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fnrs FREEDOM TO RESEARCH

Succinate Receptor as an Emerging Target in Ischemic Stress

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1. Introduction

Renal ischemia/reperfusion (I/R) is the leading cause of acute kidney injury, and necessarily occurs during kidney transplantation or cardiovascular surgery. Renal ischemic preconditioning (RIP) includes the mechanical or pharmacological maneuvers aiming to reduce the ischemic insult. However, the current RIP methods fail to completely mitigate I/R injuries that still lead to well-established poor consequences for kidney function. During ischemia, succinate concentration increases in intracellular and extracellular compartment. The intracellular effects of succinate during ischemia are well-studied, in contrast with its extracellular impact, notably mediated by its interaction with the Succinate Receptor (SUCNR1), highly expressed by macrophages. SUCNR1 has recently emerged as an ischemic stress sensor, and we hypothesize that it may represent an innovative drug target in pharmacological RIP. Additionally, preliminary observations from our laboratory showed a significant decrease in kidney injuries following I/R in *Sucnr1* knocked-out mice compared to wild-type.

2. Objectives

Our research project plans to answer these outstanding questions :

1. What is the *in vivo* role of SUCNR1 during renal I/R, with a specific focus on the contribution of the SUCNR1 expressed by macrophages ?
2. What is the *in vivo* impact of the SUCNR1 pharmacological modulation on the RIP, and what are the mechanisms of action for various SUCNR1 ligands ?

Our experimental strategy consists in renal I/R model, applied both to (i) macrophages and proximal tubular cells, and (ii) transgenic mice lines (conditional *Sucnr1*-KO and *Sucnr1* tagged with *StayGold*, a photostable and bright green fluorescent protein). The impact of their exposition with SUCNR1 ligands will also be studied.

3. Renal I/R murine model

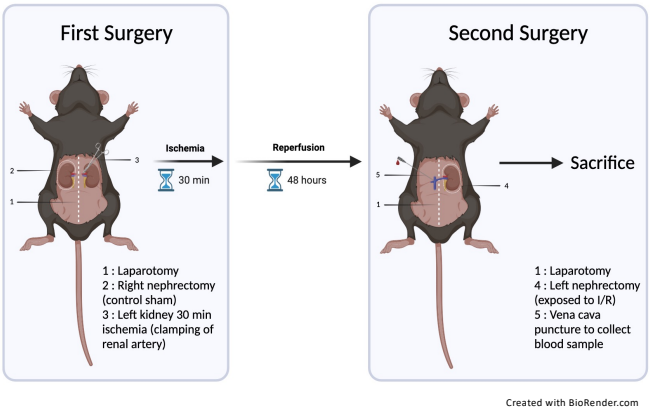

***Figure 1* : Mice kidney 30 min ischemia/48 hours reperfusion microsurgical protocol**

4. Results

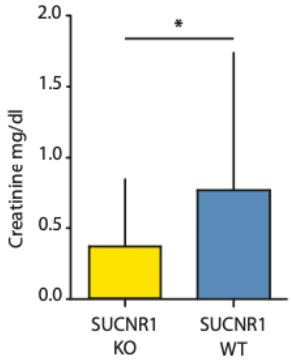

***Figure 2* : Renal I/R in SUCNR1 WT mice (*Suncr1* $^{+/+}$) compared to SUCNR1 KO (*Sucnr1* $^{-/-}$)**

Mice were subjected to 30-minute ischemia followed by 48-hour reperfusion. Blood was collected by puncture of the vena cava at the time of sacrifice. Serum creatinine was measured using HPLC .

N = 27, p = 0.034

5. Research project

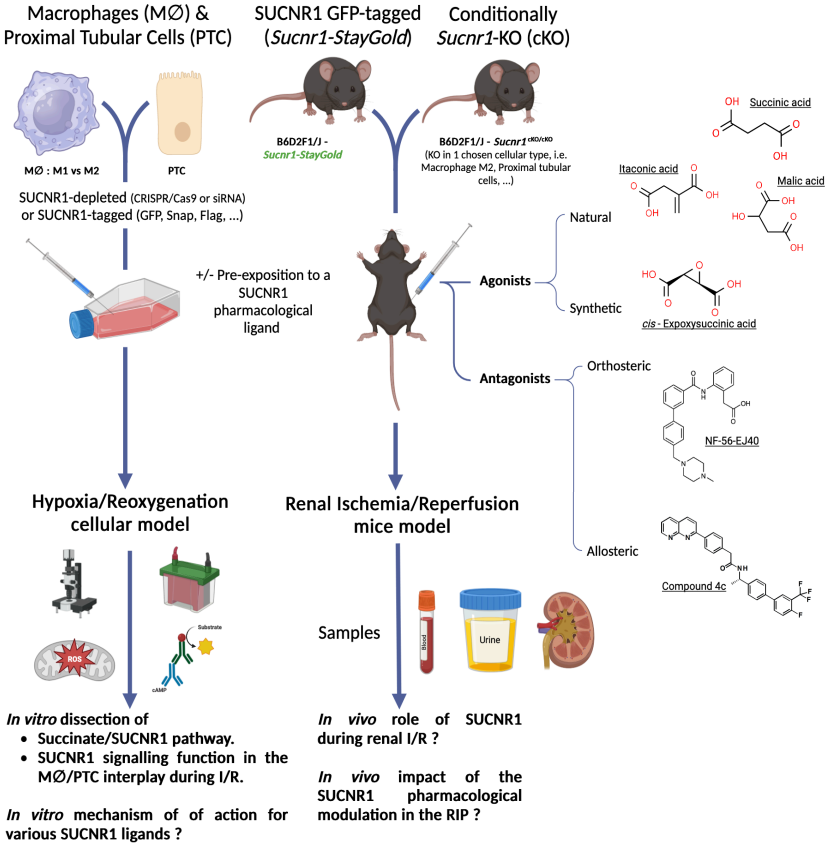

***Figure 3* : Experimental *in vitro* & *in vivo* strategies**

6. Conclusions

The succinate/SUCNR1 pathway constitutes a potential source of innovative drug targets for advanced clinical solutions for patients affected by I/R-related acute kidney injuries.

Studying this axis both *in vitro* and *in vivo* aims to dissect it, understand its effect on I/R, and validate pharmacological ligands of SUCNR1 as therapeutic tools.