduce general inflammatory status in the body.
- Statins have anti-inflammatory proprieties and may attenuate loss of kidney function.

Kidney Int. 2005; 68(1) 237-45

CARDIOVASCULAR REPERCUSSION OF KIDNEY DISEASES AND "VICE VERSA"

- **Although inflammation may mediate progressive renal injury, the relationship between statin use, markers of inflammation, and the rate of kidney function loss is to be interpreted.**
- **In some studies higher levels of TNF and CRP are independently associated with faster rates of kidney function loss in CKD.**
- **Statins appear to prevent loss of kidney function to a greater extent in individuals with greater presence of inflammation.**

Circulation, 2003; 107:87-92.

INFLAMMATION AND OUT RENAL RISKS IN CKD

- Metabolic disturbances in dialysis patients' cause significant tissue damage.
- Its well-documented that the metabolic disturbances cause an increase in markers of inflammation in dialyses patients.

- TGF-β, TNF, IL-1, IL-6 were analyzed in our Hospital;
- The data is to be published;

BIOMARKER OF INFLAMMATION AND PROGRESSION OF KIDNEY DISEASE

- In recent literature there are meny articles related to inflammation in CKD;
- Higher CRP and TNF are indepedently associated with faster rate of kidney function loss ;
- Pravastatin appears to prevent loss of kidney function if greater evidence of inflammation was present;

(Kidney Int. 2015; 68(1)237-45);

CONCLUSION

- Immunologic patterns of immune CKD are well known (like lupus nephritis Goodpasture syndrome, different type of glomerulonephritis and so on).
- It is important to note, inflammation is present in CKD, as cause or as result of these diseases.
- It's to be underlined that inflammation is ubiquitous, and the worst resolution of inflammation is fibrosis;
- Today some therapeutic intervention could performe immunomodulation with possibility to decrease fibrosis formation;

THANK A LOT FOR YOUR ATTENTION

THANK FOR COLLEAGUES FROM PITTSBURGH UNIVERSITY, USA, FOR ASSISTANCE