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agenda

- Summary on comparison between CLAD and cGVHD of the lung
- Discussion points
- Future directions
- Outcomes of Lung Transplant in cGVHD patients
- Use of MSC in CLAD preliminary single centre report

CLAD ➡ cGVHD of the lung

O-CLAD (BOS)

- FEV1 decline = or> 20% with respect to Best value post Tx
- Onset: late and laggard
- DD bronchial stenosis/infections
- CT scan : air trapping ,BC
- BAL findings : neutrophilia
- Risk factors : alloimmune/autoimmune/non allo-autospecific (infections, Reflux)
- Therapy: low level of evidence on ECP (stabilization)/TLI
- Ongoing Clinical study on anti Rock2 belumesudil
- Survival : > 4 yrs

BOS (GVHD)

- % predisted but…basal Post Tx value may vary for other causes
- Onset : median 13 months post tx ?
- DD : infections
- CT scan : air trapping ,BC
- BAL findings : neutrophilia
- Risk factors : male gender, conditioning (?) HLA match, a and c GVHD (>)type of IS,gender disparities infections…
- Therapy: ECP (stabilization)/Jak inhibitors (caution)/anti Rock2 belumesudil (low level of evidence) Lung Tx
- Survival 73 % at 5 yrs

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CLAD ➡ cGVHD of the lung

R-CLAD = RAS

- FEV1 decline & restrictive patterm (FVC/TLC)
- Onset: rapid and early
- DD infections/pleural or extrapulmonary causes of restriction
- CT scan : infiltates, ULF, PPFE
- BAL findings : neutrophilia/eosinophilia
- Risk factors DAD, ↑BAL levels of alarmins HMGB1, de novo DSA, specific anti HLA mismatch.
- Therapy: No effect of ECP/case reports on antifibrotics /REDO
- Median survival ≈1.5 yrs
- REDO

Restrictive GVHD

- Basal Post Tx value sometimes lacking
- Onset : 15 post tx months
- DD Other causes of restriction (skin /muscle)/ infections. Genetic- NON genetic -ILD?(!Assess pre Tx presence of minimal abnormalities) .
- BAL findings : neutrophilia
- CT scan : infiltates, ULF, PPFE, NSIP pattern /OP (?)
- Risk factors : type of IS, infections, a and c GVHD (<)lower IS, previous Thoracic irradiation /Age?/ previous chronic lung disease
- Therapy: ECP?/Jak inhibitors (caution)/anti Rock2 belumesudil (stilllow level of evidence) Lung Tx
- Survival similar to BOS 70 % at 5 yrs?

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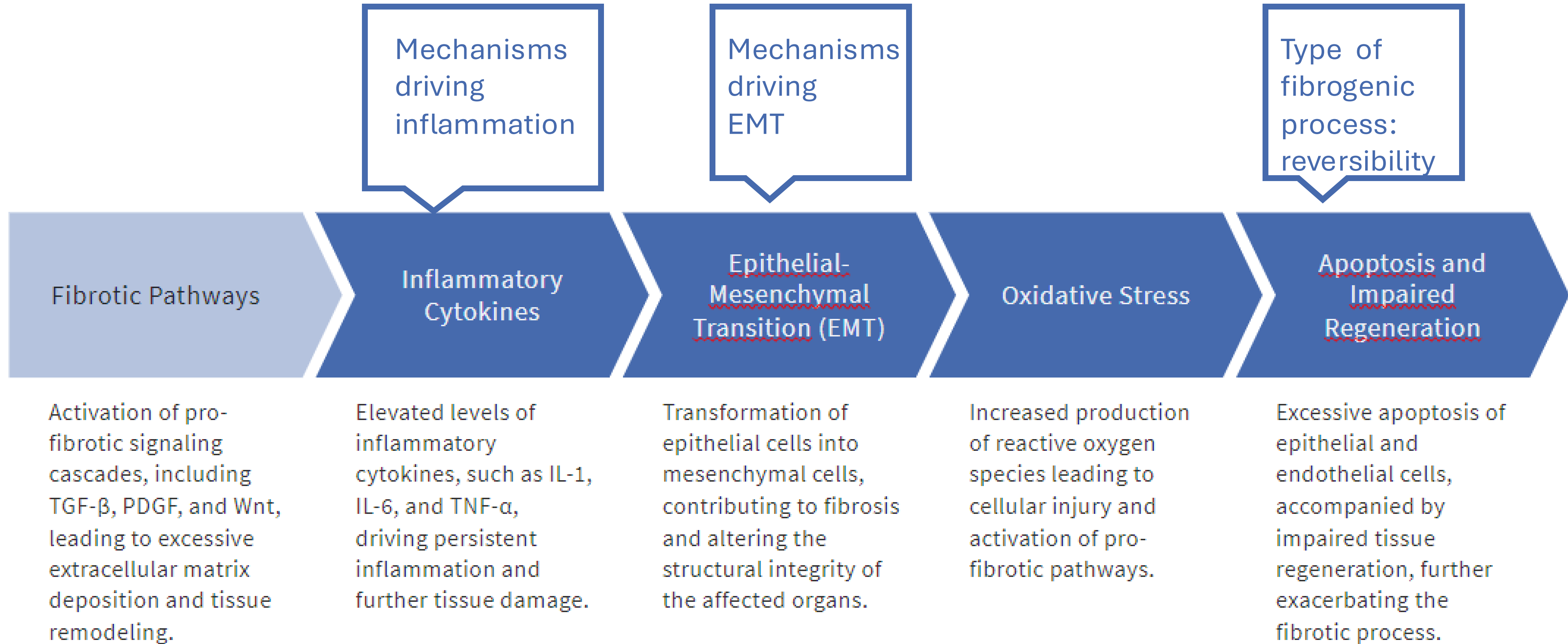
PATHOGENIC MECHANISMS
Mechanisms driving inflammation
Mechanisms driving EMT
Type of fibrogenic process: reversibility
Fibrotic Pathways
Inflammatory Cytokines
Epithelial-Mesenchymal Transition (EMT)
Oxidative Stress
Apoptosis and Impaired Regeneration
Activation of pro-fibrotic signaling cascades, including TGF-β, PDGF, and Wnt, leading to excessive extracellular matrix deposition and tissue remodeling.
Elevated levels of inflammatory cytokines, such as IL-1, IL-6, and TNF-α, driving persistent inflammation and further tissue damage.
Transformation of epithelial cells into mesenchymal cells, contributing to fibrosis and altering the structural integrity of the affected organs.
Increased production of reactive oxygen species leading to cellular injury and activation of pro-fibrotic pathways.
Excessive apoptosis of epithelial and endothelial cells, accompanied by impaired tissue regeneration, further exacerbating the fibrotic process.

Discussion points

- GVHD restrictive phenotype
  - Pre Tx HRCT scan necessary (not always available)
  - Pre and Post lung Tx LFT necessary (Not always available)
  - Chronic : reversible or irreversible ? OP vs PPFE/NSIP
  - Hystological evaluation is rare
  - Exclusion of other causes of Restriction /concomitant diseases
  - The role of autoimmunity / autorective B cells

Future directions

- Clear definition of restrictibve pulmonary GVHD
- Early identification of cGVHD at risk patients
- Identification of common / different risk factors
- Identify common/ diffeent pathogenic patwhays susceptible of therapeutic targeting
- Multicentric studies possibly targeting both GVHD and CLAD patients (as it happend for iCSA/ Belumesudil)