ISCHEMIA REPERFUSION INJURY [IRI]

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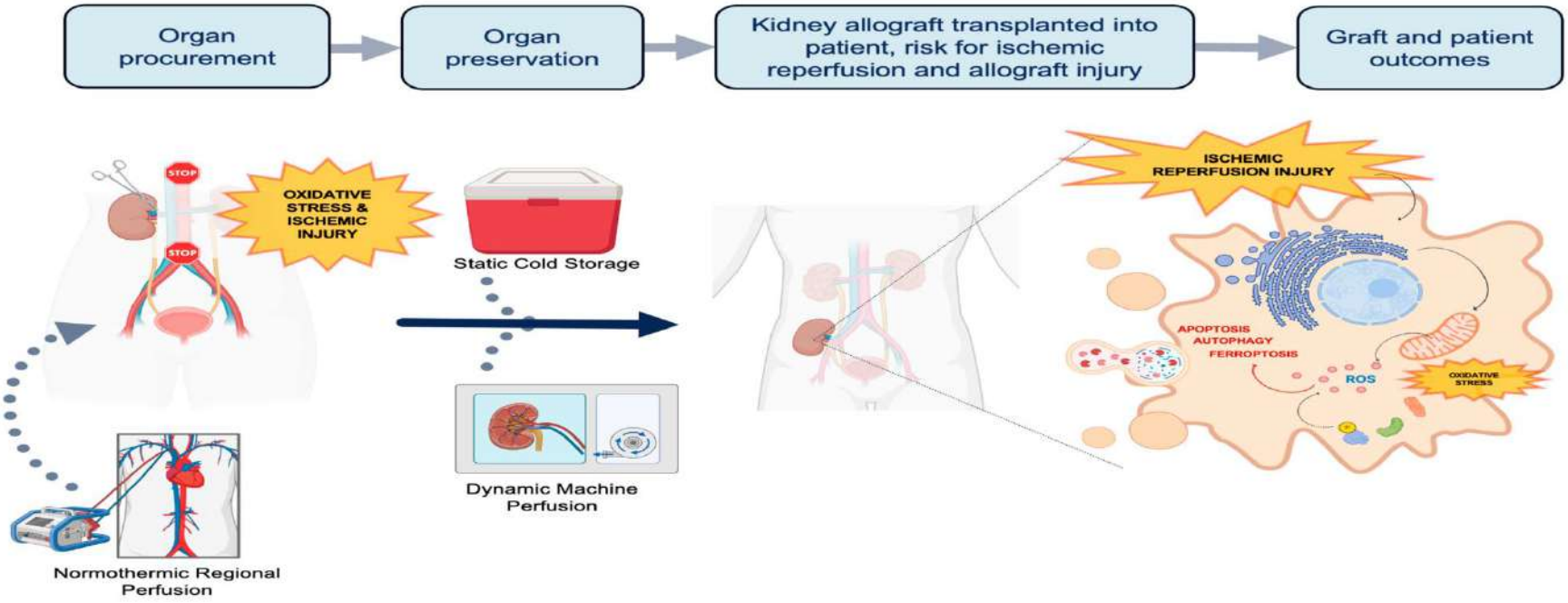
INTRODUCTION

Ischemia and reperfusion injury (IRI) is a complex pathophysiological phenomenon, inevitable in kidney transplantation and one of the most important mechanisms for non- or delayed function immediately after transplantation.

Renal IRI is a known risk factor for DGF , acute kidney injury and acute /chronic rejection .

DCD donors and extended criteria donors are more vulnerable to IRI since donor kidneys suffer from prolonged cold ischemia time, increased donor age or comorbidity of the donor.



PATHOGENESIS

ISCHEMIC INJURY

- **Metabolic Switch**: Deprived of oxygen, cells switch from aerobic to **anaerobic metabolism** - depletion of **ATP**.
- **Intracellular Acidosis**: Anaerobic glycolysis - **lactate accumulation**.
- **Ionic Imbalance**: Failure of ATP-dependent pumps (Na+/K+ ATPase, Ca2+ ATPase) - influx of sodium and water (**cellular oedema**) and a toxic build up of **cytosolic calcium**.
- **Priming for Damage**: ATP breakdown products like **hypoxanthine** accumulate, serving as precursors **for ROS.**

REPERFUSION INJURY

- **ROS Burst**: The sudden reintroduction of oxygen leads to a "burst" of **Reactive Oxygen Species (ROS)** production.
- **Mitochondrial Dysfunction**: ROS and calcium overload trigger the opening of **mitochondrial permeability transition pores .**
- **No-Reflow Phenomenon**: Despite clearing the physical obstruction, microvascular blood flow remains compromised due to endothelial cell swelling, microthrombi (clots), and intense vasoconstriction.

CASCADE OF IRI

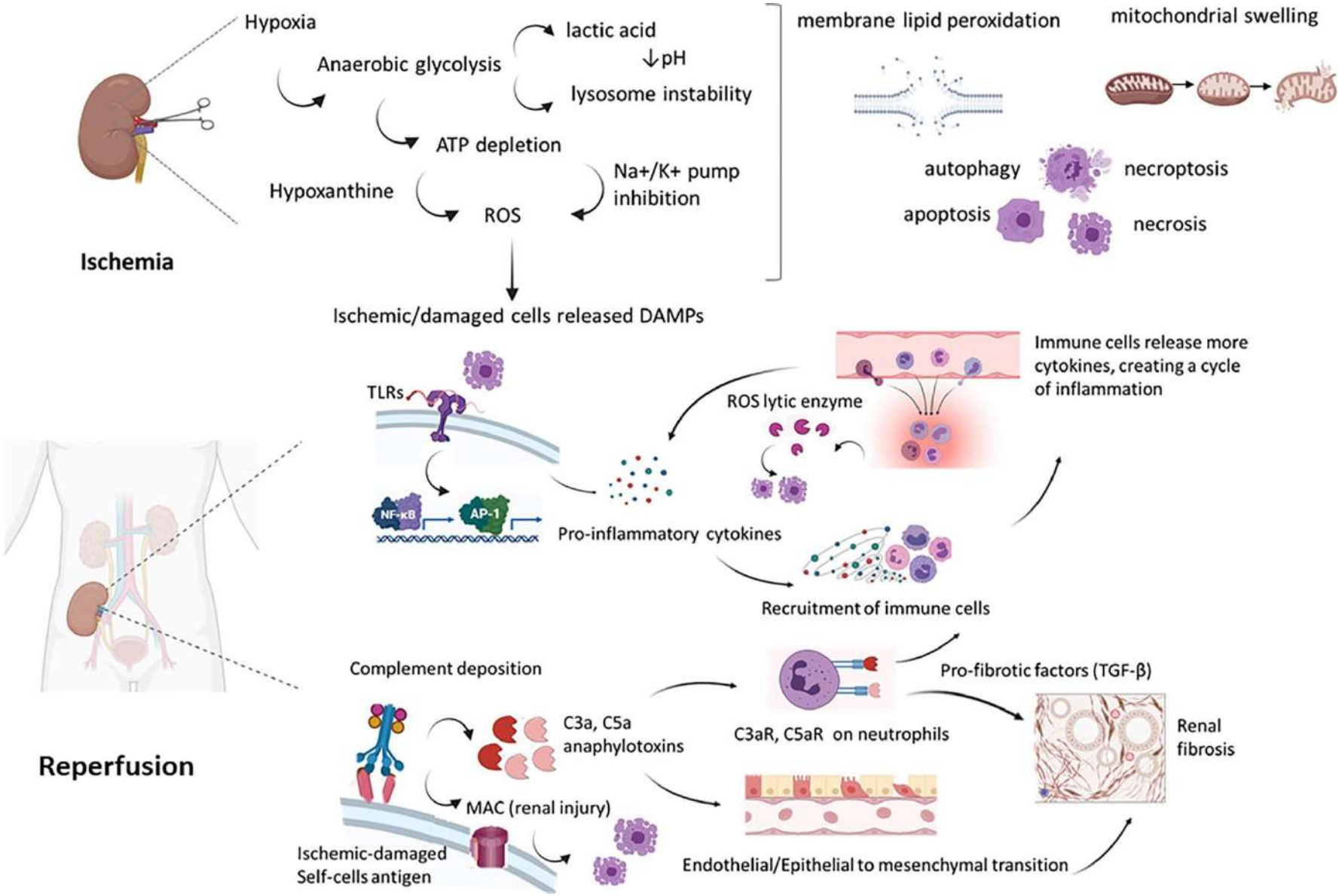
Initial cellular damage - activates both innate and adaptive immune responses.

- **Innate Immune Activation**: Dying cells release **Damage-Associated Molecular Patterns (DAMPs)**, such as HMGB-1, which activate **Toll-Like Receptors (TLR2/4)** on tubular and immune cells.
- **Complement System**: Ischemia triggers the **lectin and alternative complement pathways**, leading to the formation of the **Membrane Attack Complex (MAC)**, which directly lyses tubular cells and recruits neutrophils.
- **Sterile Inflammation**: Infiltrating **neutrophils and macrophages** release more ROS and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), creating a "vicious cycle" of tissue destruction.

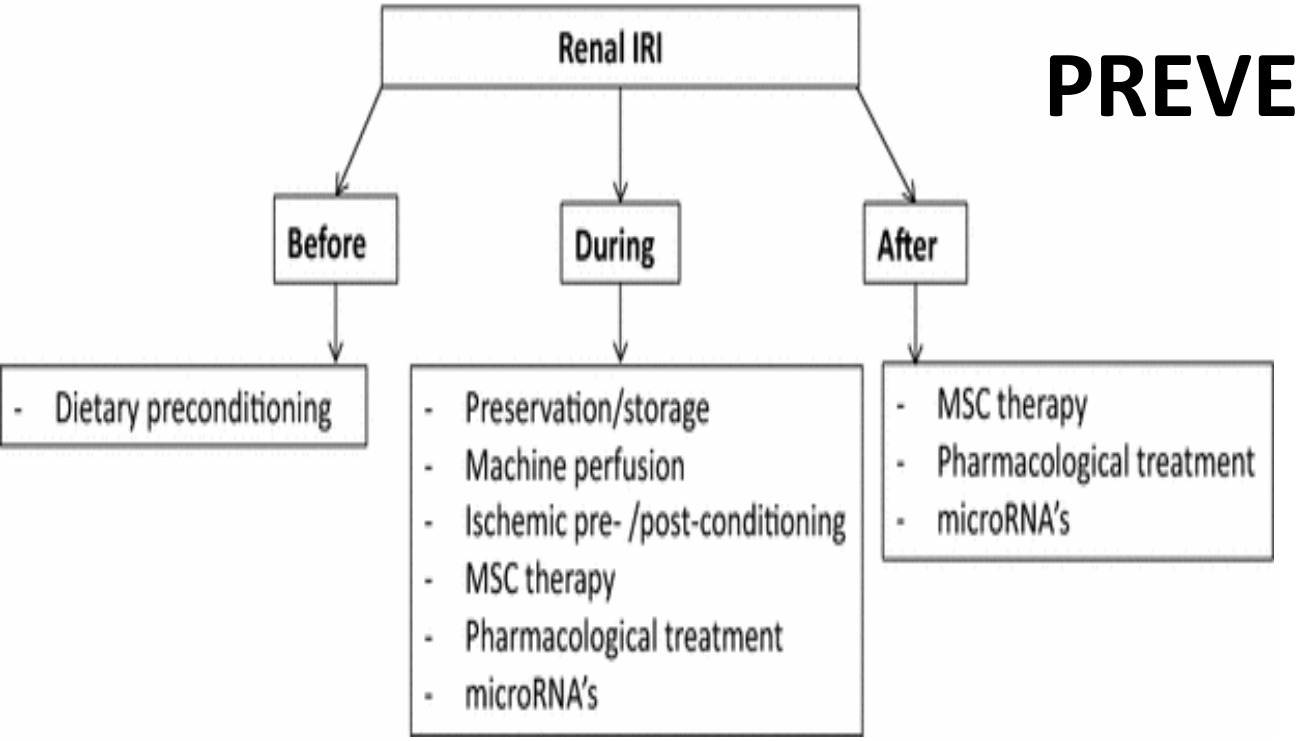
IRI activates forms of programmed cell death:

- **Apoptosis:** Regulated cell death via caspases.
- **Necroptosis:** A regulated form of necrosis (non-apoptotic) involving the RIPK3 protein.
- **Ferroptosis:** Iron-dependent cell death characterized by lipid peroxidation.
- **Autophagy:** Initially, this is a protective mechanism to remove damaged organelles, but if prolonged, it can switch to a harmful process.

MOLECULAR CASCADE OF IRI



PREVENTION OF IRI



1] Cold Storage- Reducing the temperature of the kidney to 4 °C reduces enzyme activity, decreases oxygen requirement and lowers metabolism by 58 %.

2] Machine perfusion / **HTK** Reperfusion fluid.

3] Under investigation to mitigate IRI : **PEG-Lipid** to reduce oxidative stress, **Diannexin** to protect endothelial cells, and **I5NP**.

4] MSCs induce a shift from a pro-inflammatory to an anti-inflammatory environment by promoting **Regulatory T cells (Tregs)** and modulating the behavior of macrophages, T cells, and natural killer cells.

DONOR PRE TREATMENT

- The main goals of donor management : maintenance of an adequate volumia, the optimization of cardiac output and blood pressure in order to ensure adequate perfusion pressure and blood flow avoiding the use of a significant amount of vasoactive drugs.

- Donor pre-treatments are usually classified in physical (including hypothermia and remote ischemic preconditioning) or pharmacological approaches (including dopamine and steroids).

- Remote ischemic preconditioning (RIPC) has been used as a strategy to reduce acute kidney injury.

Composition - HTK

Component	Function
Histidine	pH buffering
Mannitol	Osmotic agent, reduces edema
Tryptophan	Membrane stabilization
Low potassium	Reduces cardiac toxicity
Low viscosity	Enhances perfusion and cooling

WHY RL IS NOT AN IDEAL PERFUSION SOLUTION?

- High Na & Cl levels - increases fluid entry into cells ; membrane integrity / cell swelling , poor ischemic tolerance
- Contains Ca - Ca influx -> mitochondrial damage / activates apoptosis
- Contains lactate as buffering agent - poor maintenance of pH and biochemical stability.

- **HTK contains -Histidine** (buffer)**Tryptophan** (membrane stabilizer)**Mannitol** (osmotic/antioxidant)**Ketoglutarate** (ATP precursor).