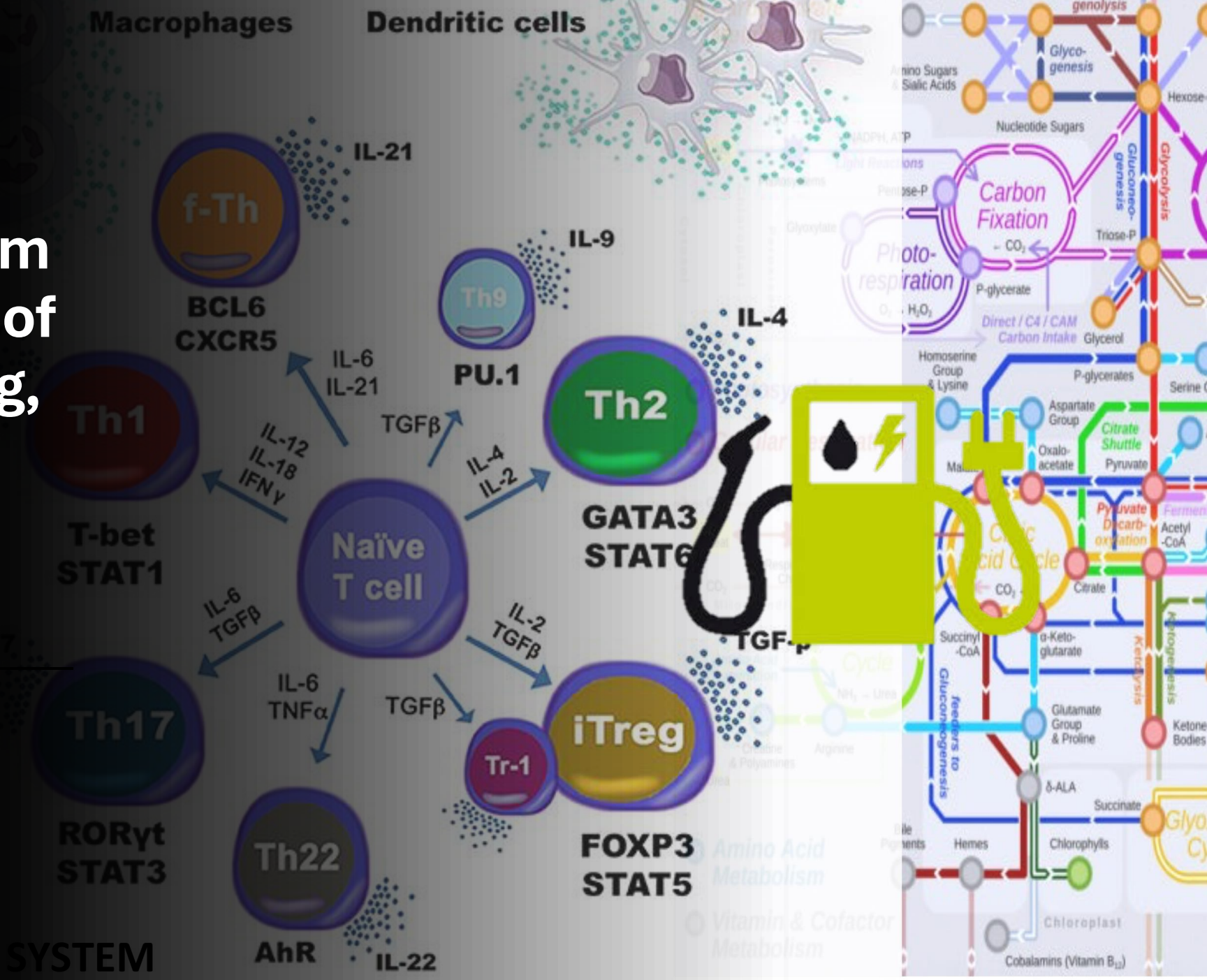
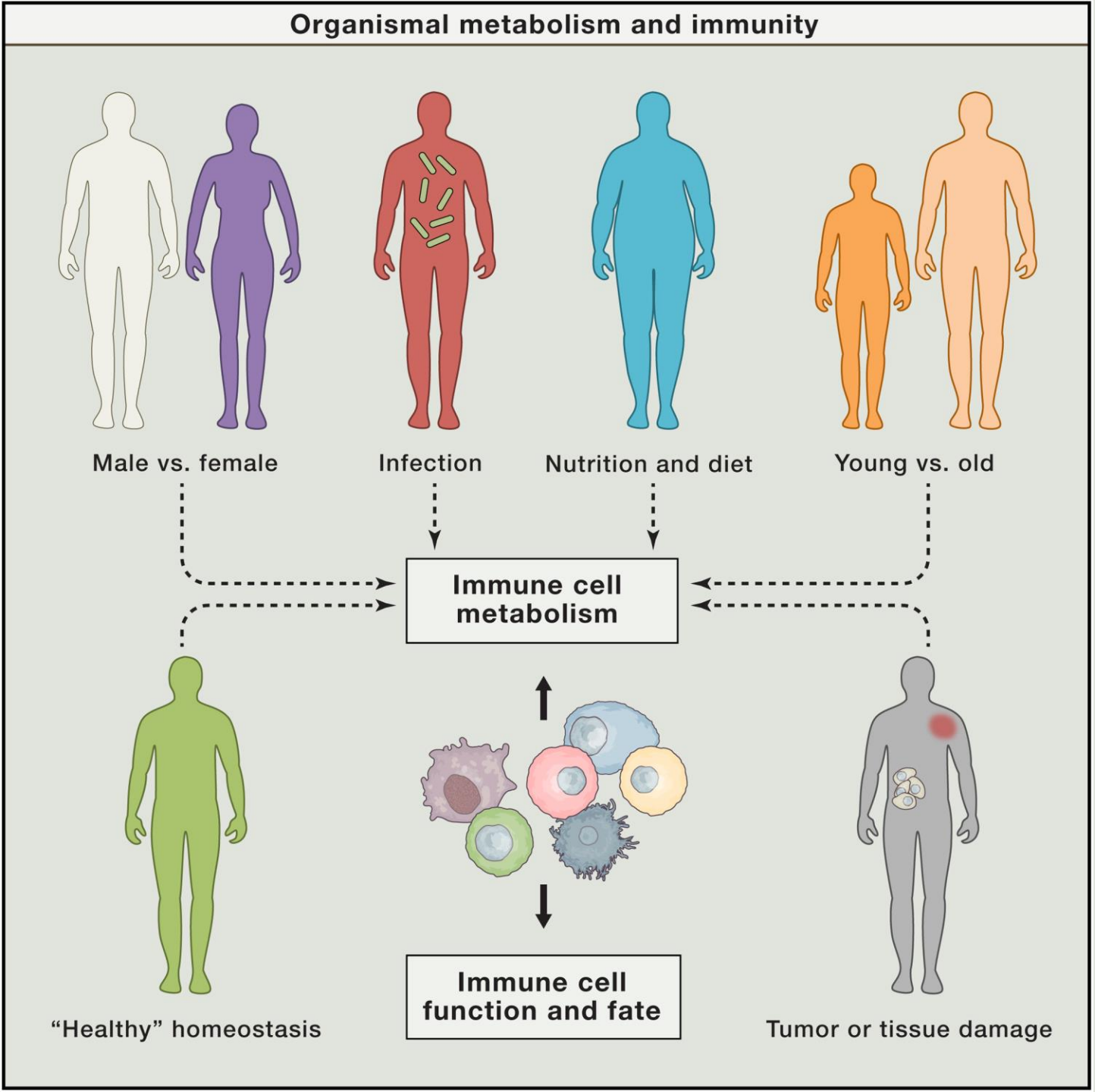
Immunometabolism at the intersection of metabolic signaling, cell fate, and systems immunology

Michael Ash DO, ND, BSc, RNT





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1. Immune cells possess unique skills essential for host defense and tissue homeostasis, but these can also lead to diseases if not properly managed.
2. Unlike other cells, immune cells respond to environmental signals and can differentiate into various functional states.
3. They can transform from dormant sentinels into active pathogen-killing machines, migrate across tissues, modulate surface receptors, undergo clonal expansion, and secrete large volumes of effector molecules.
4. Immune cells have the capability to influence neighboring cells, playing a crucial role in controlling local cell populations.
5. Following an immune response, these cells can either die to reduce tissue damage or revert to a resting state, remaining ready for future responses and maintaining long-term immunity.

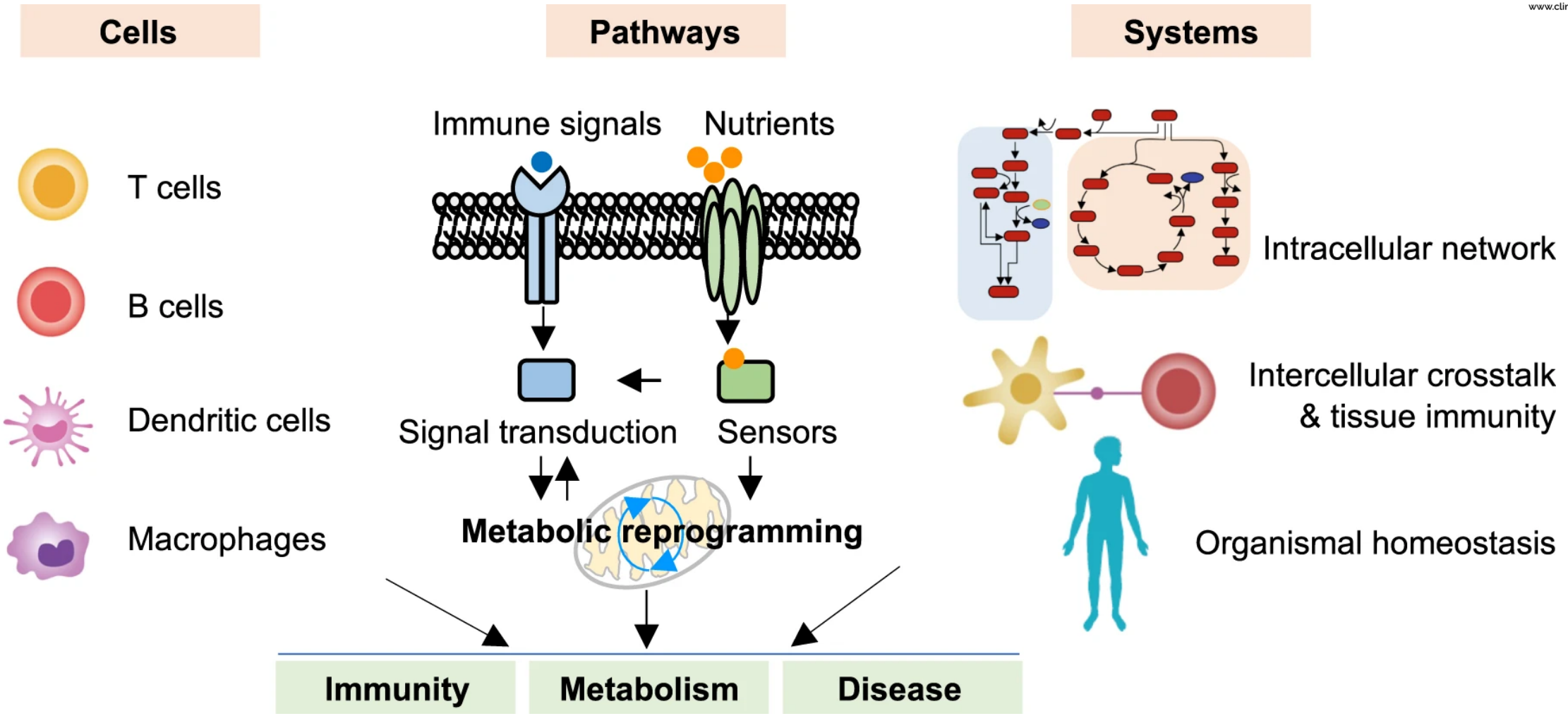
1. The activation, growth, proliferation, and engagement of immune cell effector functions are tightly connected to dynamic changes in cellular metabolism.
2. Metabolic pathway utilization in immune cells is influenced by external factors such as growth factors and nutrient availability, which are affected by competition among interacting cells.
3. Internal factors also regulate metabolism, including the balance of internal metabolites, reactive oxygen species (ROS), and the ratio of reducing to oxidizing substrates.
4. Research on specific immune cells, like lymphocytes and myeloid cells, has provided significant insights into the link between cell differentiation and metabolic coordination in various environments.
5. These studies help to understand how immune cells adapt their metabolic processes to meet functional demands in different physiological and pathological contexts.

Why do we care?

- Metabolism underlies all biological functions. Immunometabolism, integrating metabolism with immunity, is crucial in immunology.
- It impacts immune cell function, influencing disease, inflammation, cancer, and maintaining organismal homeostasis.

Recall

1. The human immune system is complex, whose multitudinous cellular and molecular components work together to shape development, protect against infections, help wounds to heal and eliminate cells that trigger inflammation or threaten to become cancerous.
2. But it becomes less effective as people age or become metabolically compromised and the system's composition starts to change. In older age, and in metabolic dysfunction people become susceptible to a range of infectious and non-infectious diseases.



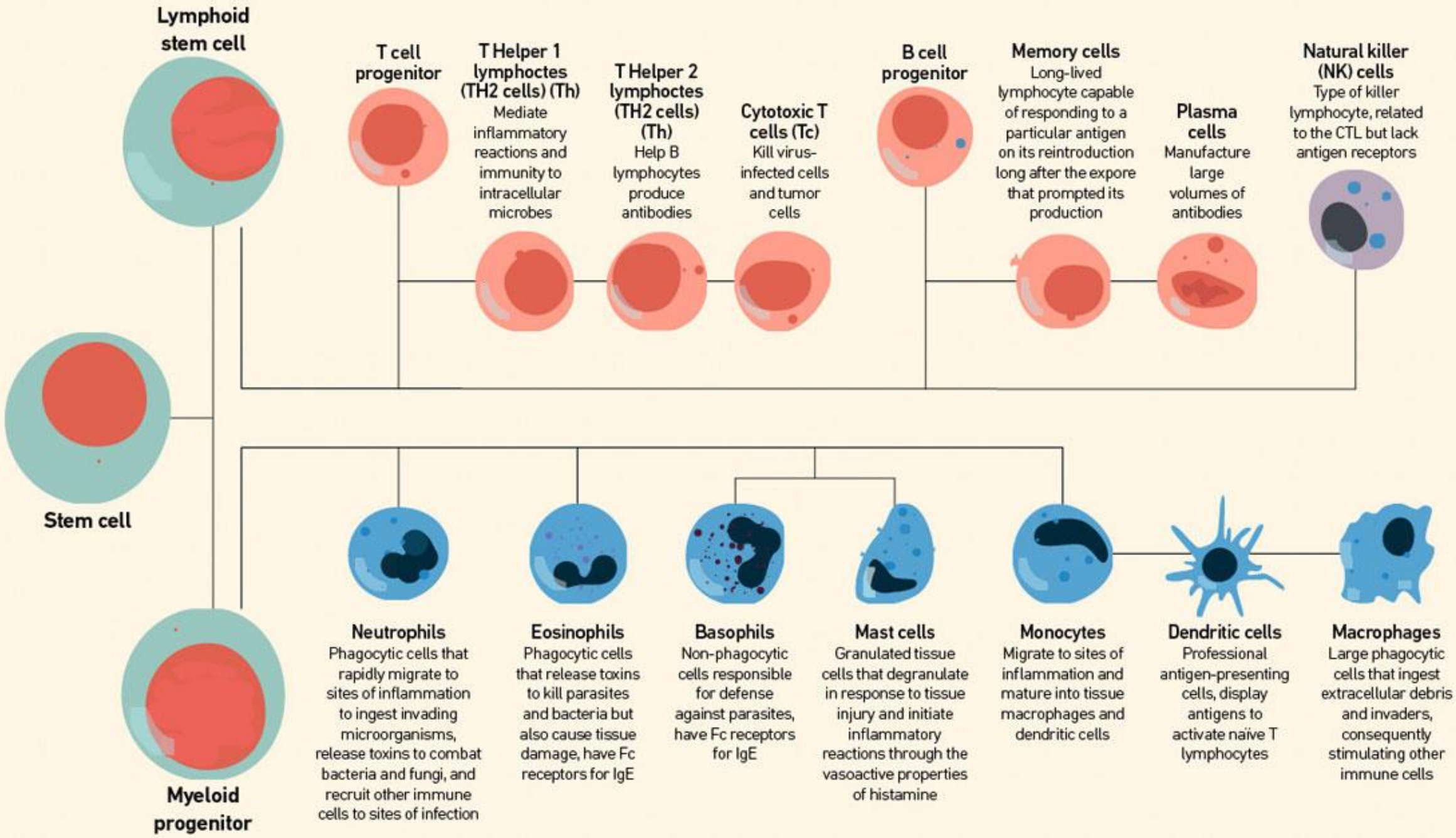
Chi, H. Immunometabolism at the intersection of metabolic signaling, cell fate, and systems immunology. Cell Mol Immunol 19, 299–302 (2022). https://www.nature.com/articles/s41423-022-00840-x

Remind ourselves

1. The immune system has two main components: a fast-acting innate system, which destroys invading pathogens indiscriminately,
2. and a more-precise adaptive immune system, whose components learn to recognize specific foreign bacteria and viruses and generate antibodies against them.

Some more detail

- The haematopoietic, or blood, stem cells (HS cells) in the bone marrow spawn the immune cells of both arms of the system.
- They differentiate into two main classes — lymphoid and myeloid — which go on to differentiate further.
- Lymphoid cells are mostly responsible for adaptive immunity, and include: B cells, which produce antibodies; T cells, which help to attack invaders and orchestrate complex immune responses; and natural killer cells, which destroy infected cells.
- Myeloid cells include a raft of cell types involved mostly in innate immunity.


Lymphoid stem cell
T cell progenitor
T Helper 1 lymphoctes (TH2 cells) (Th)
Mediate inflammatory reactions and immunity to intracellular microbes
T Helper 2 lymphoctes (TH2 cells) (Th)
Help B lymphocytes produce antibodies
Cytotoxic T cells (Tc)
Kill virus-infected cells and tumor cells
B cell progenitor
Memory cells
Long-lived lymphocyte capable of responding to a particular antigen on its reintroduction long after the expore that prompted its production
Plasma cells
Manufacture large volumes of antibodies
Natural killer (NK) cells
Type of killer lymphocyte, related to the CTL but lack antigen receptors
Stem cell
Myeloid progenitor
Neutrophils
Phagocytic cells that rapidly migrate to sites of inflammation to ingest invading microorganisms, release toxins to combat bacteria and fungi, and recruit other immune cells to sites of infection
Eosinophils
Phagocytic cells that release toxins to kill parasites and bacteria but also cause tissue damage, have Fc receptors for IgE
Basophils
Non-phagocytic cells responsible for defense against parasites, have Fc receptors for IgE
Mast cells
Granulated tissue cells that degranulate in response to tissue injury and initiate inflammatory reactions through the vasoactive properties of histamine
Monocytes
Migrate to sites of inflammation and mature into tissue macrophages and dendritic cells
Dendritic cells
Professional antigen-presenting cells, display antigens to activate naïve T lymphocytes
Macrophages
Large phagocytic cells that ingest extracellular debris and invaders, consequently stimulating other immune cells

What happens eventually?

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Any cell in the body can become senescent, typically when damaged by a mutation. Once in this state, cells start to secrete inflammatory signals, flagging themselves for destruction (Apoptosis/Autophagy).

This is an important anti-inflammatory/anticancer and wound-healing mechanism that works well in youth. But when too much damage accumulates with ageing — and immune cells themselves also become senescent — the mechanism breaks down.

Senescent immune cells, attracted by the inflammatory signals from senescent tissue, secrete their own inflammatory molecules.

So not only do they fail to clean up properly, but they also add to the inflammation that damages surrounding healthy tissue. The phenomenon is known as **‘inflammaging’ or ‘sterile inflammation’**

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Matzinger's 1994 "danger" theory posits damaged cells trigger immune responses via damage-associated molecular patterns (DAMPs). DAMPs, recognised by pattern recognition receptors (PRRs), include histones, DNA, HMGB1, heat shock proteins, and ATP.

Her realisation? Cells die in two ways: programmed cell death, where the cell shrivels up, never releasing its contents, and a cell being killed, when its contents are let out, sending a signal there is damage. "Things that are dangerous are things that cause damage. If you don't cause damage you're not dangerous.

Sterile infl

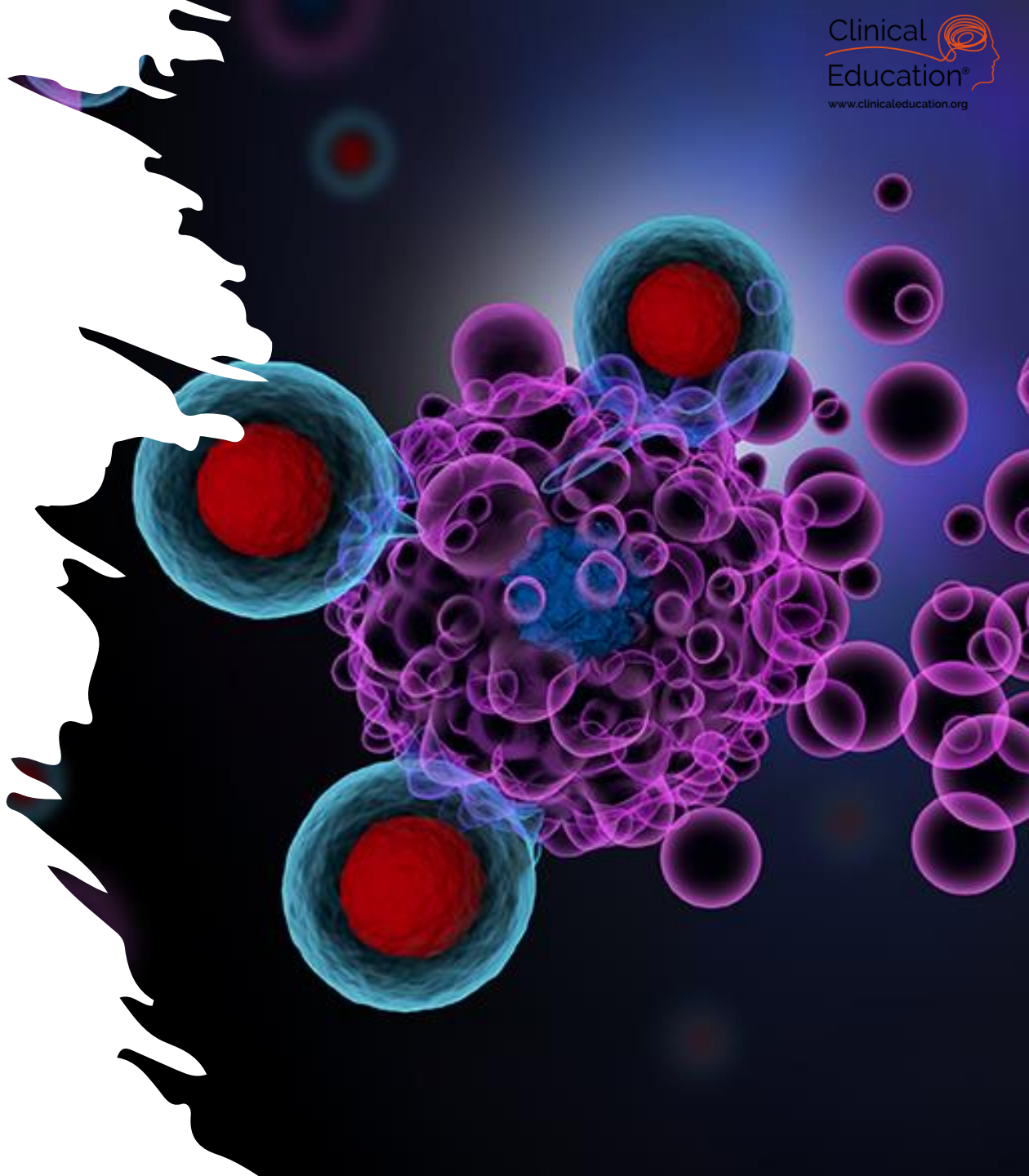
The role of the NLRP3 inflammasome is **pivotal in the pathophysiology and progression of diabetes mellitus (DM), encompassing both type 1 (T1D), or type 2 (T2D)**. As part of the innate immune system, NLRP3 is also responsible for the chronic inflammation triggered by hyperglycaemia.


Inflammation +
Type 2 Diabetes

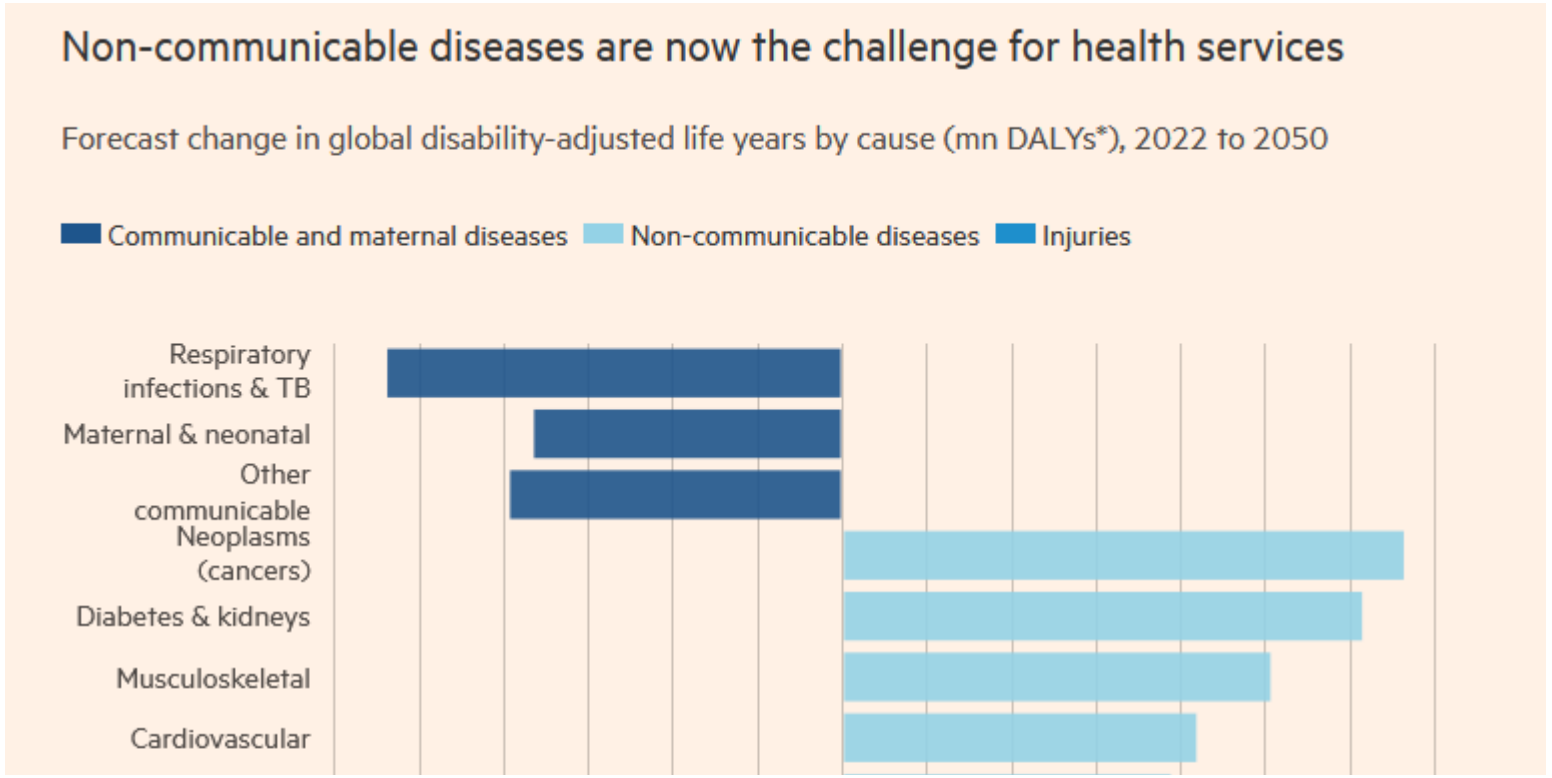
Troubling future of metabolic induced meta-inflammation

- New figures (May 2024) from Diabetes UK show cases of type 2 among under-40s have increased to almost 168,000 from 120,000 in 2016/17 a 40% increase.

- Diagnoses are rising at a significantly faster pace than among over-40s, for whom the increase was 25% in six years
- There are more than 1.2 million people who may be living with type 2 diabetes and have not yet been diagnosed. More than 5.6 million people now live with diabetes in the UK




IT'SUGAR
YOU KNOW YOU WANT IT
IT'SUGAR
ABSOLUTELY NO NUTRITIONAL VALUE ADDED
IT'SUGAR
CANDY IS ALWAYS THE ANSWER
TAKING GREAT PLEASURE IN GREAT PLEASURE
YOU KNOW YOU WANT IT
LESS RULES MORE SUGAR



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Institute for Health Metrics and Evaluation

Burden of disease scenarios for 204 countries and territories, 2022–2050

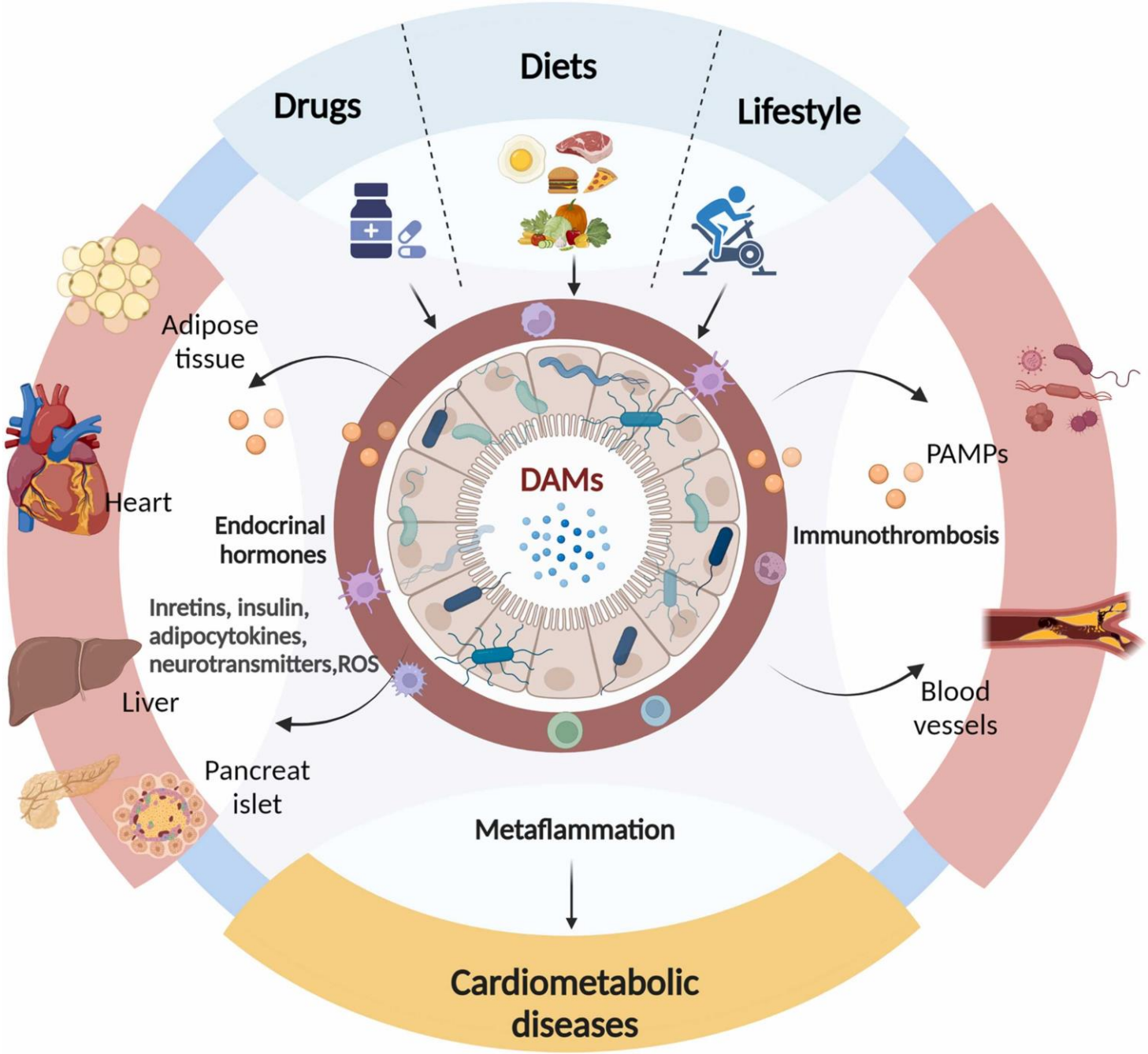
Published May 16, 2024, in The Lancet

According to the study – done by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington – **the world experienced a 49% increase in the number of global DALYs, or disability-adjusted life years (lost years of healthy life due to poor health and early death), attributable to metabolism-related risk factors** between 2000 and 2021.

FT: 16.5.24

Why is the Gastrointestinal Immune System so viable

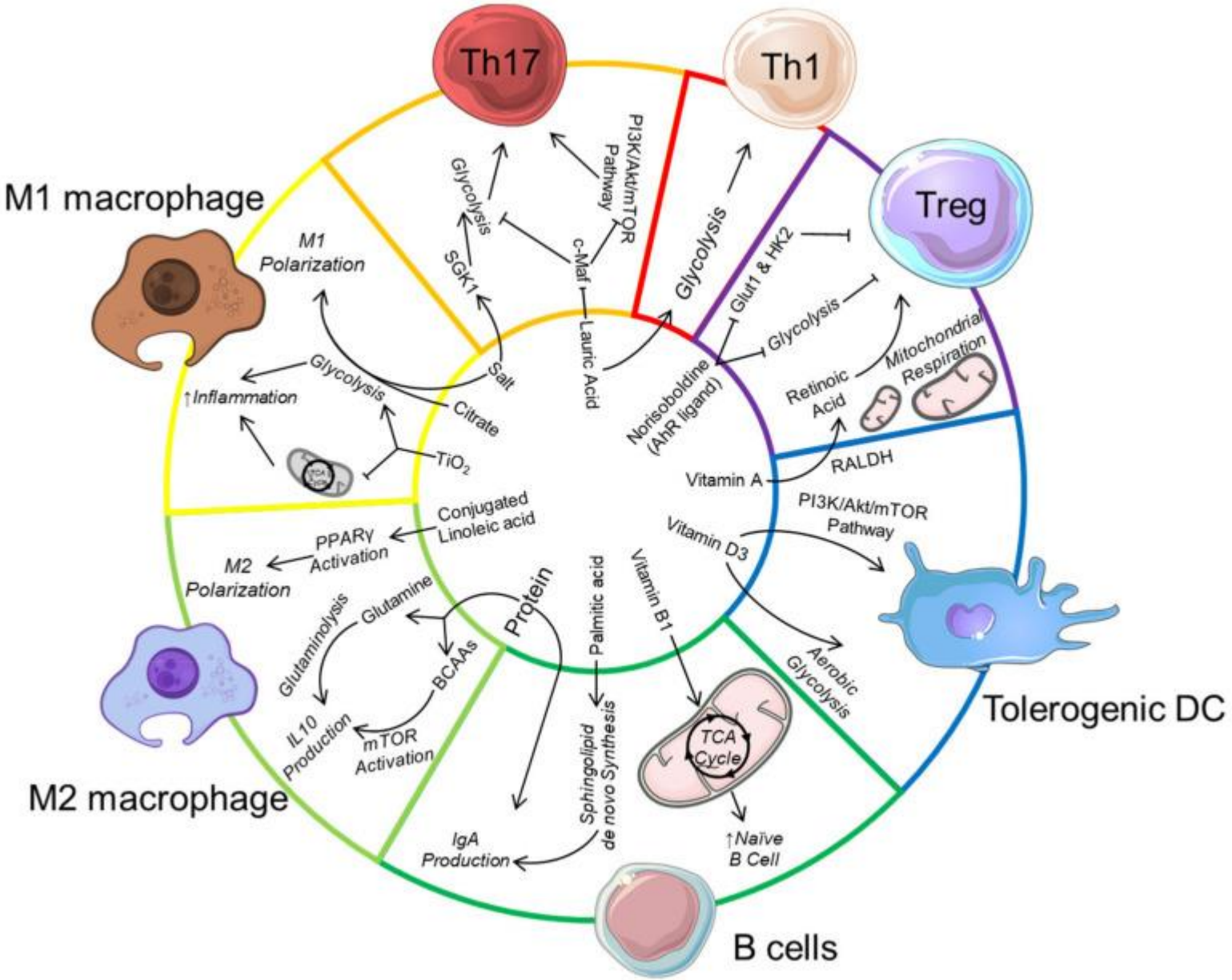
- Emerging insights into diet-microbiota interactions indicate that nutrition has a dominant influence on the composition—and metabolic output—of the intestinal microbiota, which in turn has major consequences for host immunity and inflammation.
- Emphasises the influence of diet-microbiota crosstalk on immune regulation that will have a significant impact on precision nutrition approaches and therapeutic interventions for managing inflammation, infection, and cancer immunotherapy.



Wang A, Guan B, Zhang H, Xu H. **Danger-associated metabolites trigger metaflammation: A crowbar in cardiometabolic diseases**. Pharmacol Res. 2023 Dec;198:106983.

DAMs are small-molecule metabolites, different from “molecular patterns,” that originally participate in the biological tasks and are tightly manipulated by or derived from the metabolic chaos generated by microbiota that leads to metabolic and immune dysfunction of the host

Impact of dietary-derived metabolites on host immunometabolism and gut immune cell function.



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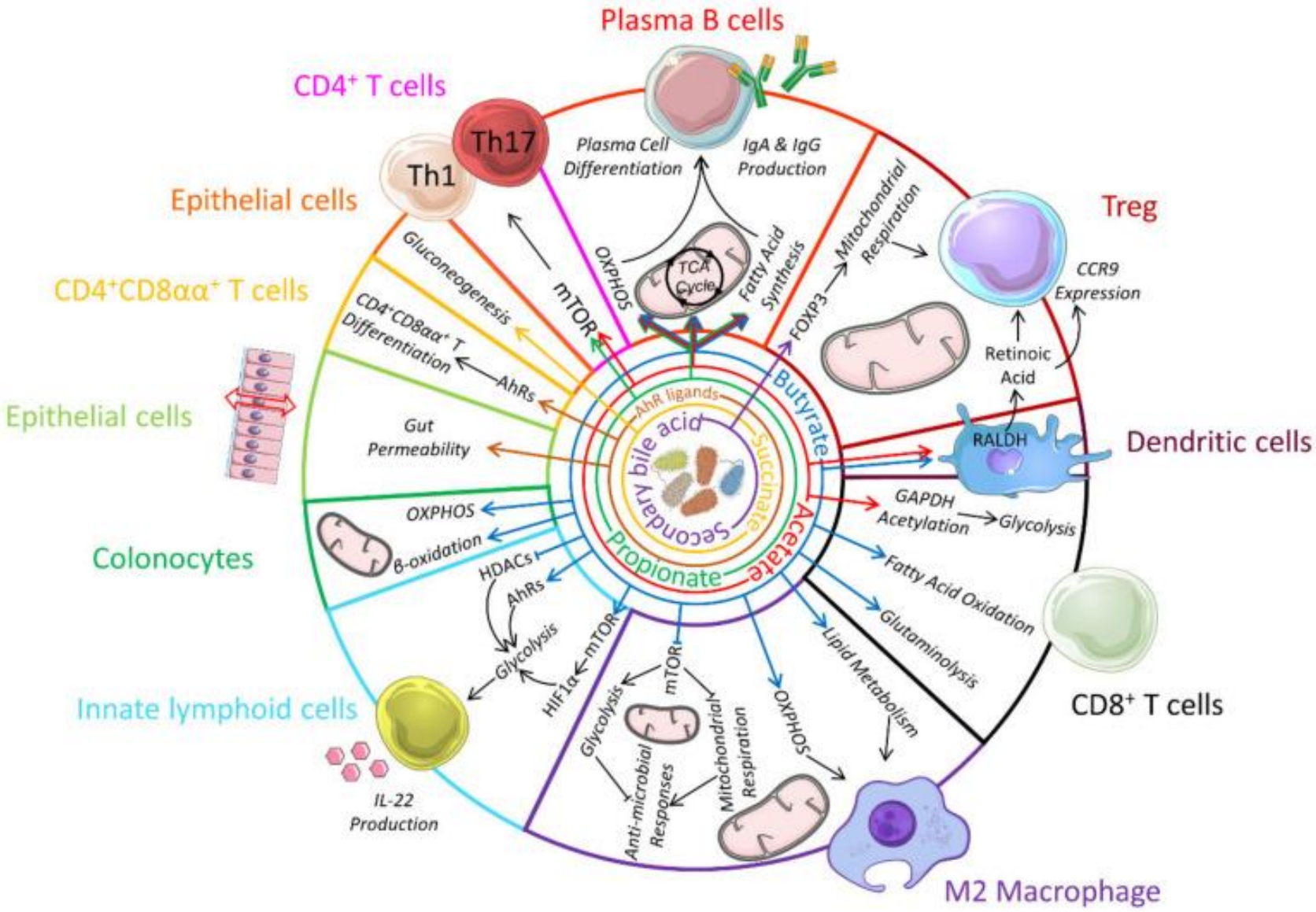

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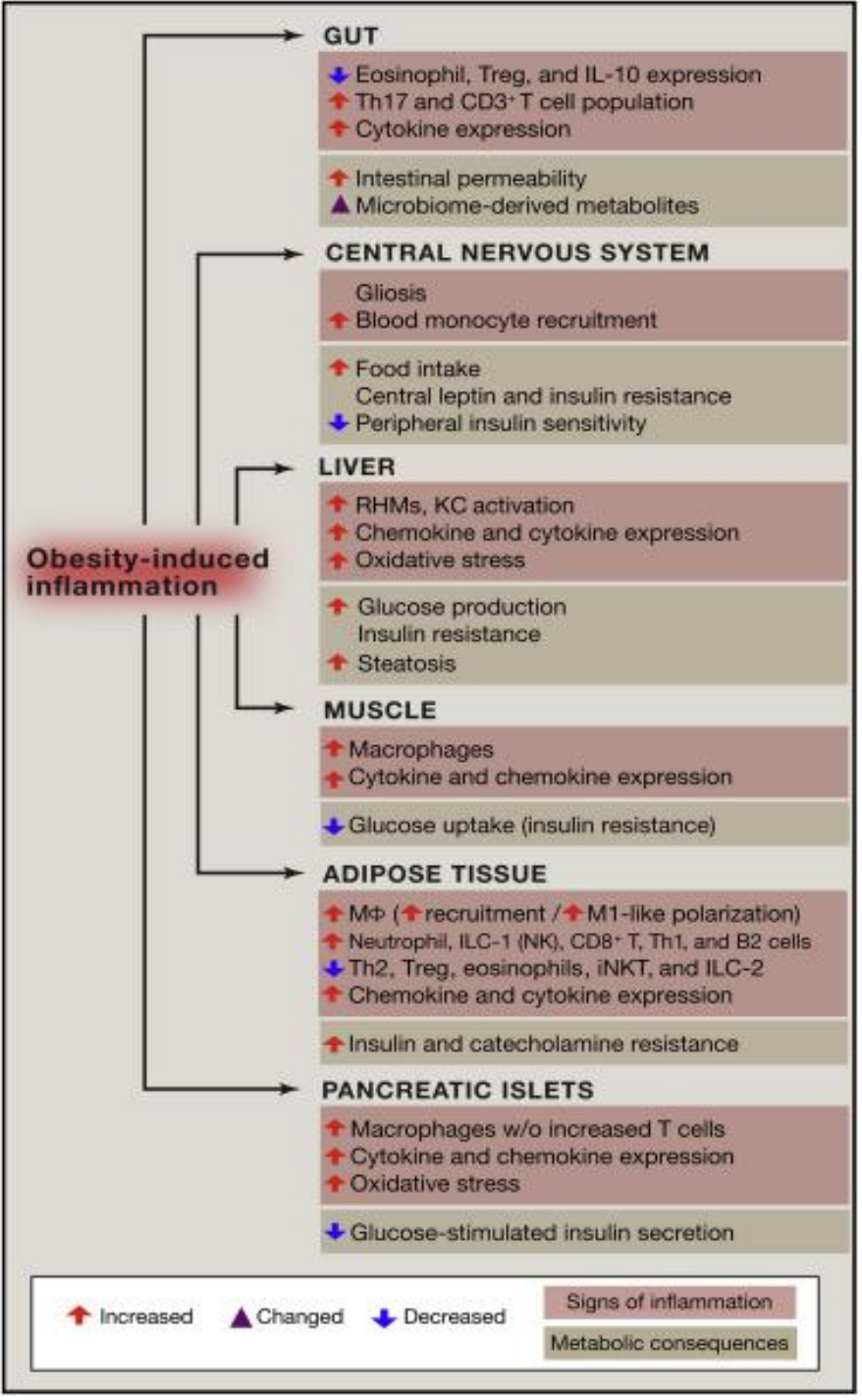

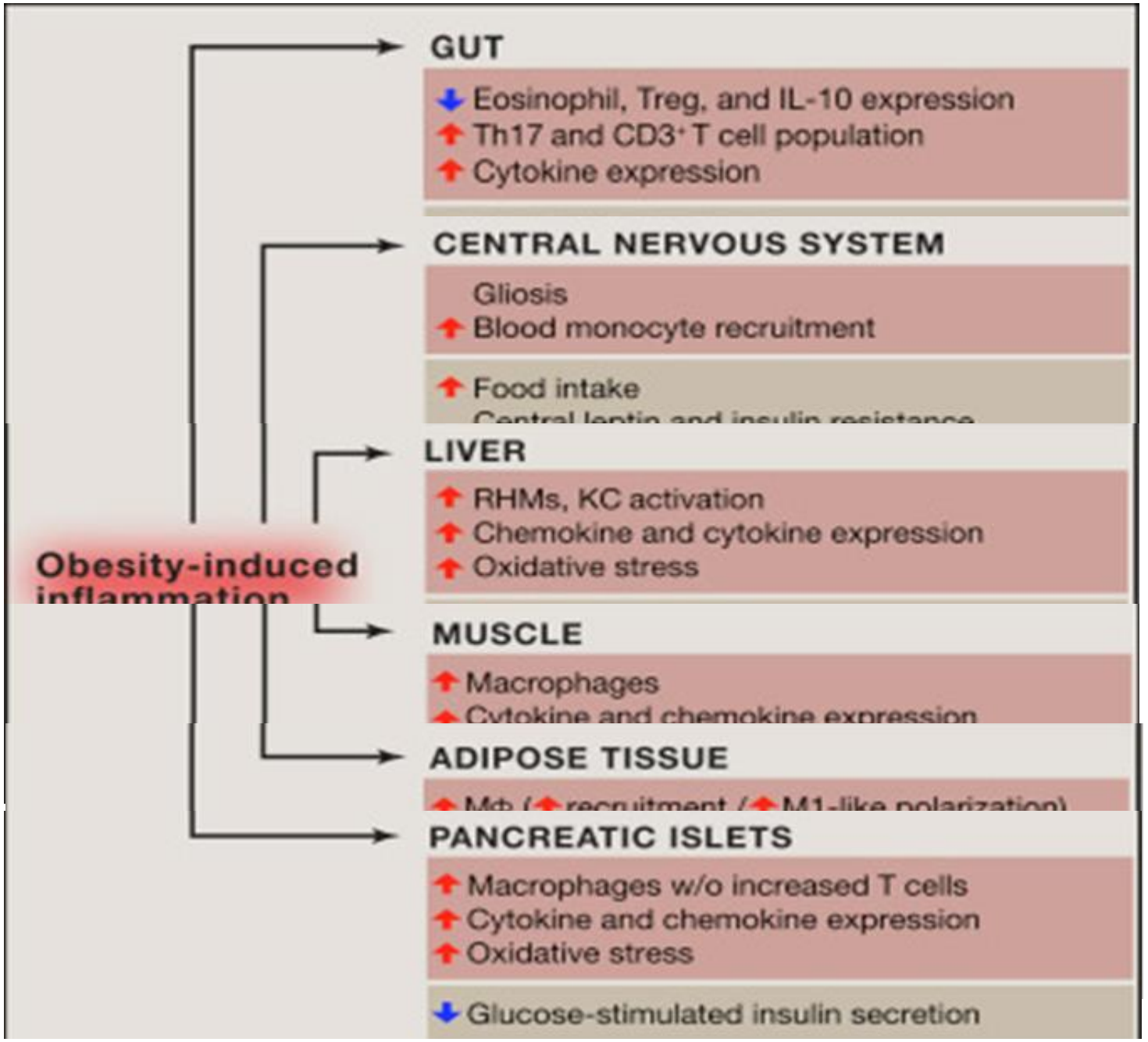

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Modulatory Properties of Food and Nutraceutical Components Targeting NLRP3 Inflammasome Activation

Key Nutritional Components and Their Sources

Phenolic Acids

- **Found in**: Vegetables, spices, fruits, cereals, oilseed wine, vinegar
  - **Sinapic Acid**: Vegetables, spices, fruits, cereals, oilseed wine, vinegar
  - **Ferulic Acid**: Fruits, vegetables, grains, beans, seeds, nuts, grasses, corn, wheat, turmeric

Polyphenols

- Includes Flavonoids, Carotenoids, Curcumin, Resveratrol

Fatty Acids and Supplements

- Omega-3 fatty acids
- Probiotics
- Vitamin D
- Melatonin
- Berberine
- Zinc

Spano M, Di Matteo G, Ingallina C, Ambroselli D, Carradori S, Gallorini M, Giusti AM, Salvo A, Grosso M, Mannina L. Modulatory Properties of Food and Nutraceutical Components Targeting NLRP3 Inflammasome Activation. Nutrients. 2022 Jan 23;14(3):490.

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- The End
- Many thanks for your kind attention