Succinate receptor as an emerging pharmacological target in renal ischemic stress

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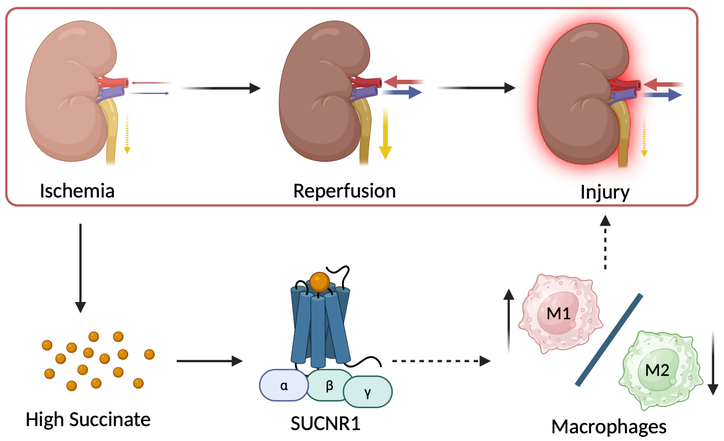
INTRODUCTION

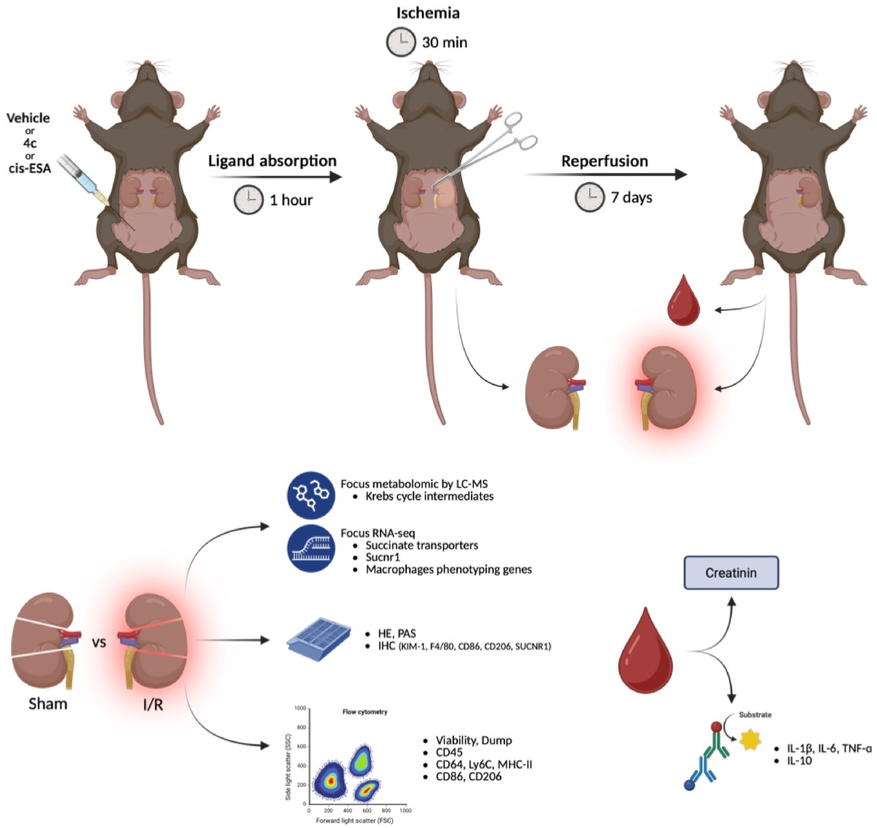
- **Succinate**, a key intermediate of the tricarboxylic acid cycle, **accumulates under various metabolic stresses** such as ischemia, inflammation, or Warburg metabolism.
- **Intracellular succinate** is a well-known **immunometabolite**, able to influence cellular energy metabolism and inflammation through epigenetic changes and post-translational protein modifications.
- Efficient mitochondrial and cellular **transporters** enable its **rapid release** into the **extracellular space**.
- **Extracellular succinate** acts as a signaling molecule through its G-protein-coupled receptor, the **Succinate Receptor** (**SUCNR1**), acting as a **metabokin** and an **alarmin**.
- **SUCNR1** is both coupled to **Gi** and **Gq**, leading to various effects in many different cell types that express it, including the **modulation of macrophage phenotype towards M1** (pro-inflammatory) **or M2** (anti-inflammatory).
- Activation of the **succinate-SUCNR1 axis** has been associated with **increased inflammation** and associated damage in models of hypoxia (diabetic retinopathy), chronic inflammation (immuno-induced arthritis), and more recently, ischaemia/reperfusion (intestinal and hepatic).



- **Macrophages** are a major contributor of the **inflammatory response** occuring after a **renal ischemia/reperfusion event** (transplantation, cardiac arrest, haemodynamic shock).
- **SUCNR1 is highly expressed by macrophages and modulates their polarisation** : a high concentration of succinate promotes an M1 (pro-inflammatory, CD86+/CD206-) phenotype, while a lower concentration promotes an M2 (anti-inflammatory, CD206+/CD86-) phenotype.

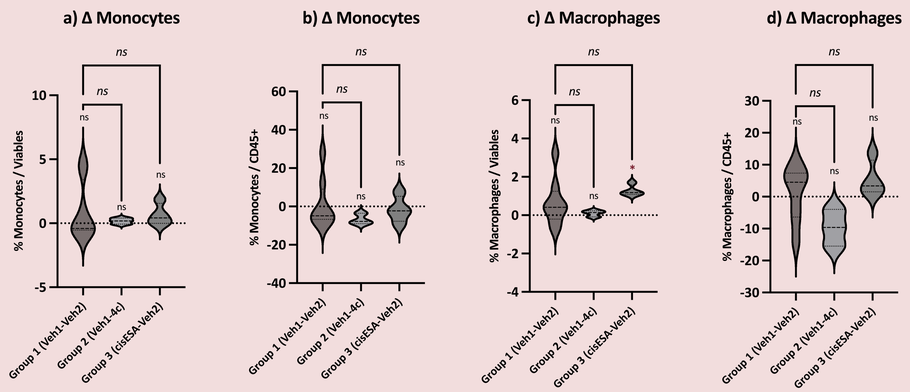
→ The objective of our study is to evaluate the impact of **pharmacological modulation** (synthetic agonist = cis-ESA ; inhibitor = 4c) of **SUCNR1** on **macrophage polarisation** and the severity of **renal damage** during the same **renal I/R event**.

METHODS



RESULTS

Fig. 1 - Monocyte & macrophage total recruitment (Δ) in the kidney after a 30-minute/7-day I/R with prior exposure to SUCNR1 ligand

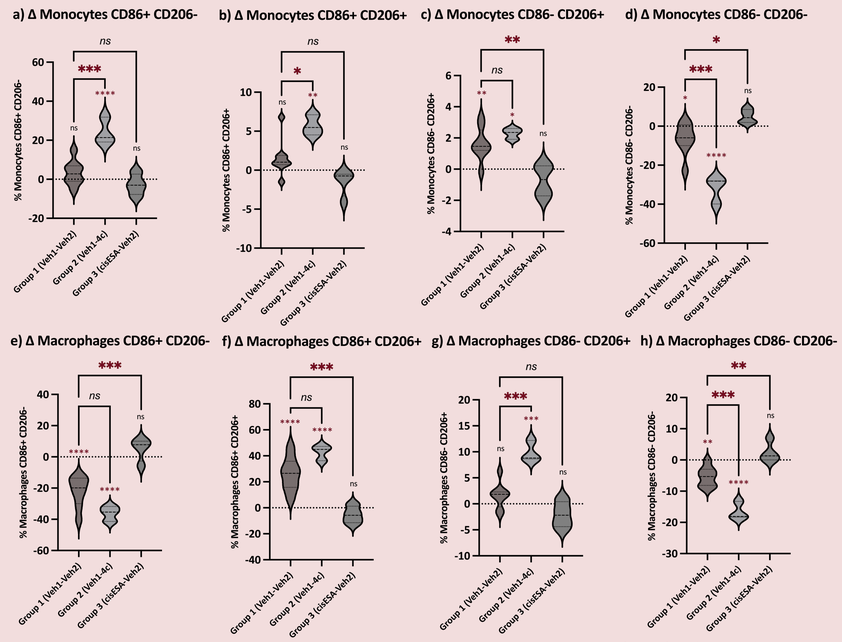


Flow cytometry assessment of the percentage of monocytes (Ly6C+) and macrophages (CD64+, MHC2+) in kidneys that have or have not undergone I/R, compared to the total number of viable cells and CD45+ cells. The absolute difference (Δ) between the control kidney (right) and the I/R kidney (left) is expressed as a percentage on the y-axis. The x-axis represents exposure to SUCNR1 ligands.

a-d) No monocyte or macrophage recruitment after 30 min/7 days of I/R (left kidney) compared to the control (right kidney).

RESULTS

Fig. 2 - Monocyte & macrophage subtypes recruitment (Δ) in the kidney after a 30-minute/7-day I/R with prior exposure to SUCNR1 ligand



Flow cytometry assessment of the percentage of CD86+ and/or CD206+ cells among monocytes (Ly6C+) and macrophages (CD64+, MHC2+) in kidneys that have or have not undergone I/R. The absolute difference (Δ) between the control kidney (right) and the I/R kidney (left) is expressed as a percentage on the y-axis. The x-axis represents exposure to SUCNR1 ligands.

a-b) Increased recruitment of CD86+/CD206- and CD86+/CD206+ monocytes in 4c group. **c)** Inverted recruitment of CD86-/CD206+ monocytes in cis-ESA group. **d)** Increased derecruitment of CD86-/CD206- monocytes in 4c group, in opposition to a positive recruitment in cis-ESA group.
e) Inverted recruitment of CD86+/CD206- macrophages in the cis-ESA group. **f)** Inverted recruitment of CD86+/CD206+ macrophages in the cis-ESA group. **g)** Increased recruitment of CD86-/CD206+ macrophages in the 4c group. **h)** Increased derecruitment of CD86-/CD206- macrophages in 4c group, in opposition to a positive recruitment in cis-ESA group.

CONCLUSION

- **In the absence of SUCNR1 ligand exposition before renal I/R (vehicle)**
  - No change in the total number of monocytes and macrophages
  - Monocytes : recruitment of CD86-/CD206+ and derecruitment of CD86-/CD206-
  - Macrophages : derecruitment of CD206- and recruitment of CD86+/CD206+
- Exposition to **SUCNR1 inhibitor (4c)** before renal I/R seems to **favour the phenotype switch of monocytes and macrophages, particularly from CD206- to CD206+**, in comparaison to the vehicle control
- Exposition to **SUCNR1 agonist (cis-ESA)** before renal I/R seems to **lessen the phenotype switch of monocytes and macrophages** in comparaison to vehicle control

→ **These preliminar datas suggest SUCNR1 as a therapeutic target to mitigate I/R-mediated kidney injuries.**

CONTACT

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