Pleiotropic activities of succinate: the interplay between gut microbiota and cardiovascular diseases

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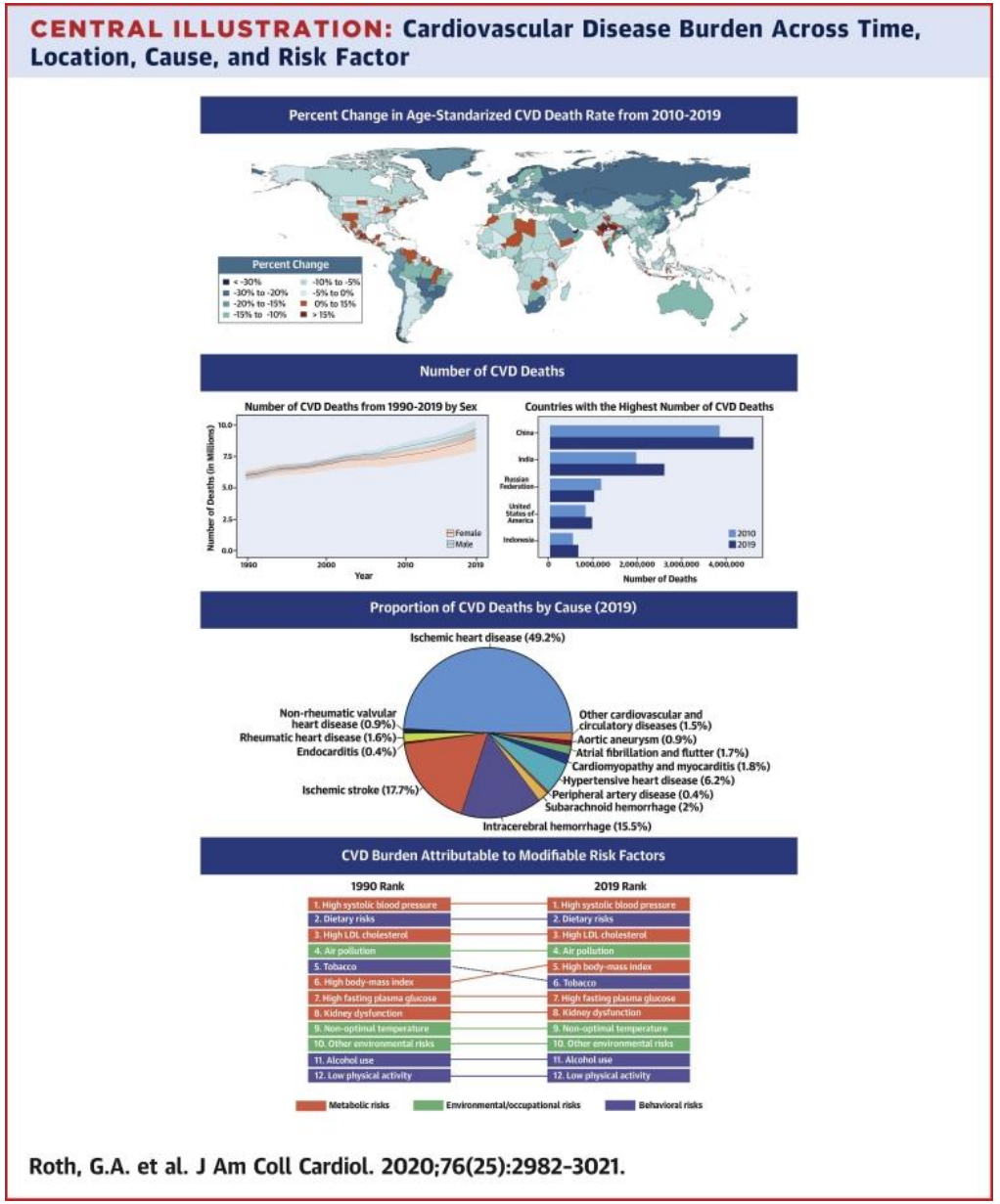
Highlights

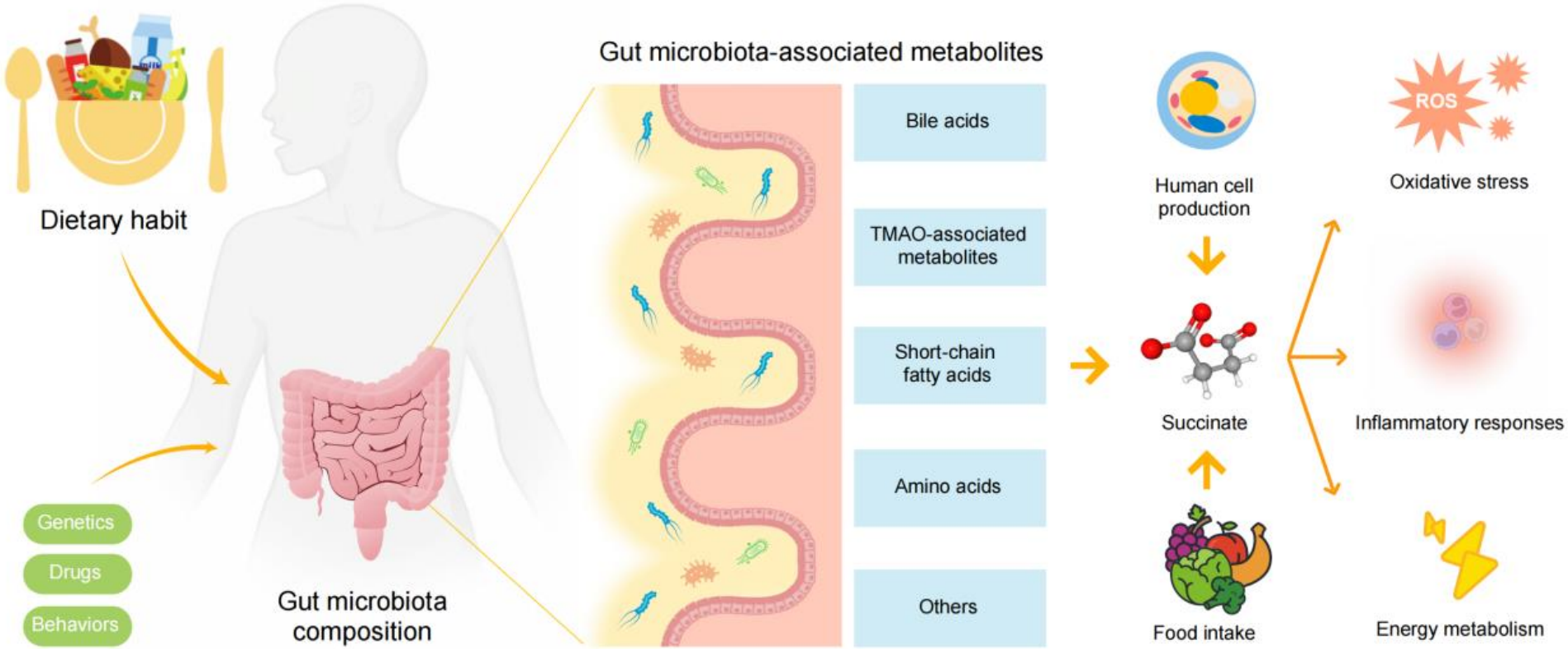
- **Cardiovascular diseases (CVDs)** continue to be a significant contributor to global mortality, imposing a substantial burden and emphasizing the urgent need for disease control to save lives and prevent disability.
- The **gut microbiota**, through changes in microbial compositions and functions, plays a crucial role in influencing local and systemic effects on host physiology and disease development, **with its metabolites acting as key regulators.**
- Gut microbiota-associated metabolite **succinate involves in various pathophysiological pathways** closely related to CVD pathogenesis, including immunoinflammatory responses, oxidative stress, and energy metabolism.
- The burgeoning evidence surrounding the role of succinate in the gut microbiome carries significant implications for our comprehension of host-microbiome interactions and the development of new treatments for CVDs.

Introduction

- Cardiovascular diseases (CVDs) are the leading cause of mortality and disability, imposing a substantial medical and economic burden worldwide. According to the latest Global Burden of Disease 2019 Study, there were over 500 million diagnosed cases of CVDs, resulting in 18.6 million deaths in 2019.



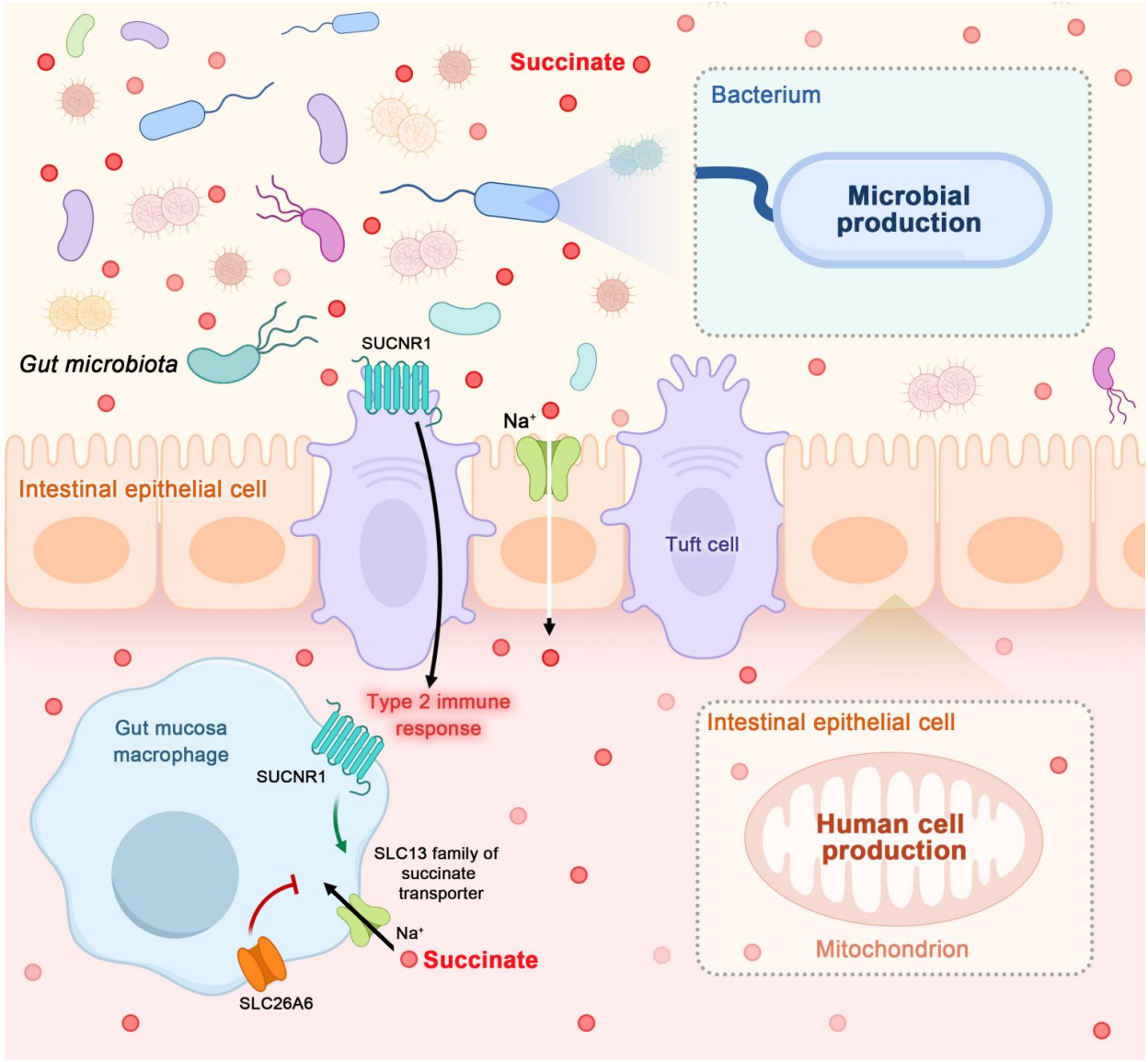
Introduction



Gut microbiota is closely related to the occurrence and development of CVDs. Short-chain fatty acids, bile acids, amino acids and TMAO-related metabolites play important roles in the pathogenesis of CVDs.

Biosynthetic pathway of succinate

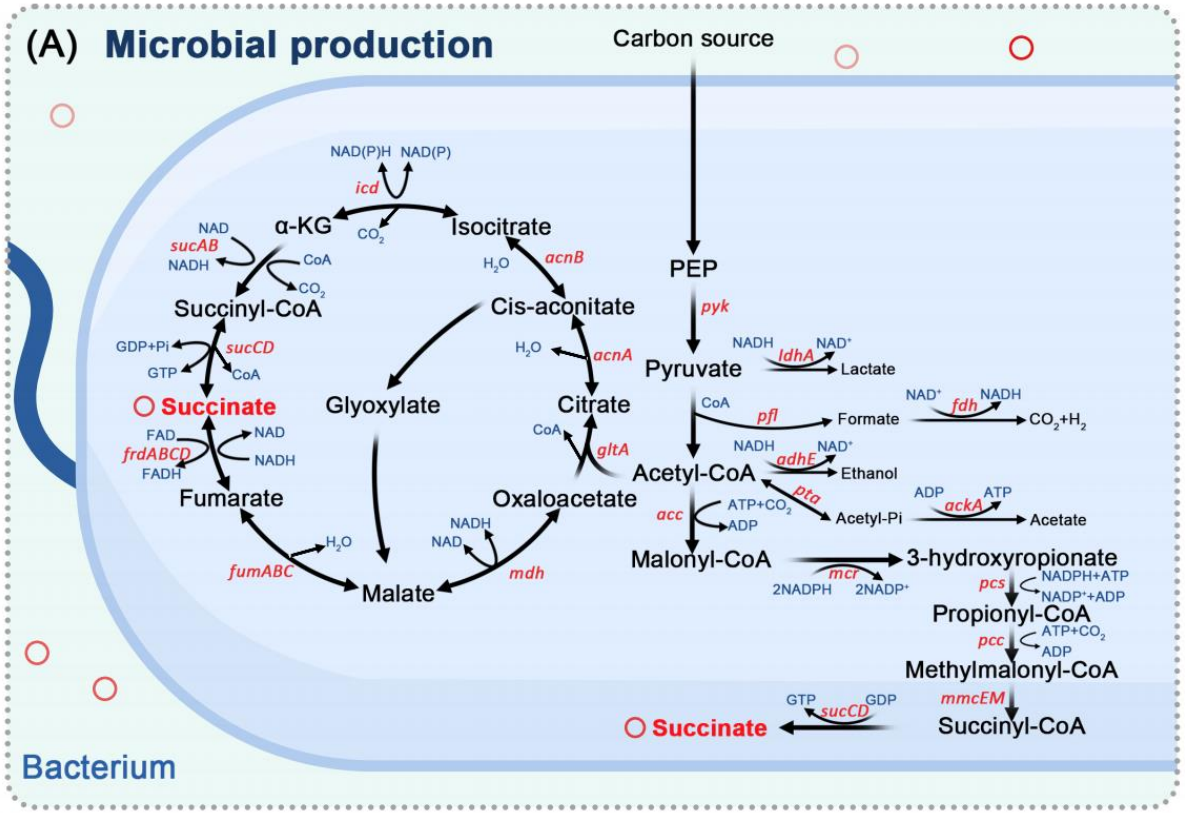
- ✓ **Succinate,** a C4-dicarboxylic acid, is synthesized by both human cells and gut microbiota;
- ✓ The charged nature of succinate enables its transport across plasma membranes, facilitated by the **SLC13 family of Na+-dependent transport proteins**.
- ✓ Succinate plays a crucial role in extracellular signaling by stimulating the **G protein-coupled succinate receptor (SUCNR1, also known as GPR91)**, which is abundant in various tissues and cells.



Biosynthetic pathway of succinate

Biosynthetic pathways of succinate production in gut microbiota

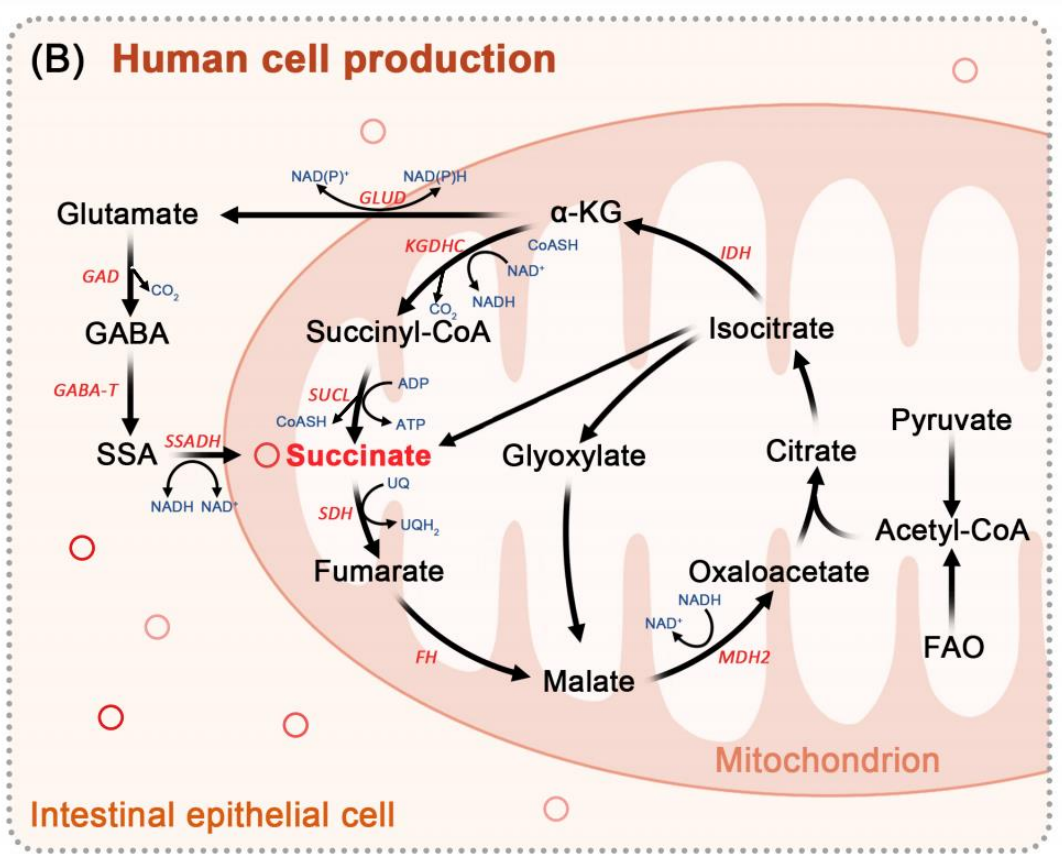
- ✓ Succinate is commonly generated through **a partial branch of the tricarboxylic acid (TCA)** cycle in microbial carbohydrate fermentation.
- ✓ Succinate can be produced through the **glyoxylate shunt pathway and the 3-hydroxypropionate pathway**.



Biosynthetic pathway of succinate

Biosynthetic pathways of succinate production in human cells

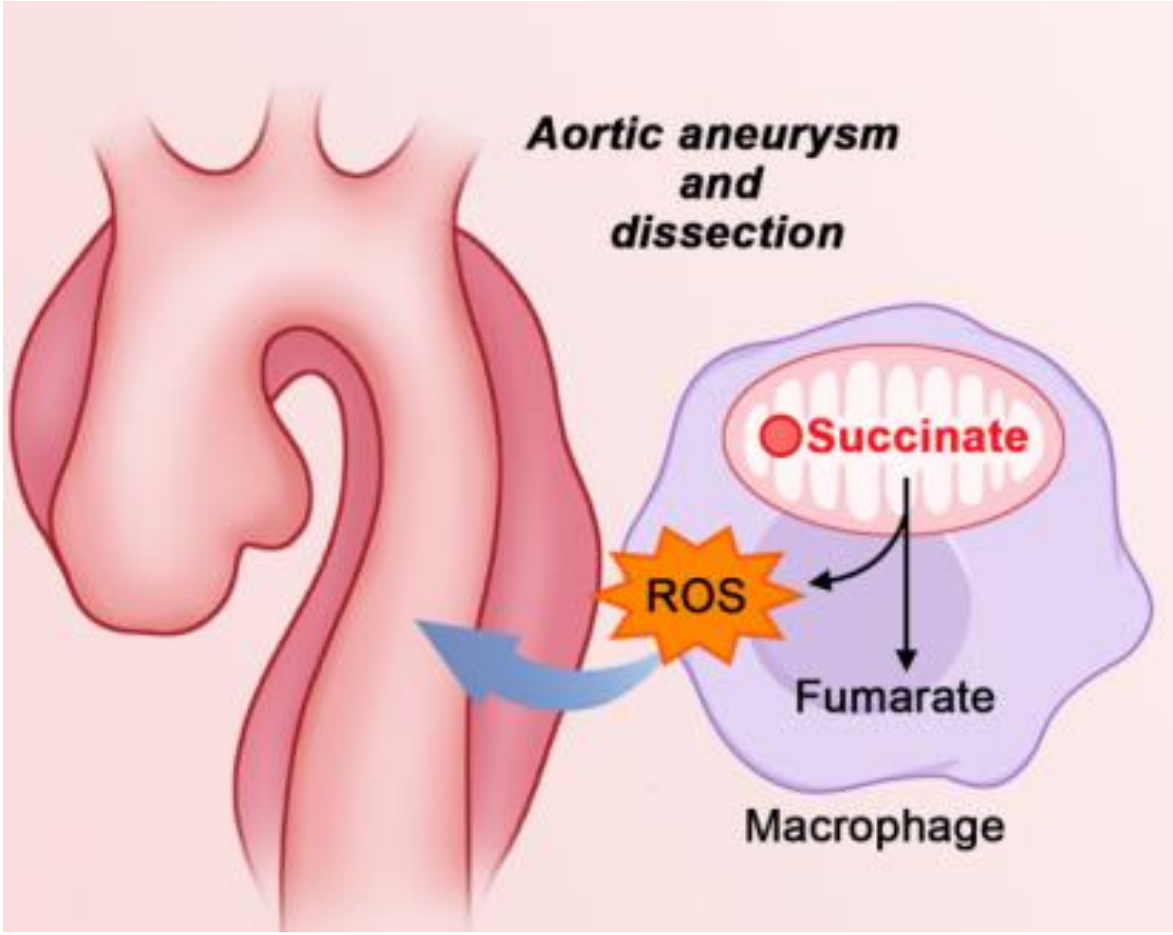
- ✓ Succinate is produced by **TCA cycle in human mitochondria;**
- ✓ In cells relying on anaerobic glycolysis or experiencing hypoxic conditions, alternative metabolic pathways are activated, leading to the accumulation of mitochondrial succinate. These pathways include the reductive branch of the TCA cycle through reverse succinate dehydrogenase activity, the GABA shunt, and glutamine-dependent anaplerosis.



Succinate in cardiovascular diseases

Succinate and aortic aneurysm and aortic dissection (AAD)

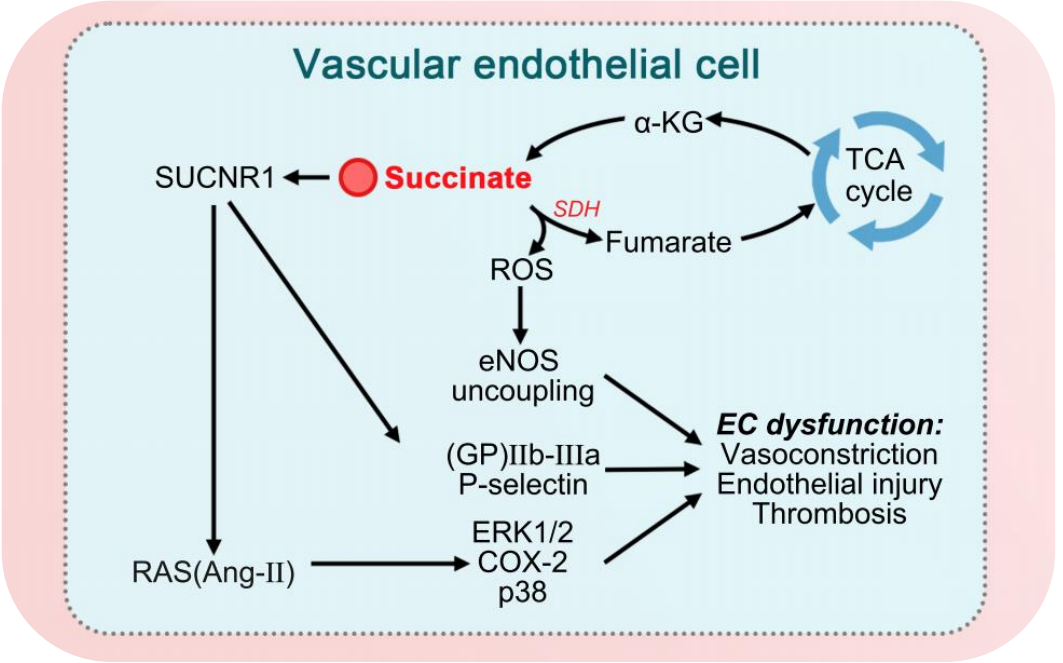
- ✓ Non-targeted metabolomics indicated that compared with healthy controls, the levels of succinate were found to be **elevated in AAD cases;**
- ✓ The addition of **succinate** worsened AAD formation in mice, leading to increased mortality rate, higher AAD incidence, and enlarged aortic diameter, **primarily through the excessive production of reactive oxygen species (ROS)**.



Succinate in cardiovascular diseases

Succinate and Atherosclerosis (AS)

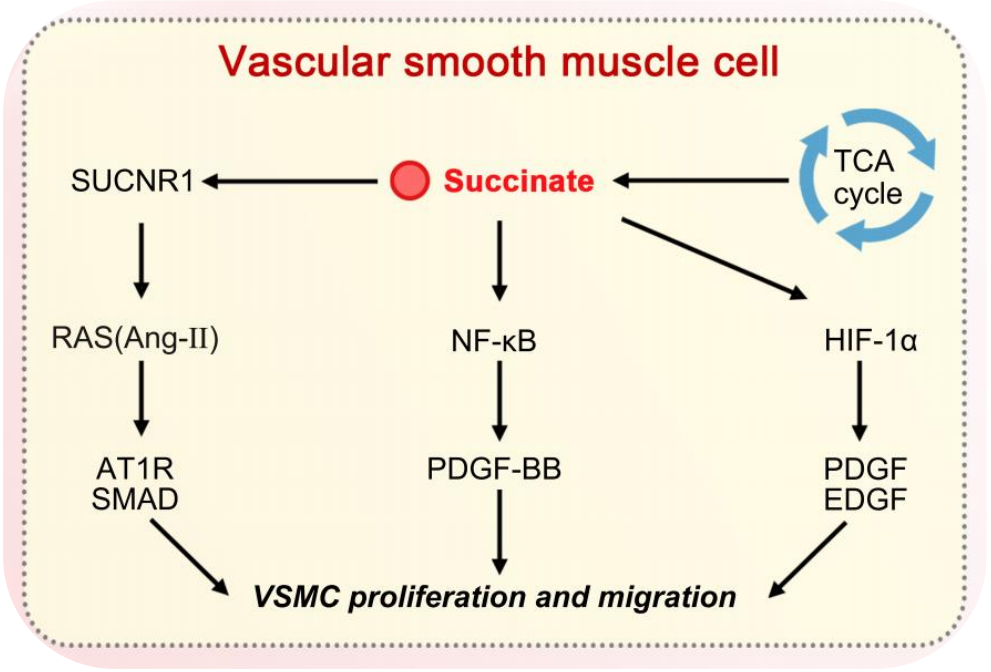
- ✓ Succinate plays an important role in the pathogenesis of AS - **endothelial cells**
- Succinate activates the **renin-angiotensin system** by interacting with SUCNR1 receptor, leading to endothelial dysfunction;
- Succinnate promotes platelet adhesion to endothelial cells, which leads to **inflammation and thrombosis**.
- Succinate promotes the production of ROS and causes endothelial cell damage.



Succinate in cardiovascular diseases

Succinate and Atherosclerosis (AS)

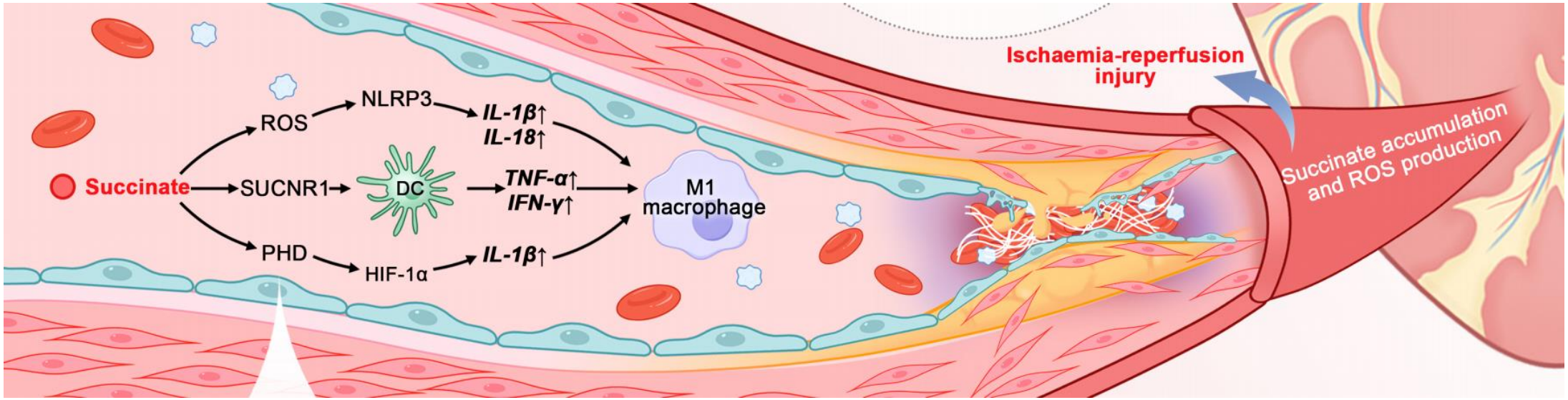
- ✓ Succinate plays an important role in the pathogenesis of AS - **smooth muscle cells**
- Succinate activates **RAS system** by binding to SUCNR1 receptor. It promotes fibrosis, proliferation and hypertrophy of smooth muscle cells through **SMAD pathway**.
- Succinate promotes proliferation and migration of smooth muscle cells through **NF-kB** and **HIF-1α** pathway.



Succinate in cardiovascular diseases

Succinate and Atherosclerosis (AS)

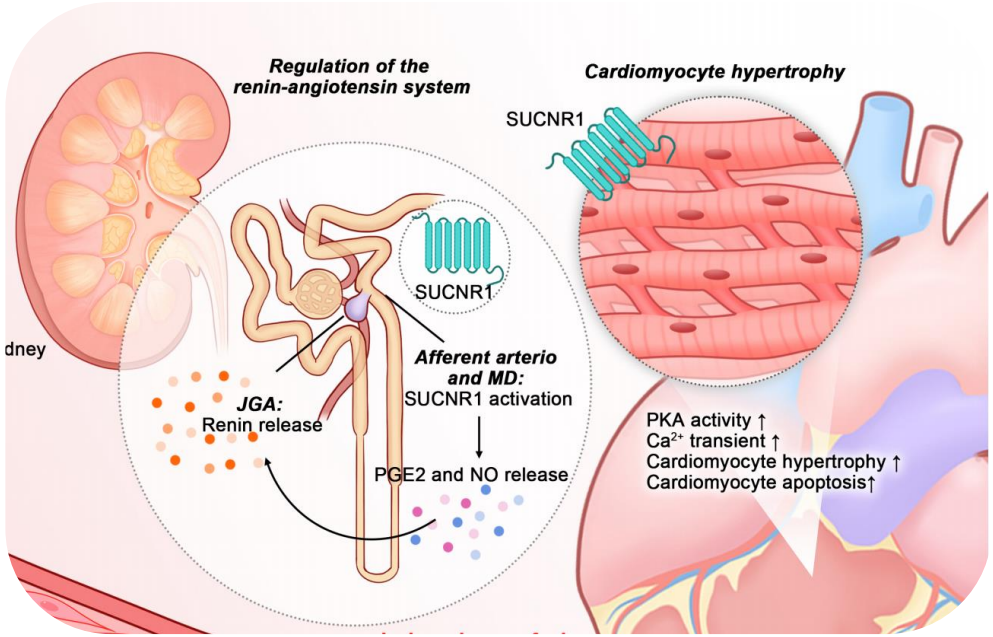
- ✓ Succinate plays an important role in the pathogenesis of AS - **immune cells**
- The interaction between succinate and GPR91 promotes the production of **pro-inflammatory factors** such as IL-1β, IL-18, TNF-α and TNF-β, which induces the polarization of proinflammatory phenotype macrophages.
- Succinate promotes the production of interleukin by increasing **HIF-1α levels**



Succinate in cardiovascular diseases

Succinate and hypertension and cardiac hypertrophy

- ✓ Succinate promotes the **accumulation of renin and angiotensin II**, leading to hypertension;
- ✓ Succinate induces cardiac hypertrophy, primarily by initiating transcription of genes associated with cardiac hypertrophy through phosphorylation of **ERK1/2 and by promoting calcium transient**.



Summary

- **Succinate** plays a role not only in the physiological TCA cycle but also drives numerous pathophysiological processes, such as **the activation of RAS, overproduction of ROS, mediation of proinflammatory macrophages, interaction with GPR91, and involvement in energy metabolism**.

- The multifaceted activities of **succinate contribute to the onset and progression of various cardiovascular diseases**, including AAD, AS, hypertension, and cardiac hypertrophy.

- The burgeoning evidence surrounding the role of succinate in the gut microbiome carries significant implications for our comprehension of **host-microbiome interactions and the development of new treatments for CVDs**.

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