L08 b

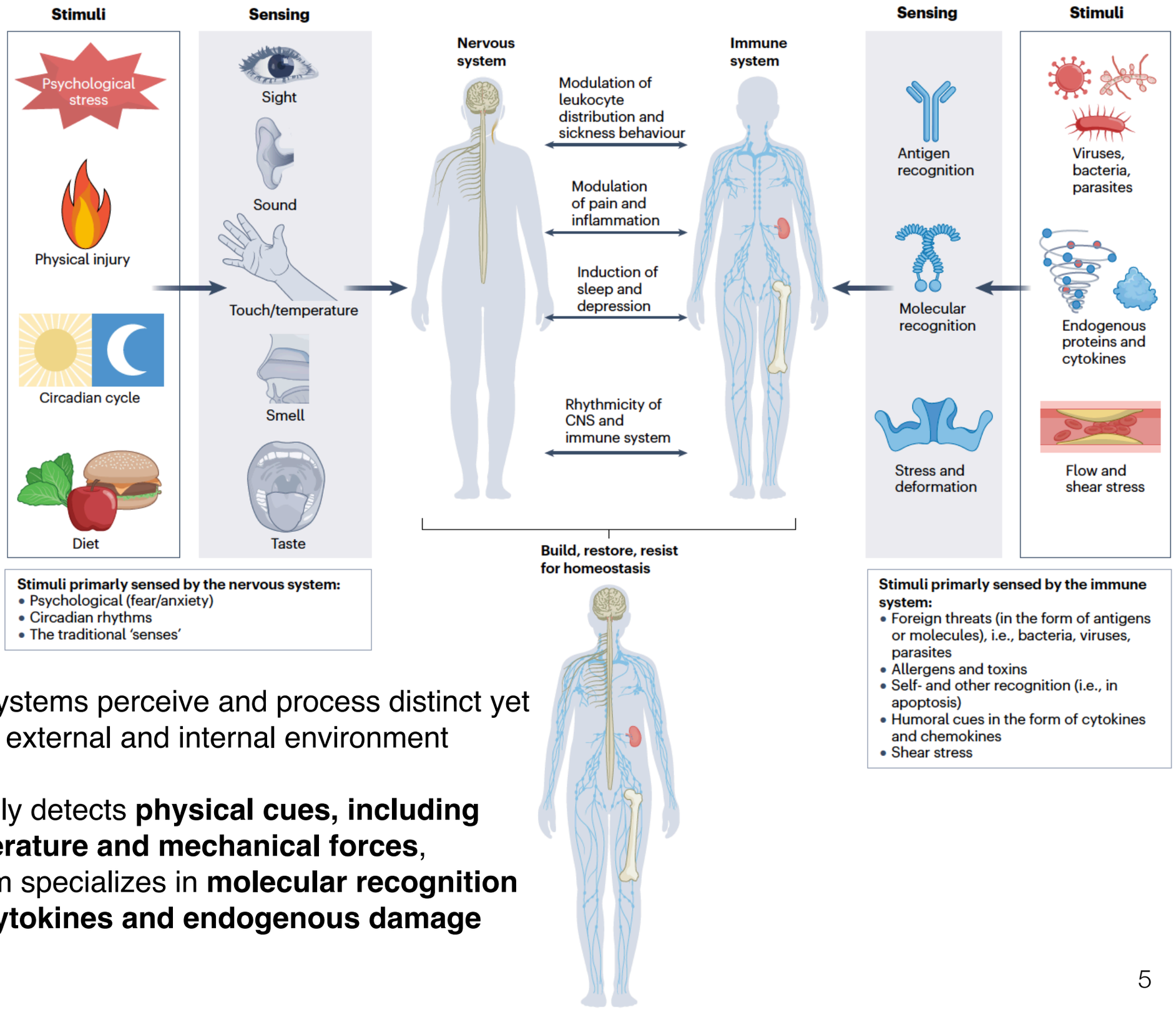
Recap

Microscale interactions and molecular recognitions have system scale consequences for human health

Human at the intersection among Nervous System - Immune System - Microbiome/Microbiota

Sensing stimuli and communicating them between the nervous and immune systems

Leunig et al., 2025

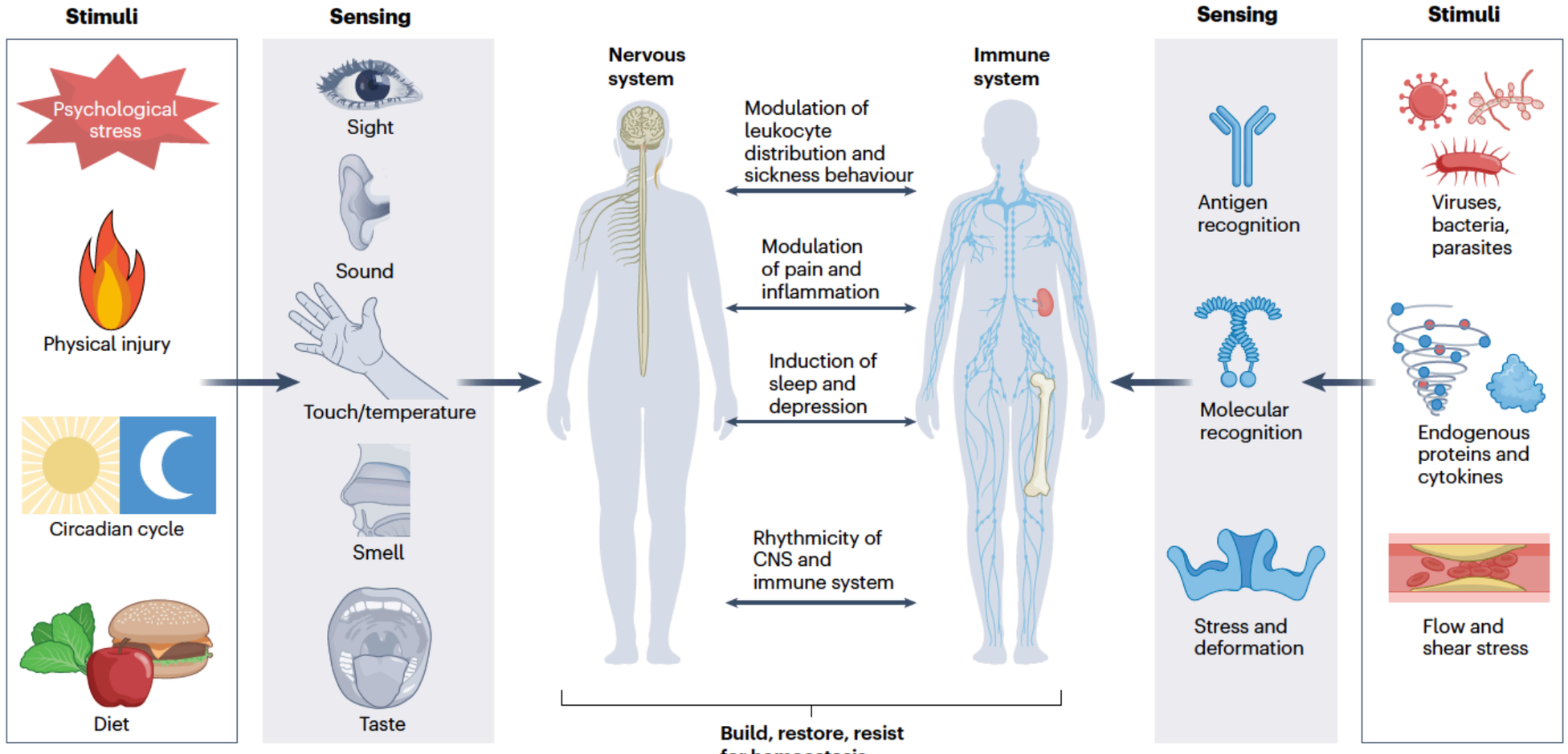


The nervous and immune systems perceive and process distinct yet overlapping stimuli from the external and internal environment

The nervous system primarily detects **physical cues, including light, sound, touch, temperature and mechanical forces**, whereas the immune system specializes in **molecular recognition of pathogens, antigens, cytokines and endogenous damage signals**

Sensing stimuli and communicating them between the nervous and immune systems

Leunig et al., 2025



Stimuli primarly sensed by the nervous system:
- Psychological (fear/anxiety)
- Circadian rhythms
- The traditional 'senses'

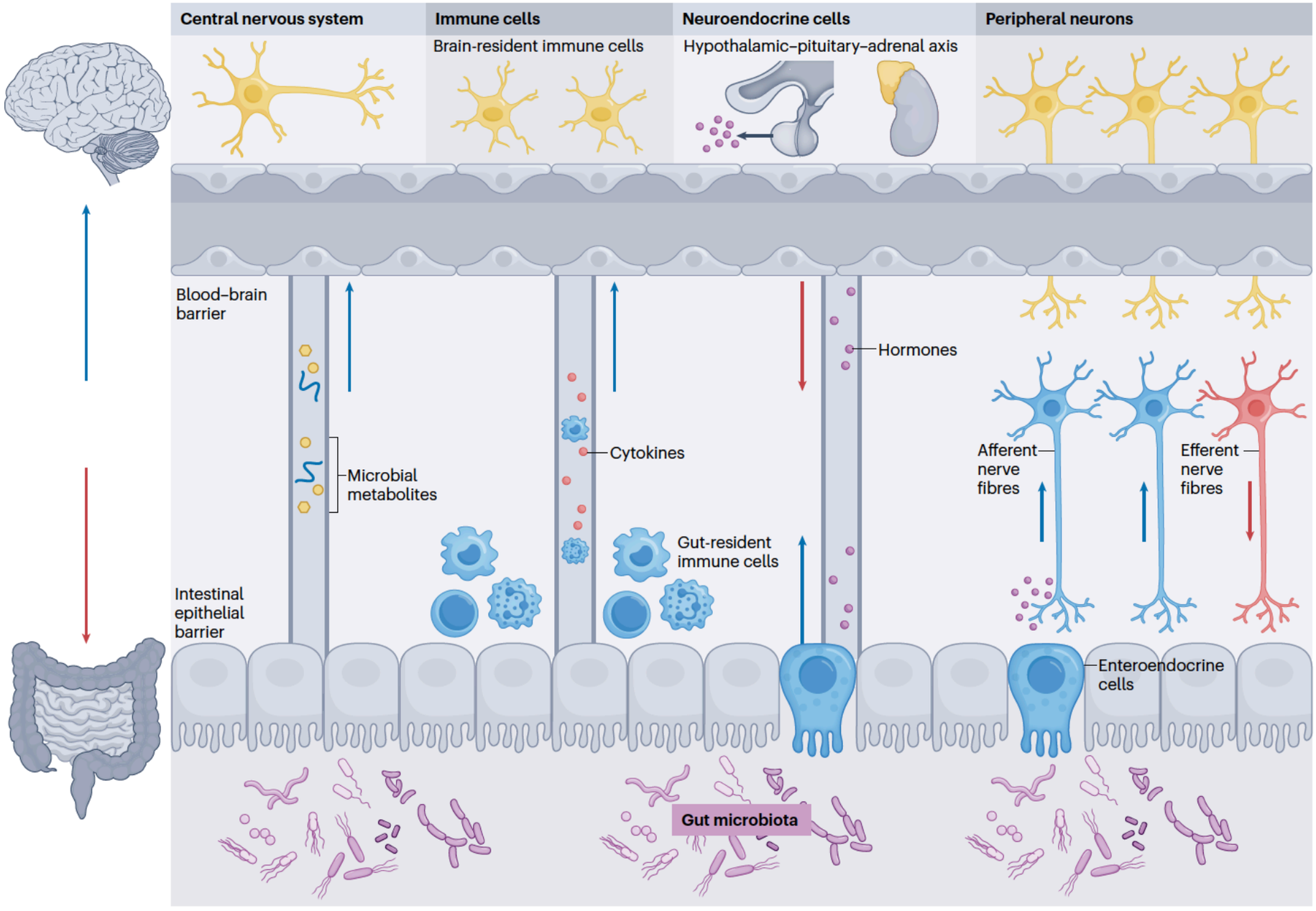
Stimuli primarly sensed by the immune system:
- Foreign threats (in the form of antigens or molecules), i.e., bacteria, viruses, parasites
- Allergens and toxins
- Self- and other recognition (i.e., in apoptosis)
- Humoral cues in the form of cytokines and chemokines
- Shear stress

Despite these distinctions, **both** systems **integrate the perceived stress, circadian rhythms and biochemical cues,** allowing for **coordinated responses to environmental and physiological challenges**

Through **bidirectional communication**, **immune-derived signals modulate neuronal activity, influencing pain, inflammation and sickness behaviours**, whereas **neural circuits regulate immune cell development and function**

Together, these systems act **together** to orchestrate **homeostasis and responses to stress and disease**

The gut microbiota–brain axis



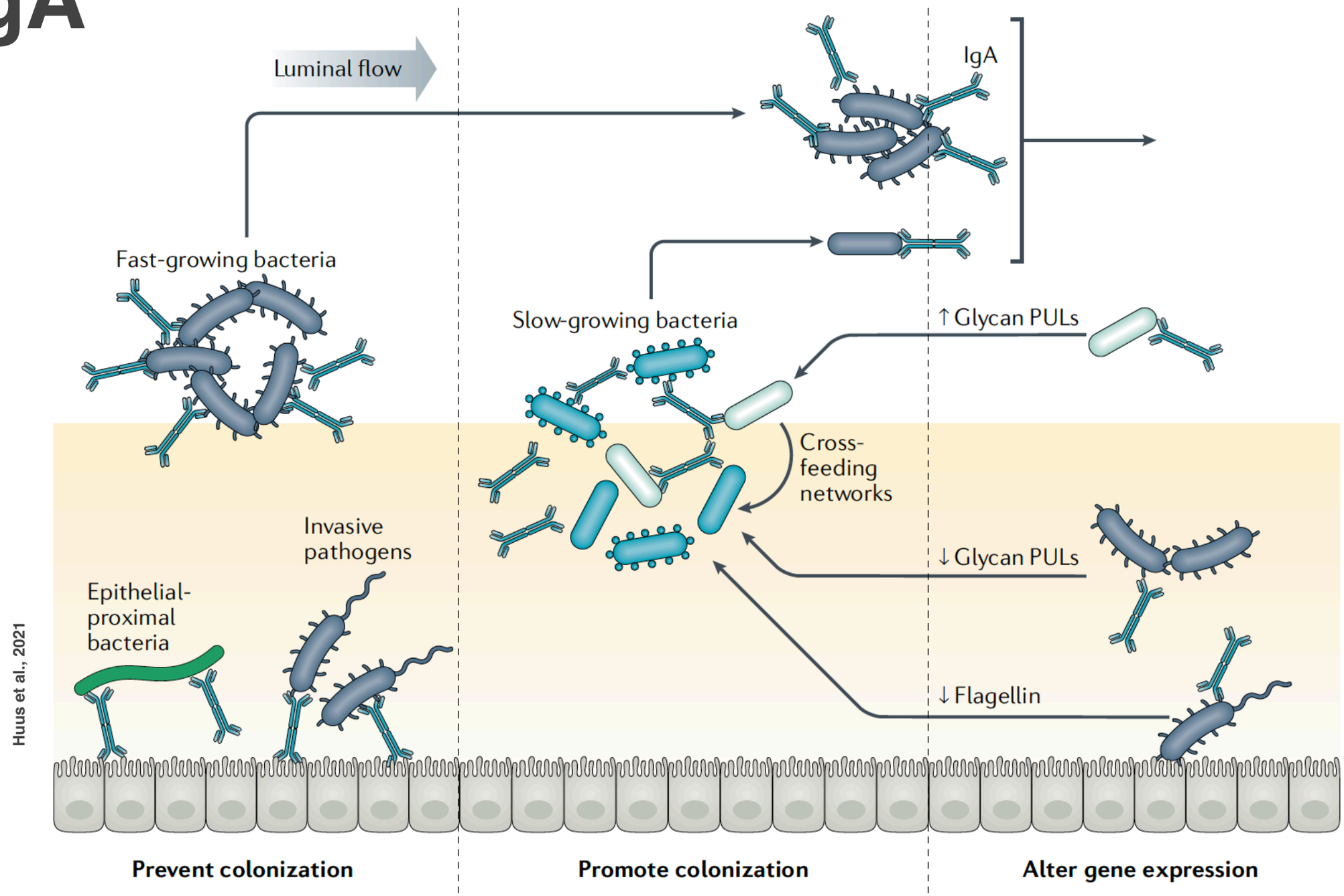
Bidirectional crosstalk between immune cells and peripheral neurons (the neuro–immune axis), between neuroendocrine cells and immune cells (the neuroendocrine–immune axis), and between intestinal epithelial cells and peripheral neurons (the intestinal neuroepithelial axis) add additional layers of complexity to these established routes of communication between the gut and the brain

Ohara and Hsiao, 2025

Immunoglobuline

IgG: Provides long-term immunity and is the most abundant in blood and extracellular fluid
IgA: Protects mucosal surfaces (e.g., in the respiratory and gastrointestinal tracts)
IgM: The first antibody produced during an initial infection; efficient in forming antigen-antibody complexes
IgE: Involved in allergic responses and defense against parasitic infections
IgD: Plays a role in the activation and regulation of B cells

IgA



- IgA mediates microbial homeostasis at the intestinal mucosa
- IgA acts in a context- dependent manner to shape the colonization and function of the intestinal microbiota
- PULs, polysaccharide utilization loci

The Immune System

Why do we care about the Immune system?

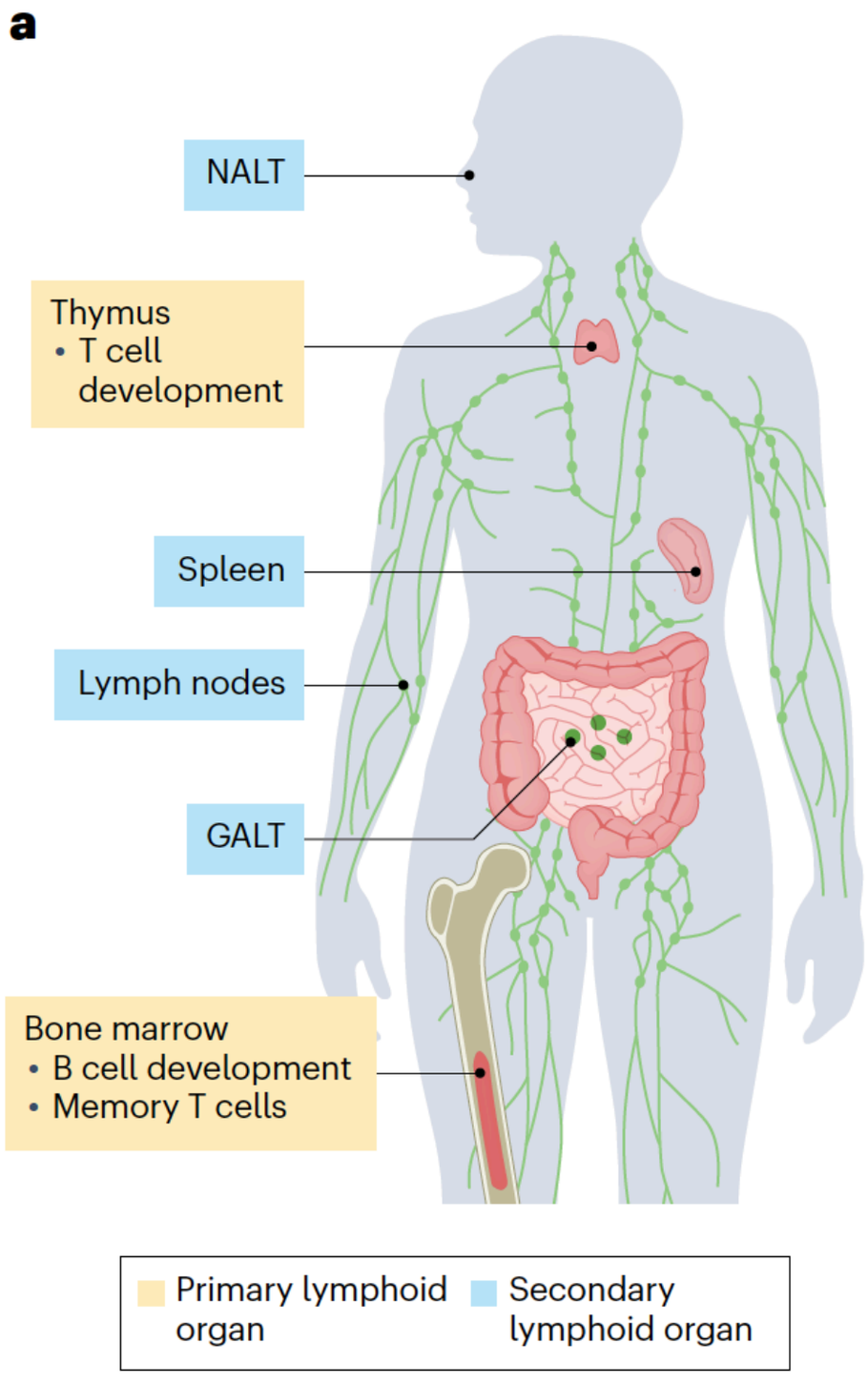
- **Peaceful coexistence, while avoiding microbial breach and takeover as well as over-exuberant immune responses, is essential for the functioning of the human ecosystem**

- **Dead cell and non-self clearance**

- **The immune system consists of well-defined regional control centres (lymphoid organs), important tissue-resident cell populations (especially at barrier tissues such as mucosal surfaces) and mobile cell populations that constantly recirculate through blood (and specialised free molecules) and tissues**

- **Two systems in one: innate (general/constitutive) and adaptive (specific/tailored/inducible)**

System architecture



Yousefpour et al., 2023

GALT, gut-associated lymphoid tissue; NALT, nasal-associated lymphoid tissue

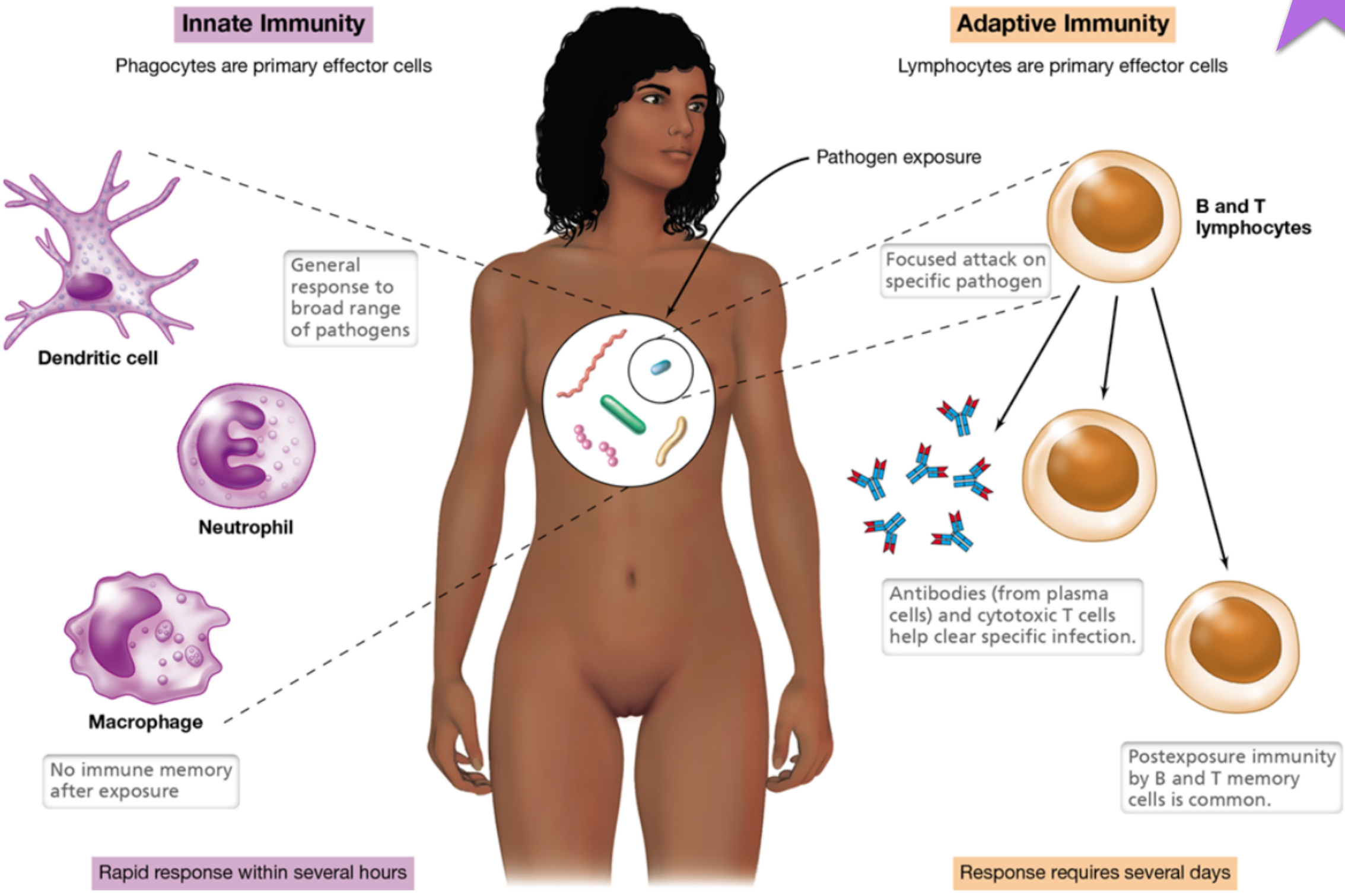
Lymphoid organs coordinate the **maturation** and **migration** of immune cells while **organizing** and **regulating** immune **responses**

Primary lymphoid organs in adults include the **bone marrow** and **thymus**, which serve as niches for **lymphocyte development**

Secondary *lymphoid organs* — which include 600–800 **lymph nodes** distributed across the body, the **spleen** and the **mucosa-associated lymphoid tissue** — **house and organize T cells, B cells and antigen-presenting cells (APCs)**

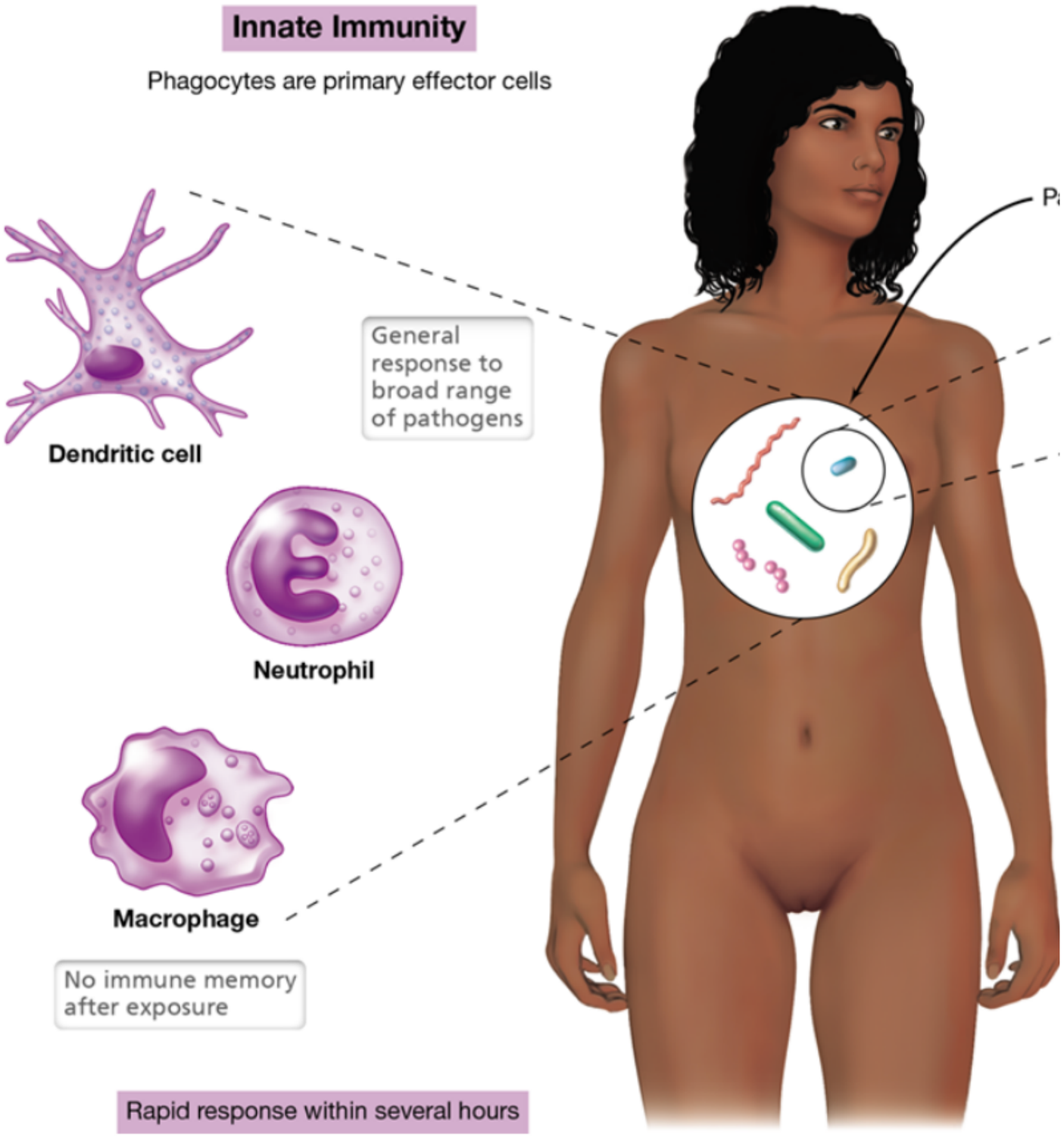
These organs serve as **command centres of adaptive immunity** where **activation** of naive **B** and **T** lymphocytes occurs and are thus **natural targets for vaccines and immunotherapies**

Innate/Constitutive *vs* Adaptive/Inducible immunity cell populations



Madigan, 2020

Innate/Constitutive *vs* Adaptive/Inducible immunity cell populations



Madigan, 2020

Innate immune cells such as macrophages, dendritic cells (DCs), and granulocytes exhibit broad recognition for molecules expressed by microorganisms, or which are released during tissue injury.

Innate cells—both resident in and recruited to tissues—comprise the early responders to pathogen encounter *in situ*

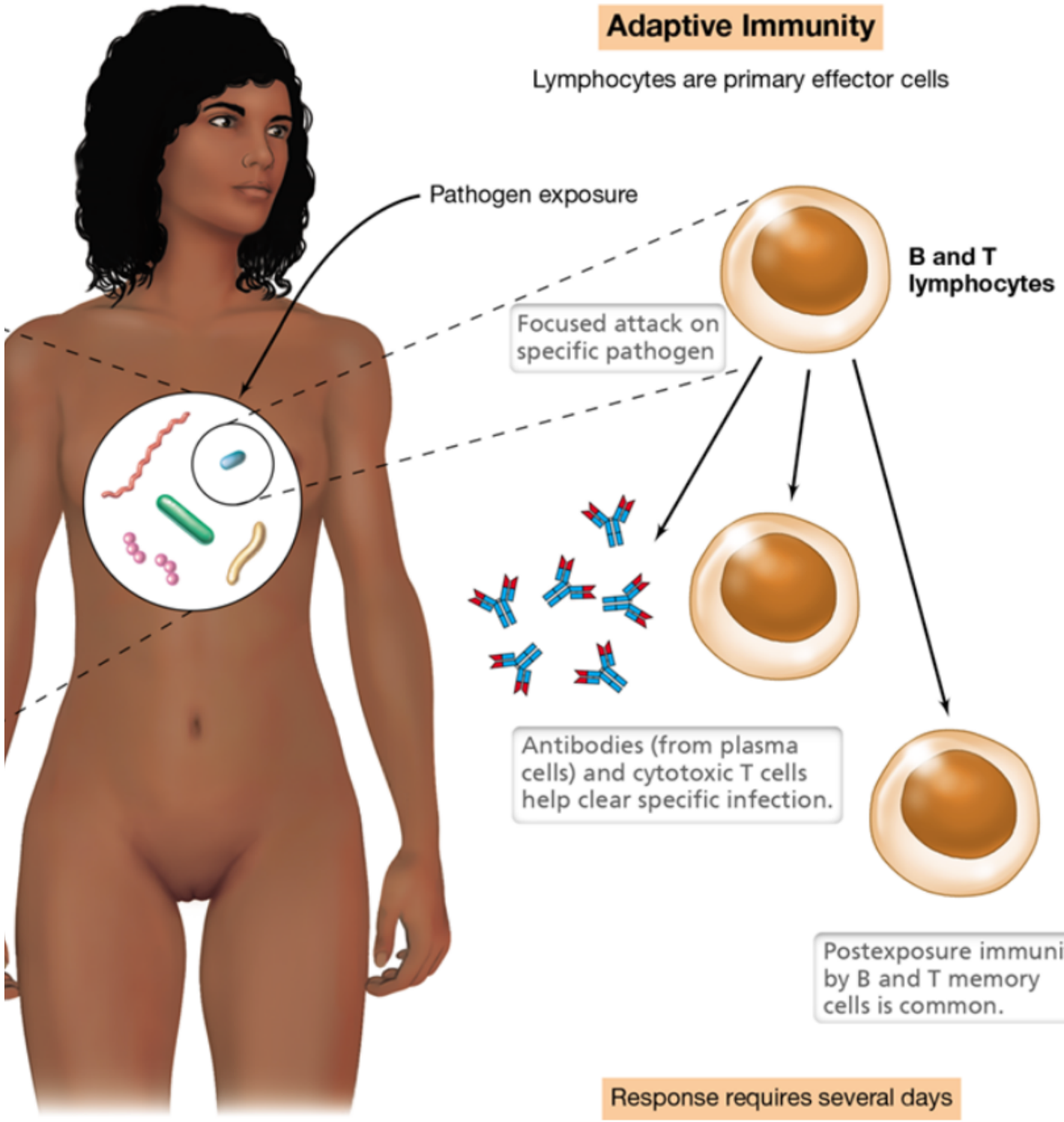
Innate/Constitutive *vs* Adaptive/Inducible immunity cell populations

Adaptive immunity develops as a result of antigen encounter and is mediated by B and T lymphocytes, collectively expressing antigen-specific receptors of diverse specificities.

T cells develop in the thymus as distinct lineages of CD4+ (T-helper) and CD8+ (cytotoxic) T cells that seed secondary lymphoid organs (spleen, lymph node), where they become activated by DC-presenting antigen

Activated CD4+ and CD8+ T cells differentiate to effector cells and migrate to tissue sites of infection for directing pathogen clearance and lysis of infected cells

Pathogen-specific B cells also become activated in lymphoid sites where they interact with CD4+ T helper cells for differentiation to antibody-producing plasma cells; circulating antibodies subsequently bind to pathogens, marking them for destruction



Immune cells can be subdivided into **“innate” or ‘’adaptive”** based on their recognition properties and functional roles

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Weisberg et al., 2021

MEMORY

Together, innate and adaptive immune processes mediate pathogen removal, with T cells playing pivotal roles in the initiation and functional regulation of these cellular and humoral immune responses

A key feature of the adaptive immunity is **immunological memory maintained by pathogen-specific memory T and B cells and antibodies in plasma**

Memory T cells derive from **activated or effector T cells** generated **during** the **initial** immune response and consist of **non-circulating tissue-resident memory T cells (TRMs)** retained in diverse tissue sites and circulating, tissue surveilling memory T cells

Humoral immunity is maintained as memory B cells and long-lived plasma cells—both largely confined to **lymphoid organs**

TRMs, in particular, coordinate immune surveillance, protection, and homeostasis, and exhibit tissue-specific adaptations TRMs are also the major adaptive immune cells in barrier sites throughout most of adult life suggesting that they play major roles in controlling immunity over a lifetime

Weisberg et al., 2021

Microbes and Immune System

- **Prenatal and early postnatal life** represent key periods of immune system development

- In addition to **genetics** and **host biology**, **environment** has a large and **irreversible role** in the immune maturation and health of an infant

- One key player in this process is the **gut microbiota**, a diverse community of microorganisms that colonizes the human intestine

- The **diet, environment and medical interventions** experienced by an infant determine the establishment and progression of the **intestinal microbiota, which interacts with and trains the developing immune system**

- *Several chronic immune-mediated diseases have been linked to an altered gut microbiota during early infancy*

- The recent rise in allergic disease incidence has been explained by the '*hygiene hypothesis', which states that societal changes in developed countries have led to reduced early-life microbial exposures, negatively impacting immunity*

Donald and Finlay, 2025

Microbial interactions with immune system are bidirectional

The **gut microbiota make a major contribution to the regulation of host T cell and B cell maturation and activity**

In turn, these lymphocytes regulate the microbiota through maintenance of the intestinal barrier and low-grade microbial translocation to other body sites

These interactions begin at the intestinal epithelium, which commensal (and pathogenic) bacteria access by breaking through the mucus layer

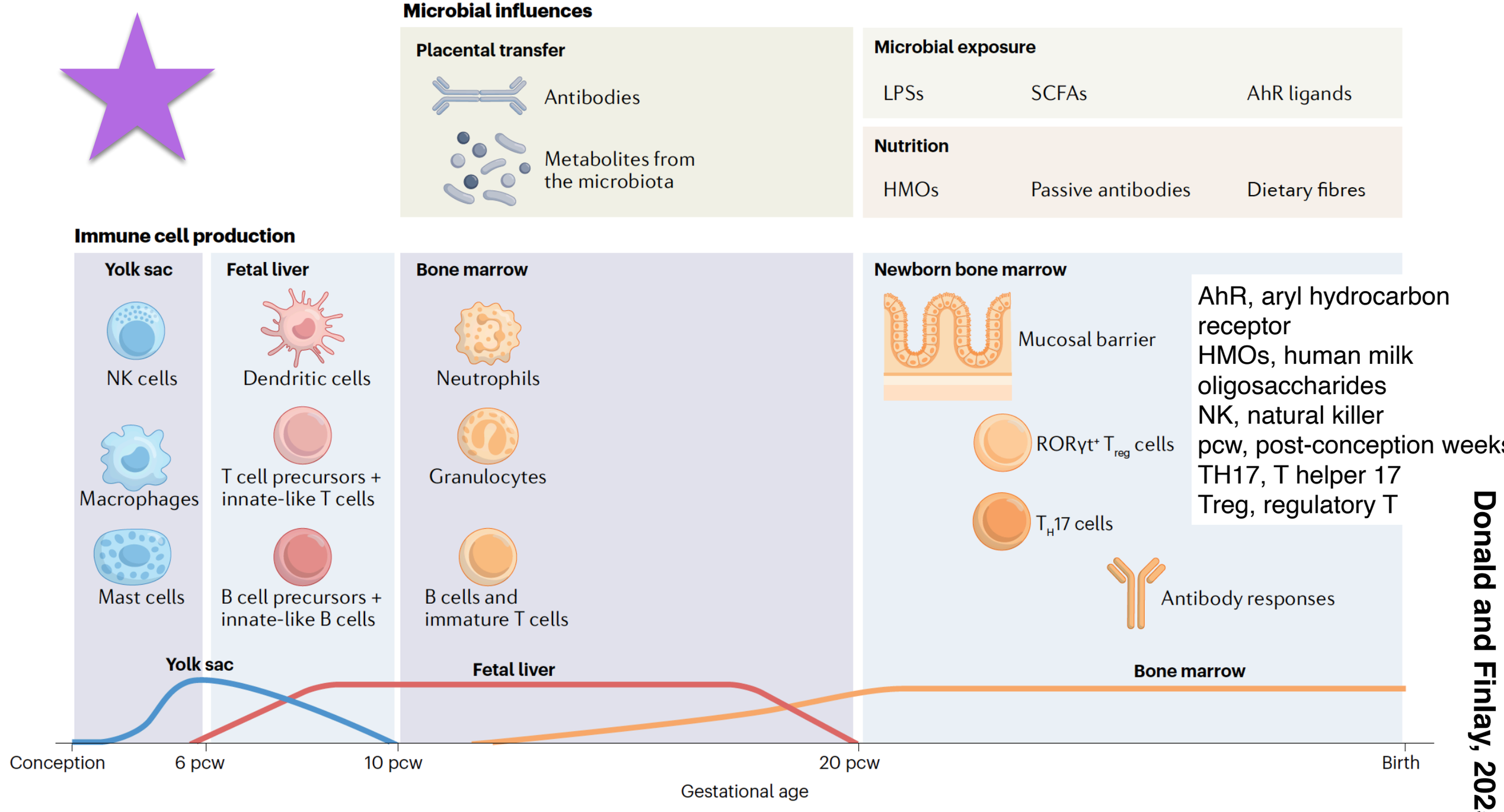
This **mucus layer is different in the small intestine** (which has a **single, tightly attached layer of mucus**) and in the **colon (where the mucus is organized into a loose outer layer and a denser, firmly attached inner layer**), with implications for the composition and function of immune cells that are resident in the gut-associated lymphoid tissue in these two regions

Pro-inflammatory lymphocytes are predominantly produced in the small intestine, whereas anti-inflammatory lymphocytes predominate in the colon

Signals from the microbiota create complex interactions between epithelial cells, dendritic cells, macrophages and innate lymphoid cells

Normally, these interactions are tightly controlled by innate and adaptive immune responses. However, a breakdown of intestinal homeostasis owing to dysbiosis can result in dysregulated systemic immune responses

Waves of immune cell production and dispersal

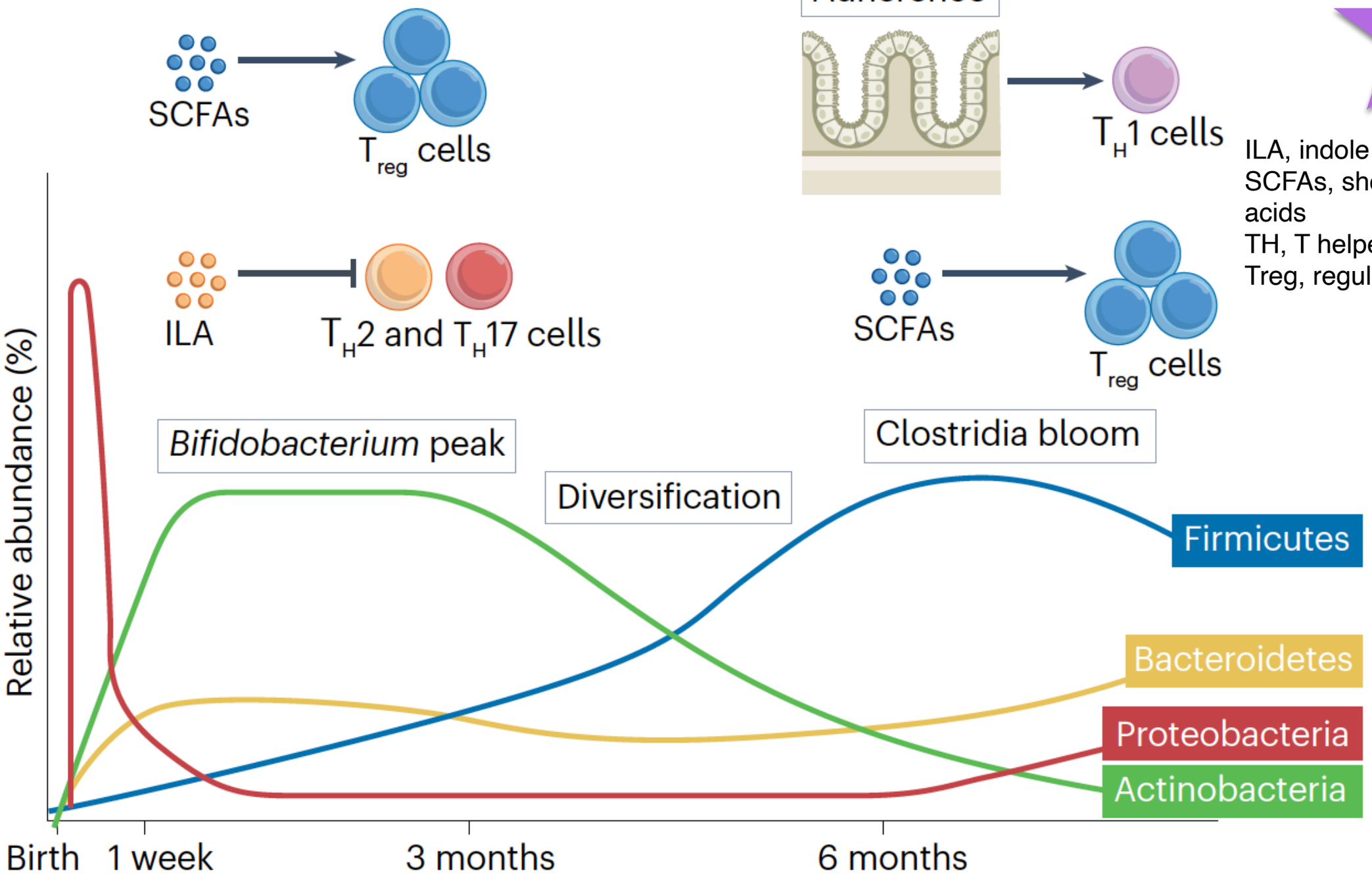


AhR, aryl hydrocarbon receptor
HMOs, human milk oligosaccharides
NK, natural killer
pcw, post-conception weeks
TH17, T helper 17
Treg, regulatory T

Donald and Finlay, 2025

- **Immune cells** arise in **three** distinct **waves** during prenatal life
- The **yolk sac, fetal liver and bone marrow** all contribute different cell types, which begin to arise at different time points **before birth**
- At **birth** and throughout the first months, immune compartments **dependent on microbial stimulation arise and develop**

Gut microbiota maturation in early life and accompanying immune phenotypes



ILA, indole lactic acid
SCFAs, short-chain fatty acids
TH, T helper
Treg, regulatory T

Donald and Finlay, 2025

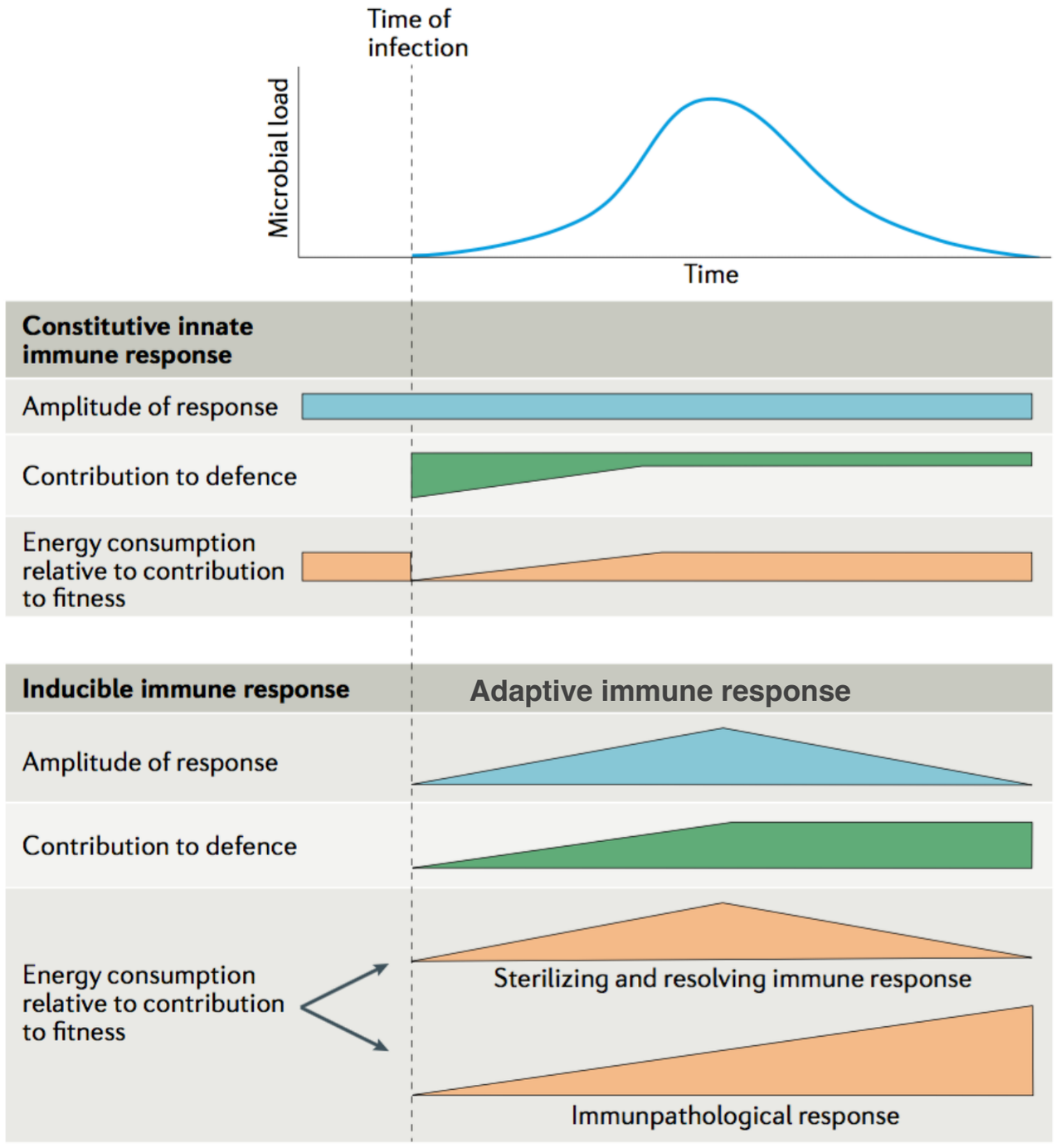
The first **3–6 months after birth** is thought to represent the '**window of opportunity**', a period during which the **gut microbiota trains the developing immune system** in the healthy, breastfed neonate

Table 1 | Features of fetal and neonatal immune development in humans and mice

Stage of development	Characteristic	Species	Refs.
Fetal development	Three sources of immune cells in the fetus: the yolk sac, fetal liver and bone marrow. Immune cells arise in three waves	Humans and mice	1,23,24
	Monocytes main immune cell type produced by the fetal yolk sac	Humans and mice	1,24–26
	DCs, T cell precursors and B cell precursors are generated by the fetal liver	Humans	1,4,24,33
	Lymph node generation occurs at 8–10 weeks of gestation	Humans	1
	Bone marrow haematopoiesis begins at 10 weeks of gestation	Humans	36,37
	Bone marrow haematopoiesis begins just before birth	Mice	38
Early postnatal development	TLR responses are dampened in the neonate	Humans	41,42
	Neonatal DCs and T cells are biased towards regulatory responses	Humans	4,43,45,46,54,55
	Neonates have dampened T_H1 cell responses	Humans	46,47,56,57
	Neonatal T cells are biased towards T_H2 cell responses	Humans and mice	56,57
	Immunosuppressive erythroid cells are abundant during early life	Humans and mice	48
	Neutrophil numbers decline after birth	Humans	34
	The neonatal intestinal epithelium is immature	Mice	50,51
	Intestinal epithelial barrier integrity is dependent on microbial colonization	Humans and mice	50
	Neonatal T cells are more innate-like and do not establish memory populations	Humans and mice	59–63
	A subset of neonatal B cells is immunosuppressive	Humans and mice	39,65

This table describes the major features of early immune system development that are highlighted in the manuscript. The species in which evidence for these features has been discovered are listed on the right. DCs, dendritic cells; T_H, T helper; TLR, Toll-like receptor.

Innate/Constitutive immune responses *versus* Inducible/Adaptive immune responses



- **Amplitude of response**
- **Contribution to defense**
- **Energy consumption**

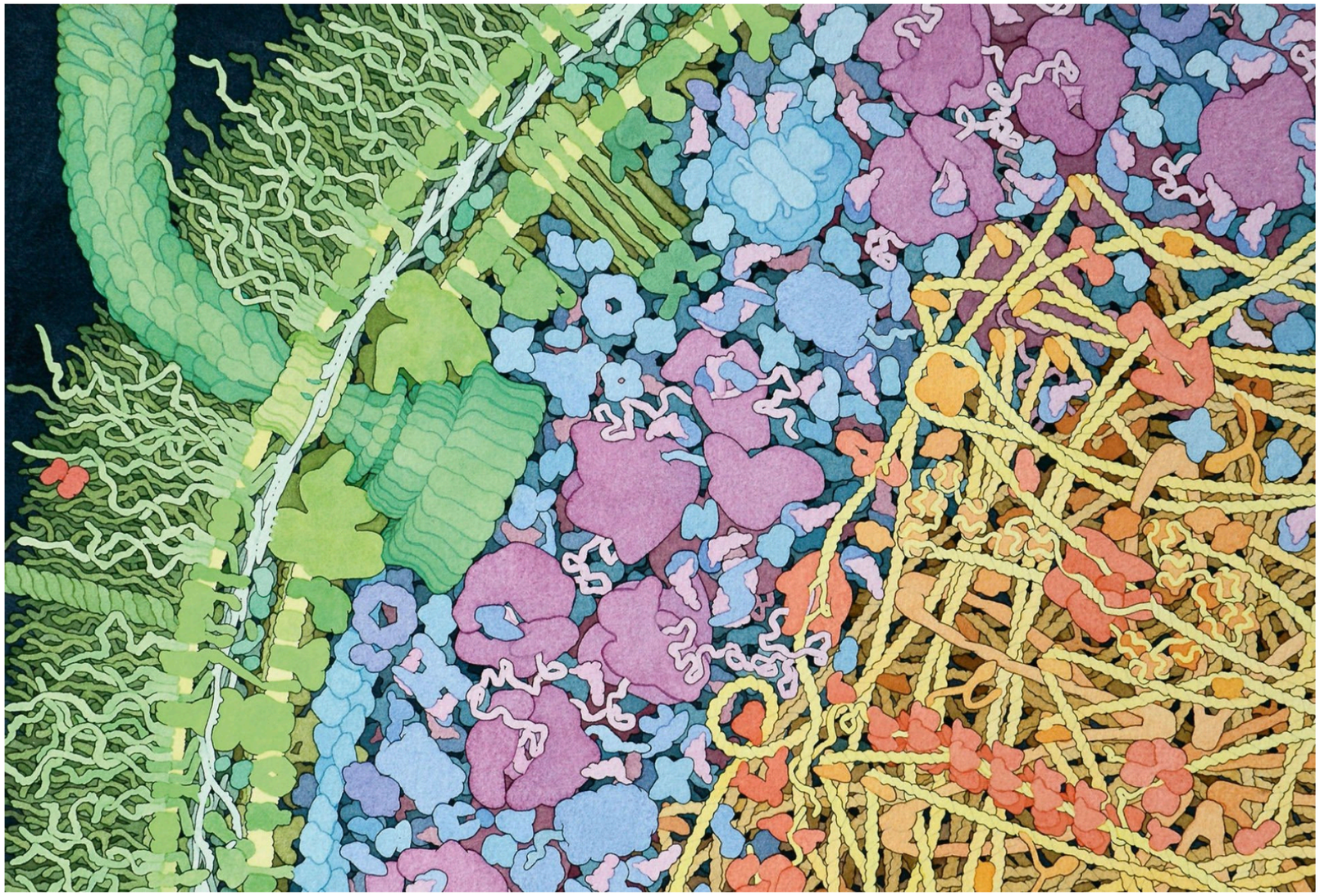
a. Sterilizing and resolving immune response, the additional energy consumption required by the inducible immune response is balanced by the re-establishment of **homeostasis**

b. **Immunopathological** response, the energy that is consumed to mount an inducible response does not benefit the host and instead leads to tissue damage and disruption of homeostasis

Paludan et al., 2021

Microbes *vs.* Immune system cells and molecules

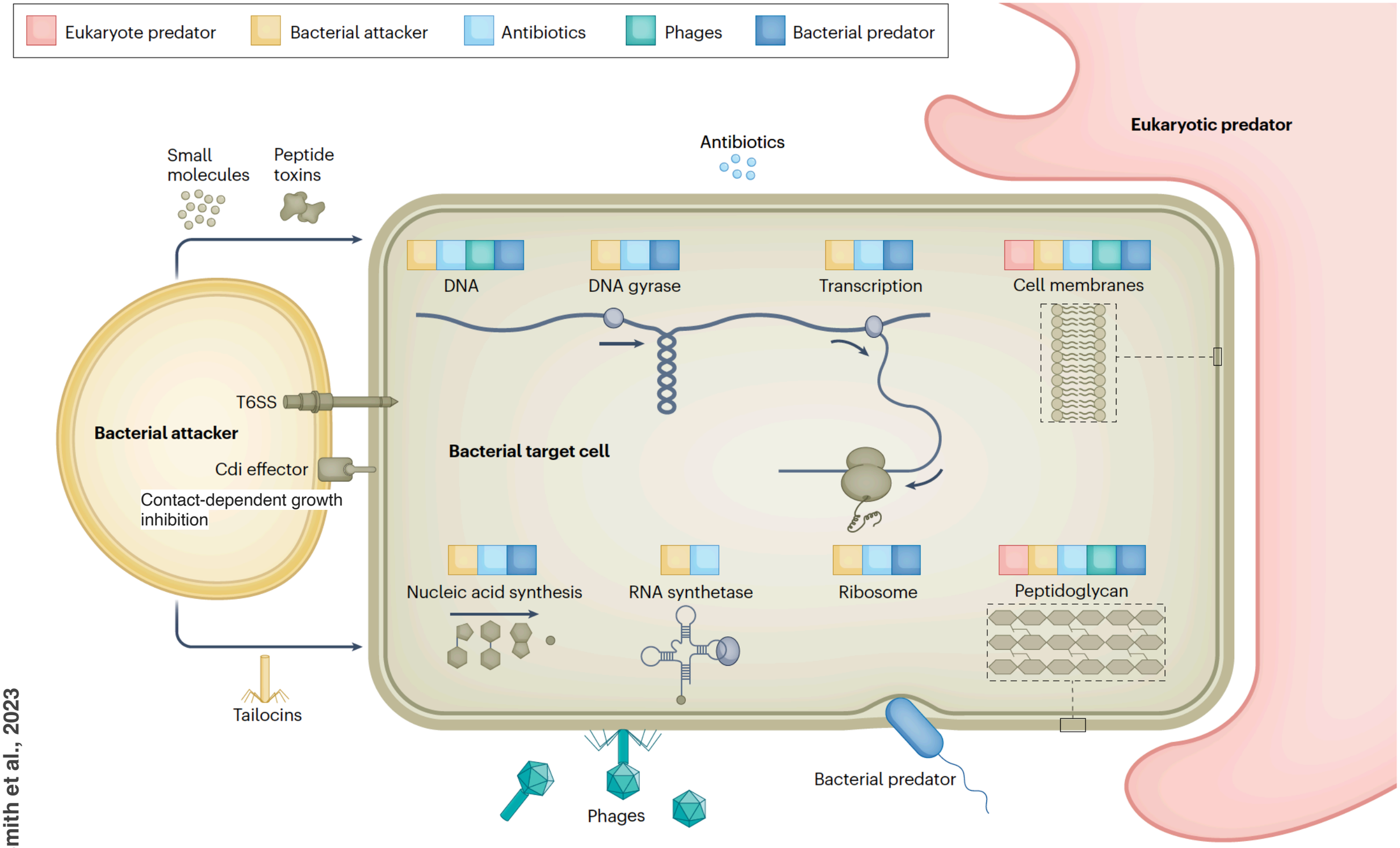
How to identify a microbe?



David S. Goodsell

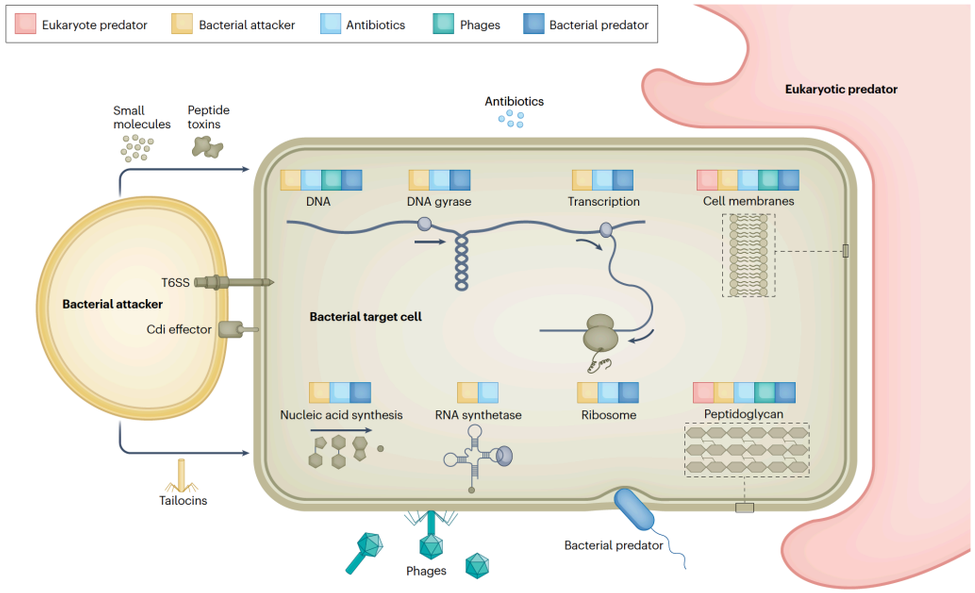
Cell surface structure
Metabolism —> molecules
Behaviour

The diverse microbial threats



Smith et al., 2023

Smith et al., 2023



- Most attacks target **core cellular processes and functions** of the microbial cell

- Microbial competitors antagonize a target bacterium via diverse mechanisms, including both **contact-dependent** weaponry (the type VI secretion system (T6SS); **Cdi effectors**) and **diffusible weaponry** (small molecules, antibiotics, peptide toxins and tailocins)

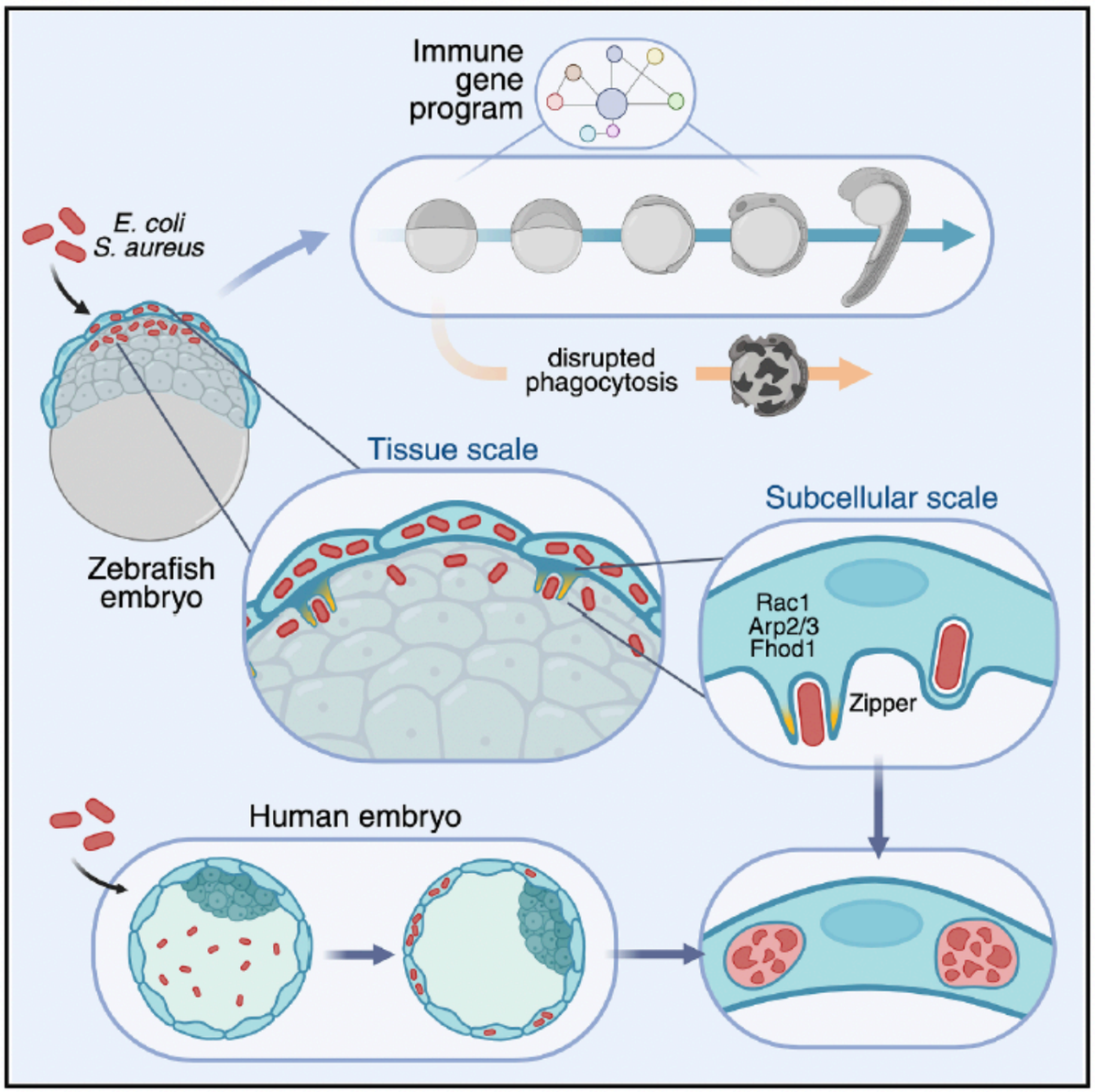
- The majority of clinical antibiotics are also derived from bacteria and other microorganisms

- Following infection of a bacterial cell, phages attack cell walls and membranes to release their progeny via cell lysis

- Some bacterial predators, such as *Bdellovibrio* species and similar organisms, invade the host cell periplasm, injecting toxins that digest various cytoplasmic components

- Many eukaryotic predators **engulf and digest target bacteria whole in phagosome compartments**

Early embryos eliminate bacteria via phagocytosis by epithelial cells



Quantitative live imaging across scales in zebrafish embryos reveals an epithelial immune program essential for development

This phagocytic clearance is conserved in mouse and human embryos, highlighting an innate defense at the onset of development

Epithelial cells provide immunocompetence to the early embryo for bacterial clearance

- **Early zebrafish embryos detect, engulf, and destroy commensal and pathogenic bacteria**
- **Clearance is performed by epithelial cells via actin-dependent zippering protrusions**
- **Bacteria induce an immune program on epithelial cells crucial for normal development**
- **Phagocytosis of bacteria is conserved in mouse and human embryos**

Roncero-Carol et al., 2025

MICROBIAL BATTLEFIELD

- An infection can be seen as a battle between the invading pathogens and the host
- Human bodies are equipped to fight off invading microbes that may cause disease
- **The immune response has to be tightly controlled to ensure a clearance of the microbes but also to prevent tissue damage and necrosis as result of sepsis**

- **Human natural defences are:**

1. **Aspecific defense: chemical and physical barriers**
2. **Costitutive / innate**
3. **Adaptive / inducible**

Innate/Constitutive immune system

An innate immune system must be specific and must:

1. **Recognize** pathogens, potentially through dedicated receptors
2. **Integrate** that information via signaling pathways
3. **Launch** a response that targets the pathogens
4. **Deal** with pathogens of various natures that can infect the host *via* **different** routes

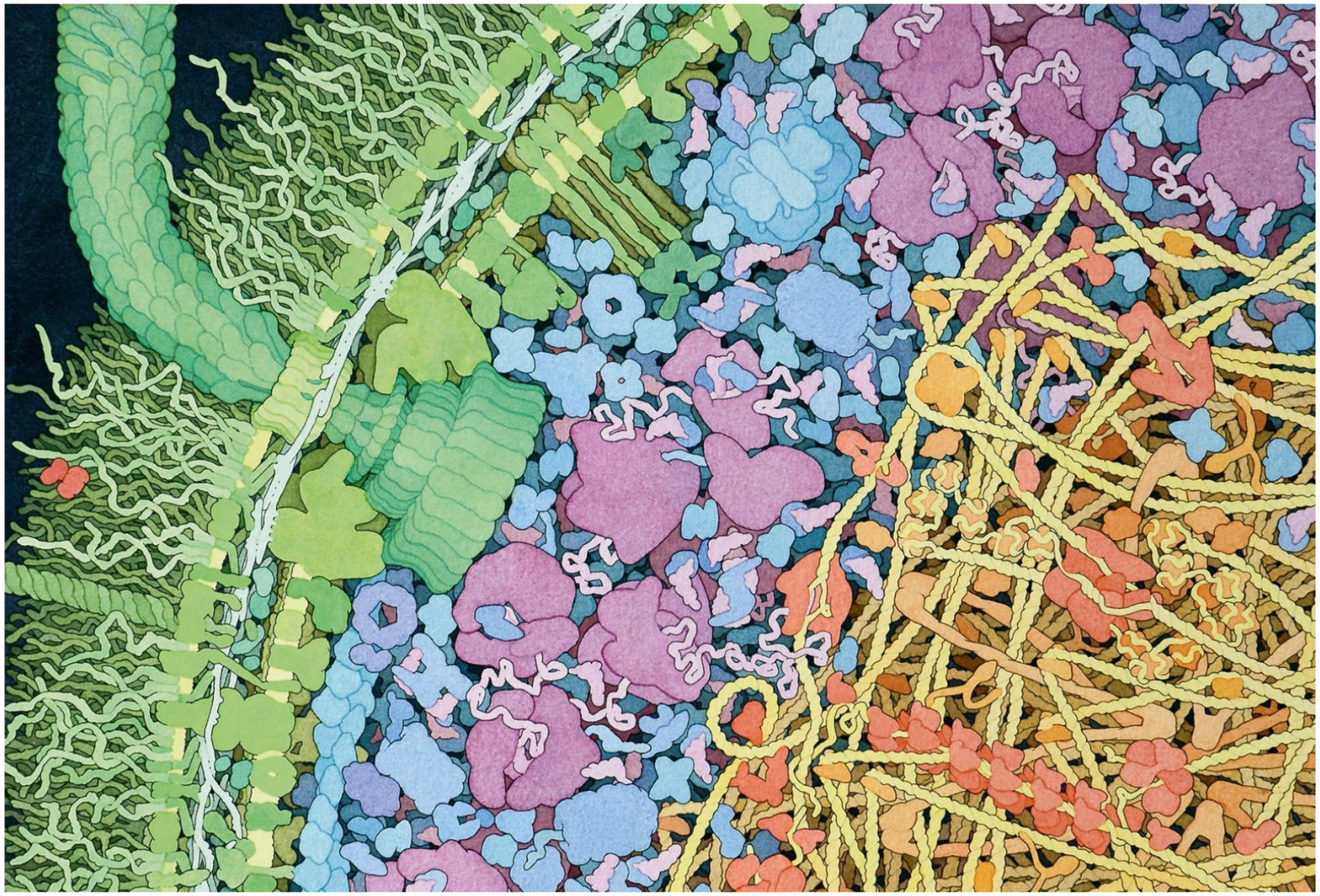
This ability requires complex **crosstalk between local and systemic** immune responses

Rare *versus* recurrent infections across an organism's life stages require different types of reactions, engaging immune responses that can be constitutive or inducible, and can have long-term memory-like effects

An immune system must **avoid pathological autoimmunity** and must regulate and keep a balanced microbiota

Trained immunity is a functional state of the innate immune system that is characterized by long-term epigenetic and metabolic reprogramming of cells associated with potent immune responses

How to recognise a microbe?



David S. Goodsell

Cell surface structure
Metabolism —> molecules
Behaviour

Virulence, I

- Bacterial **virulence**: the “relative capacity to **overcome available defenses**” (Sparling, 1983), or “the relative capacity of a microorganism **to cause damage in a host**” (Casadevall and Pirofski, 2003)

- This capability is mediated by **virulence genes/factors**, which have to fulfill three requirements:

(i) **active** in the **interaction** between pathogen and host

(ii) **direct determinants** of the pathogen damage

(iii) the **lack** of those virulence genes **in non-pathogenic strains** (Wassenaar and Gaastra, 2001)

Virulence factors associated to microbial structures

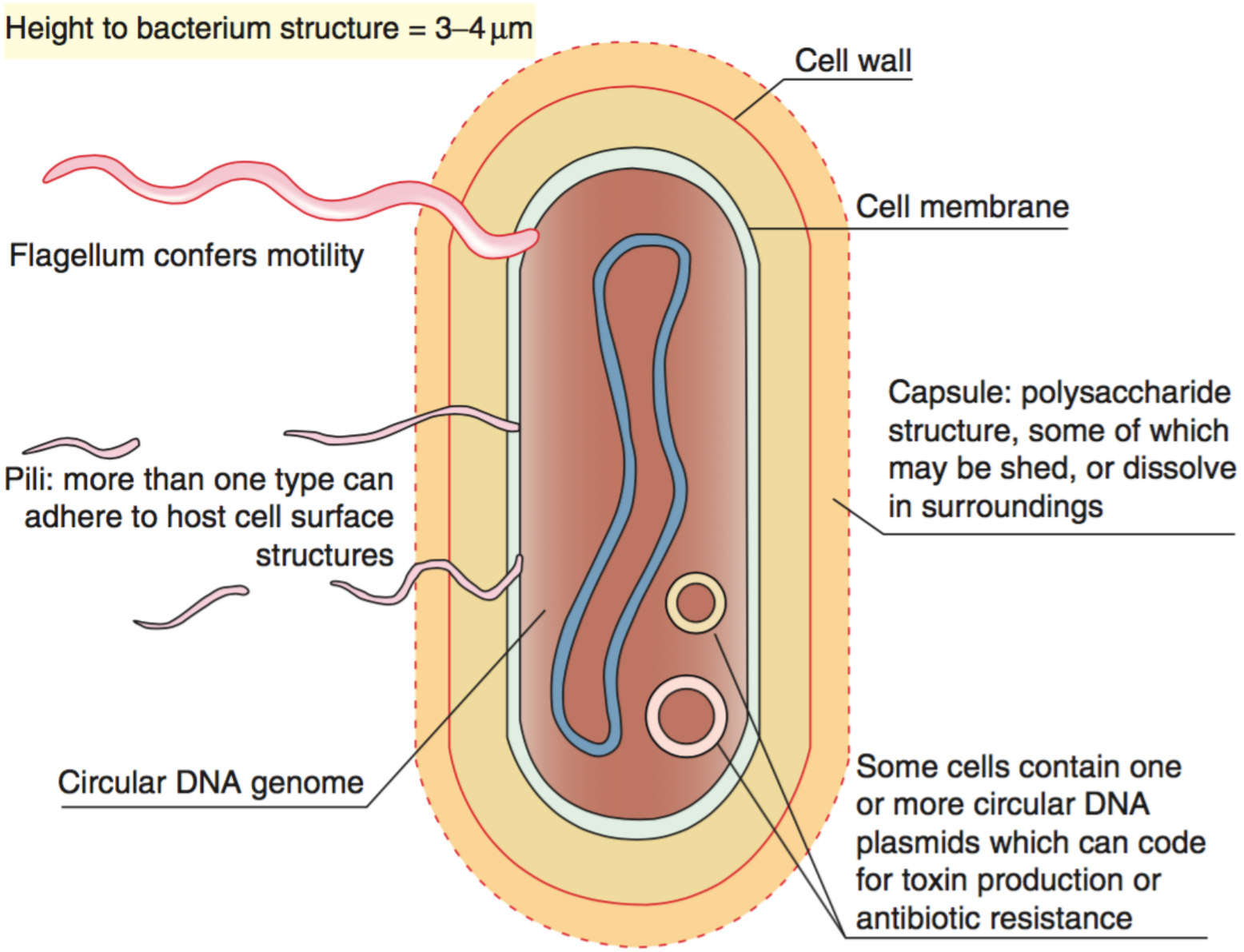


Figure 1 Structure of a bacterium. Reproduced from Bannister BA, Begg NT, and Gillespie SH (eds.) (1996) Structure and classification of pathogens. In: *Infectious Disease*, 2nd edn., ch. 2, pp. 23–34. Oxford, UK: Blackwell Science Ltd., with permission from Blackwell Publishing.

Virulence Factors

Adherence Factors: Many pathogenic bacteria colonize mucosal sites by using pili (fimbriae) to adhere to cells.

Invasion Factors: Surface components that allow the bacterium to invade host cells can be encoded on plasmids, but more often are on the chromosome.

Capsules: Many bacteria are surrounded by capsules that protect them from opsonization and phagocytosis.

Endotoxins: The lipopolysaccharide endotoxins on Gram-negative bacteria cause fever, changes in blood pressure, inflammation, lethal shock, and many other toxic events.

Exotoxins: Exotoxins include several types of protein toxins and enzymes produced and/or secreted from pathogenic bacteria. Major categories include cytotoxins, neurotoxins, and enterotoxins.

Siderophores: Siderophores are iron-binding factors that allow some bacteria to compete with the host for iron, which is bound to hemoglobin, transferrin, and lactoferrin.

Virulence, II

- Virulence as a concept is **intrinsically coupled to disease**
- **Degree of host injury** does **not** necessarily correlate with **evolutionary success** for a pathogenic microbe
- **Survival and multiplication** are clearly the **priorities** for the **microbe**
- **Disease is simply a manifestation** of the complex interactions required to accomplish these two goals within the milieu of host tissues
- **Competition** for the same resources: **nutrients and energy**
- Virulence determinants which includes all those **factors contributing to infection** and to **disease**, with the **exception of "housekeeping"** functions that are required for efficient multiplication on non living substrates
- The **virulence** of bacterial pathogens is a **complex, multifactorial process** requiring the **coordinated activity of many bacterial gene products**

Virulence, III

Why be virulent?

Hypothesis: virulence is an **unavoidable cost or side effect** of **growing within a host and transmitting to the next host**, and is maintained as the result of a ***trade-off between the costs of host pathology and the benefits of transmission to a new host***

Other hypotheses highlight the **importance of selection in non-disease settings**, where **alternative functions of virulence factors can coincidentally select for virulence factor-induced damage to human hosts**

Virulence factors are **molecular determinants** of virulence; they are pathogen components that are **non-essential to *in vitro* growth in rich media** but cause increased virulence during infection of a host

SELF or NON-SELF: how to detect?

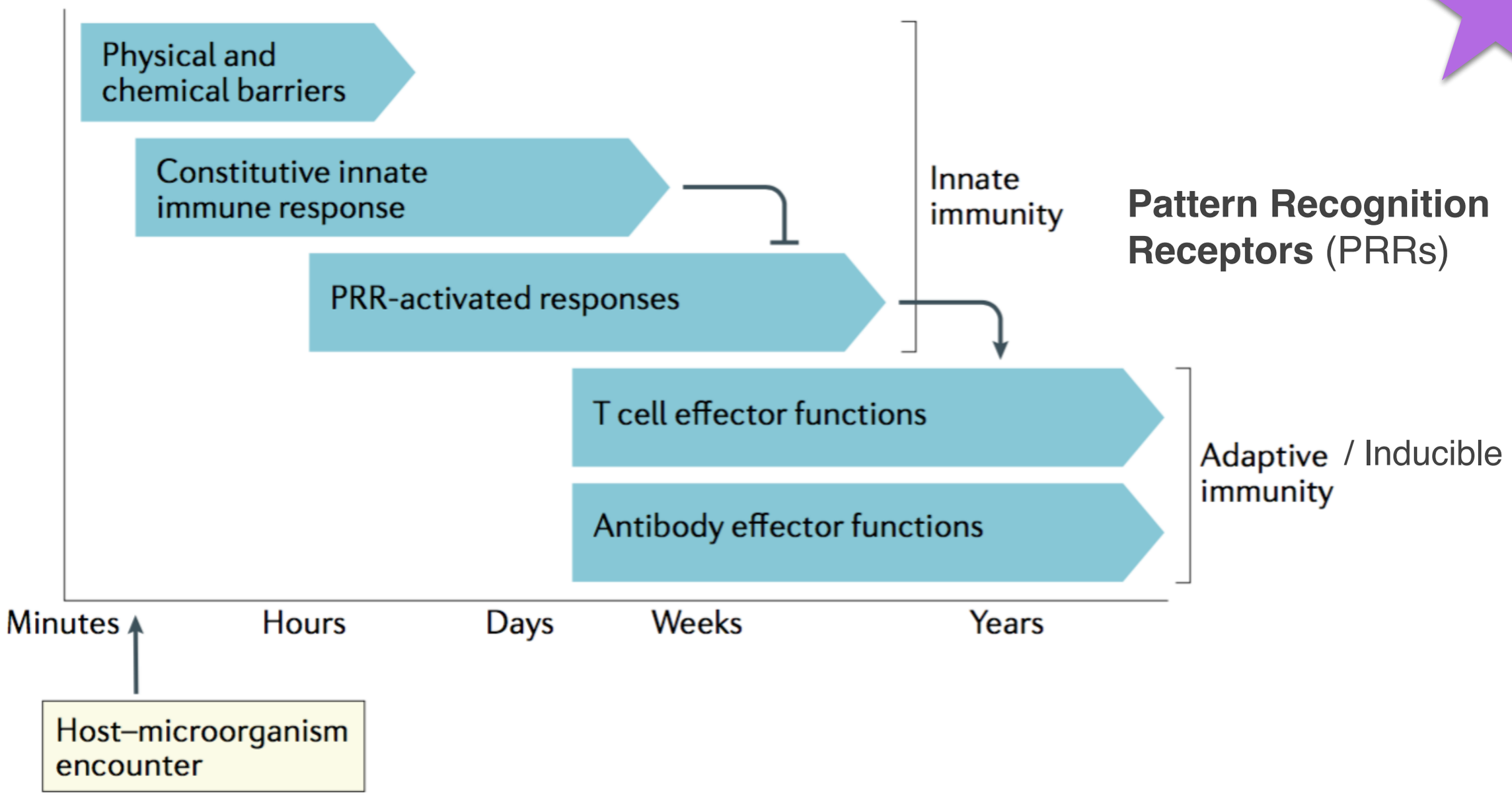
The innate immune system has the capacity to detect '**non-self**' molecules derived from pathogens, known as **pathogen/microbe-associated molecular patterns, via pattern recognition receptors**

The self–non-self theory was first formulated by Frank Macfarlane Burnet in **1959** and was refined in 1989, when Charles Janeway proposed the '**pattern recognition**' theory

It postulated that innate immune cells express distinct germ-line-encoded **pattern recognition receptors (PRRs) that recognize conserved pathogen-associated molecular patterns (PAMPs)/ microbe-associated molecular patterns (MAMPs, bacterial lipopolysaccharide, flagellin, EF-Tu, DNA, lipoproteins, peptidoglycans, and fungal chitin) unique to microbes**

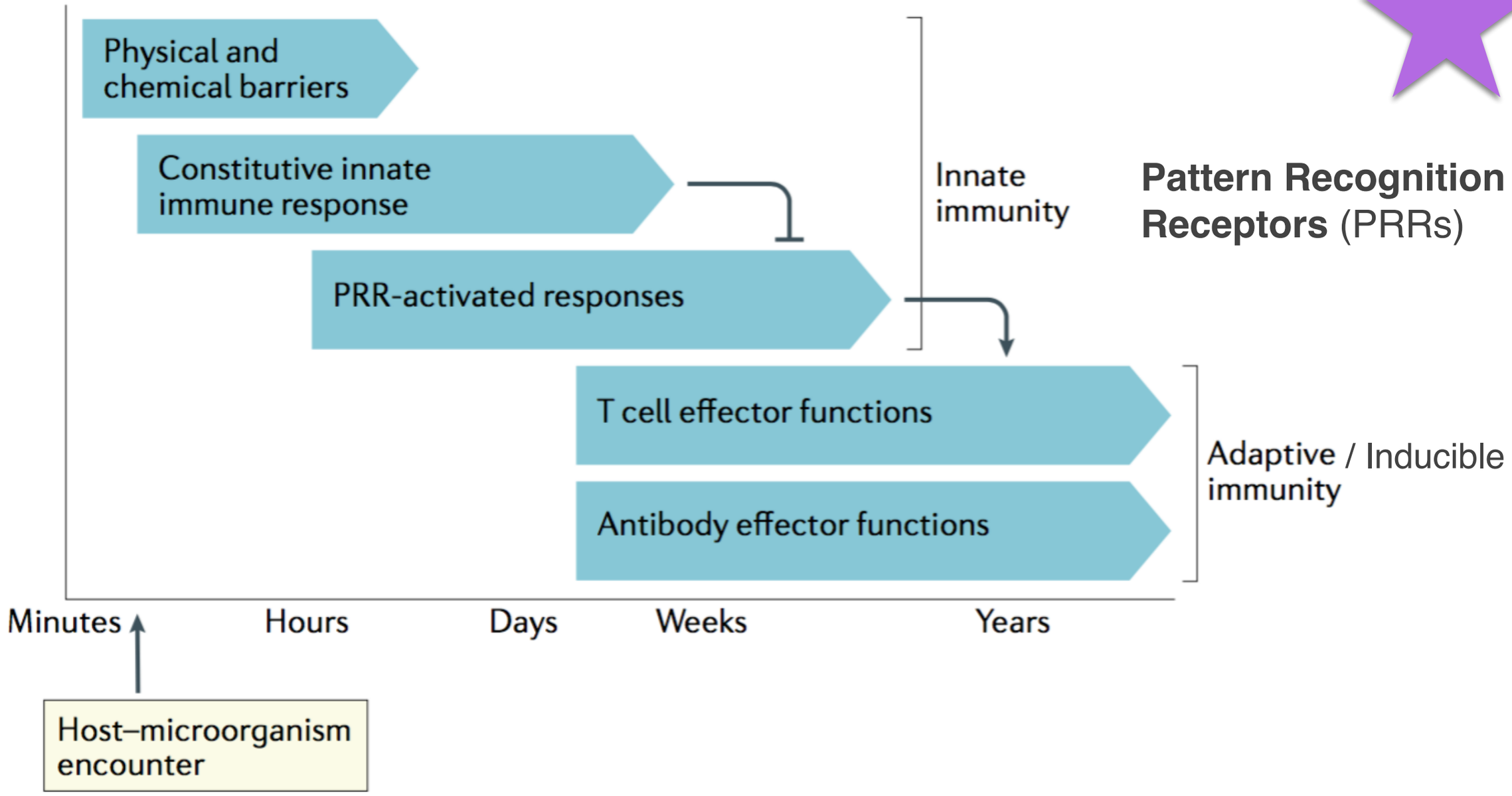
The recognition of **DAMPs,** which are produced or released by **damaged and dying cells, promotes sterile inflammation**, which is important for **tissue repair and regeneration**, but can also lead to the development of numerous inflammatory diseases, such as metabolic disorders, neurodegenerative diseases, autoimmune diseases and cancer

Time relationship among the different layers of the immune response, I



- A first layer of defence is exerted by **physical and chemical barriers**
- Constitutive **innate immune mechanisms** function as soon as a danger **signal is detected** and eliminate harmful microorganisms and host molecules **by specific non-inflammatory mechanisms** that **operate independently of PRRs**

Time relationship among the different layers of the immune response, II

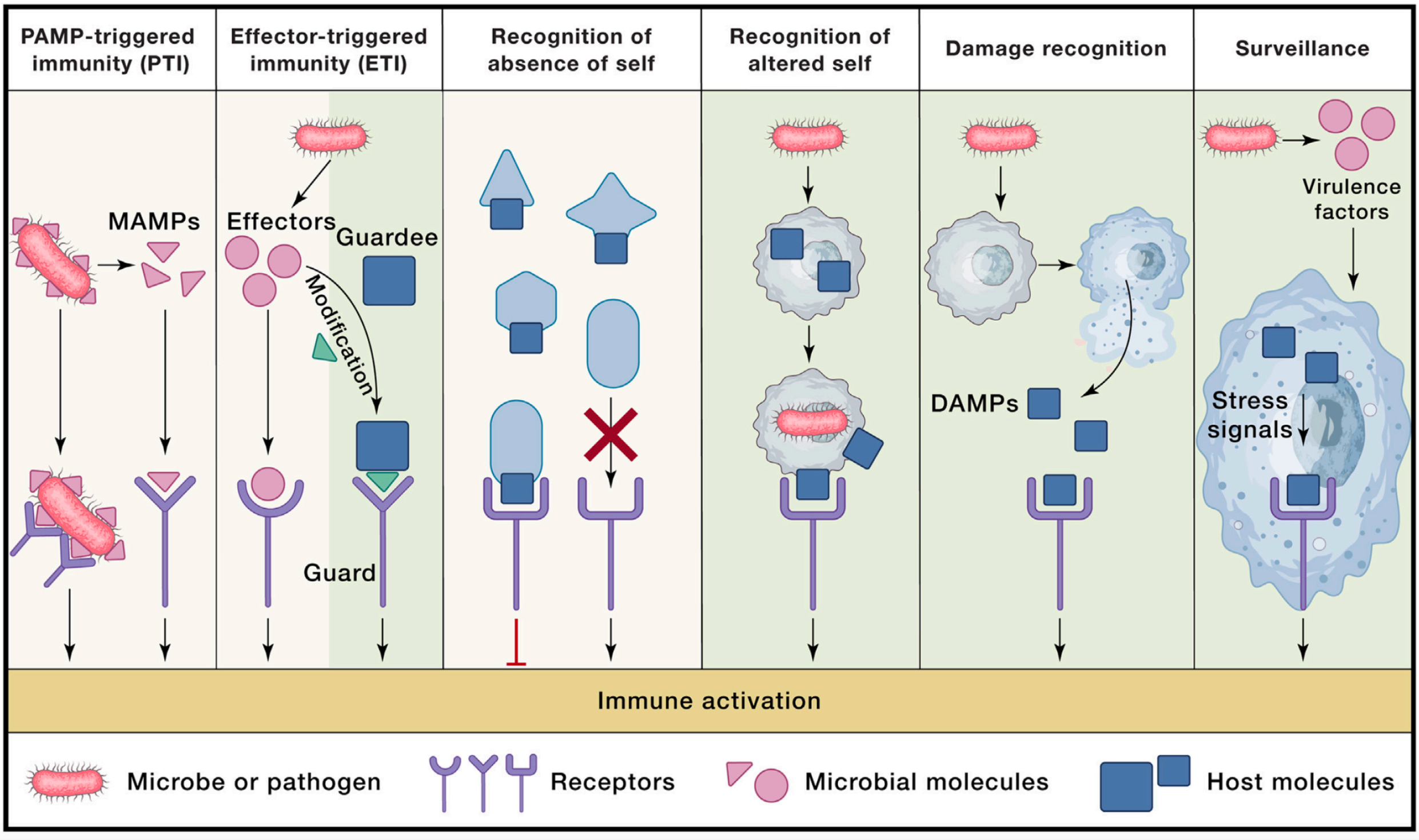


Paludan et al., 2021

Pattern Recognition Receptors (PRRs)

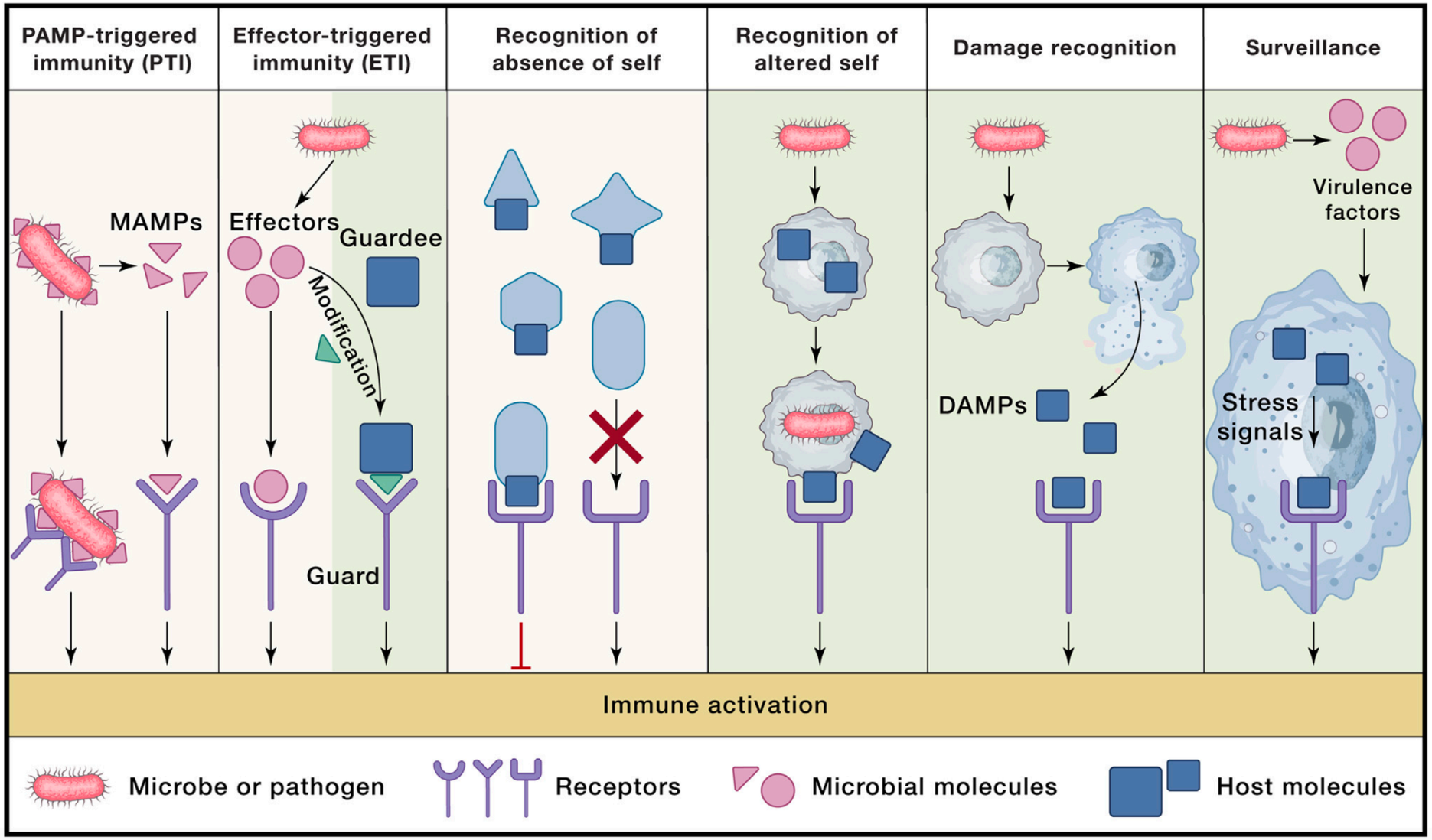
- **Constitutive innate immune** response inhibit establishment of the infection and accumulation of **PAMP**s (**Pathogen-Associated-Molecular Pattern**) and **DAMP**s (**Damage-Associated-Molecular Pattern**), thus **limiting the activation of PRR-based** inducible innate immune responses
- **If PRR-based immunity is activated**, owing to the level of PAMPs exceeding a certain threshold, this leads to inflammation and **promotes activation of the adaptive/inducible immune response** mediated by T cells and antibodies

Six overlapping mechanisms of innate sensing



Pradeu et al., 2024

Six overlapping mechanisms of innate sensing via Pattern Recognition Receptor



Macropahges, dendritic cells, neutrophils and natural killer cells have Pattern Recognition Receptors (PRRs)

Epithelial cells and endothelial cells in the blood vessel have use PRRs

Pradeu et al., 2024

Pattern Recognition Receptors

Pattern-recognition receptors (PRRs) are evolutionarily conserved structurally different receptors, that detect pathogen/microbe-associated molecular patterns (PAMPs/ MAMPs)

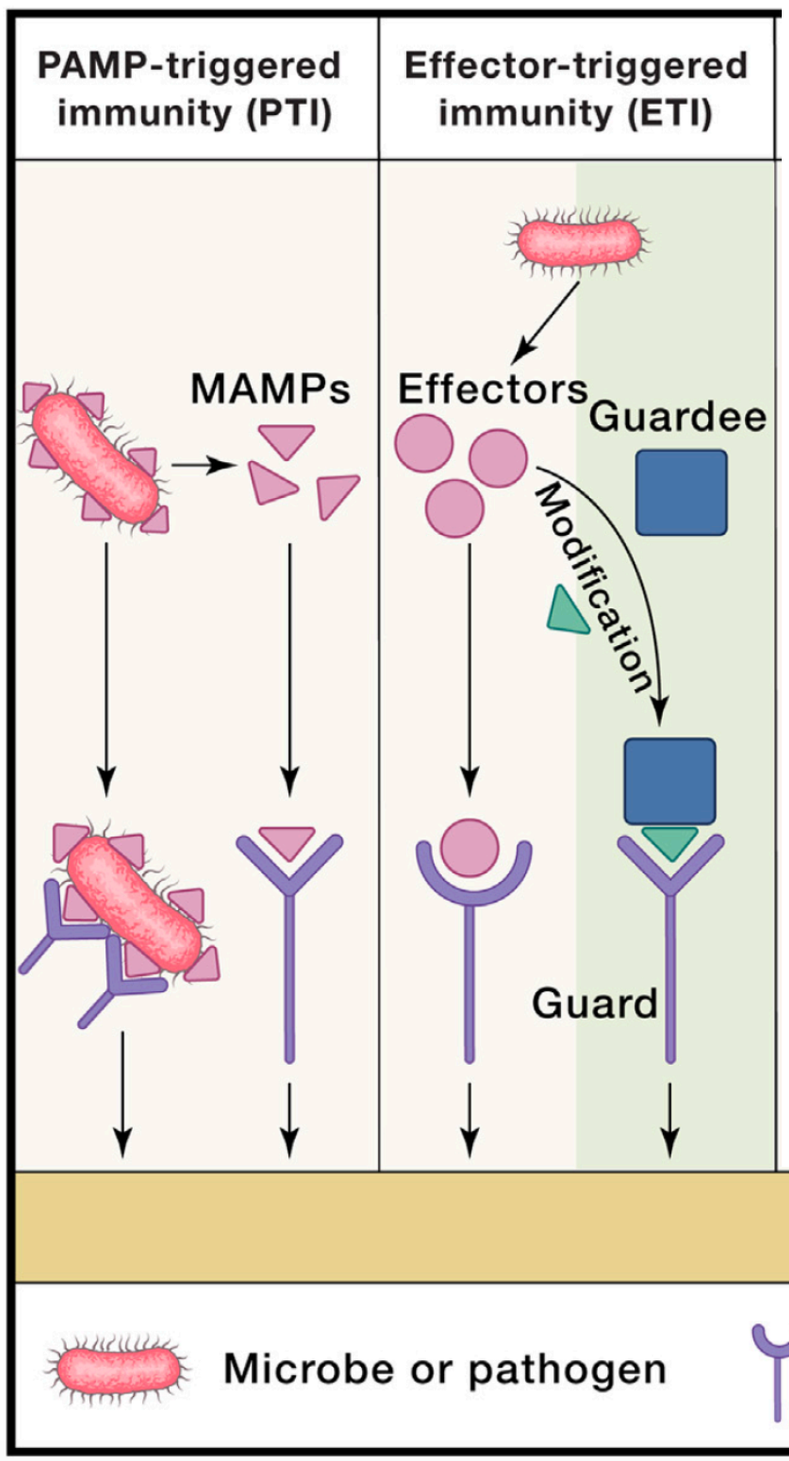
Toll-like receptors (TLRs): Ten TLRs have been identified in humans. TLRs are type I **transmembrane glycoproteins that localize to either the plasma membrane** (in the case of TLR1–TLR6, TLR10 and TLR11) or the **endosomal membrane** (in the case of TLR3, TLR7 and TLR9, for example). Ligands for TLRs include bacterial **lipoproteins and lipopeptides** (for TLR2), **double-stranded RNA** (for TLR3), **lipopolysaccharide** (for TLR4), **flagellin** (for TLR5), **single-stranded RNA** (for TLR7), CpG **DNA** (for TLR9)

NOD-like receptors (NLRs) NLRs constitute a large family of cytosolic proteins: The first family members to be discovered — nucleotide-binding oligomerization domain protein 1 (NOD1) and NOD2 — recognize **bacterial peptidoglycan** fragments and activate nuclear factor-κB (NF-κB) signalling

RIG-I-like receptors (RLRs): There are three known RLRs: retinoic acid-inducible gene I (RIG-I), melanoma differentiation associated gene 5 (MDA5) and LGP2. RLRs are expressed in the **cytosol and sense nucleic acids, such as viral RNA**

C-type lectin receptors (CLRs): The CLRs are a large family of proteins that possess one or more C-type lectin domains and one or more immunoreceptor tyrosine-based activation motifs (ITAMs). They recognize a wide range of **carbohydrate ligands** (and probably also non-carbohydrate ligands)

Mechanisms of innate sensing, I



Pradeu et al., 2024

(A) PAMPs-triggered immunity (PTI)

Structural molecules specific to a class of microbes (PAMPs/MAMPs) are recognized by **host pattern recognition receptors (PRRs)**, which trigger the immune response.
PRRs can **bind directly** to microbes (*e.g.*, PGRP-SA to Gram-positive bacteria) or more frequently sense microbes by **sensing MAMPs released by microbes** (indirect mode). **PRRs can be secreted, transmembrane, phagosomal, or intracellular.** They can initiate a transcriptional program or directly trigger effector modules.

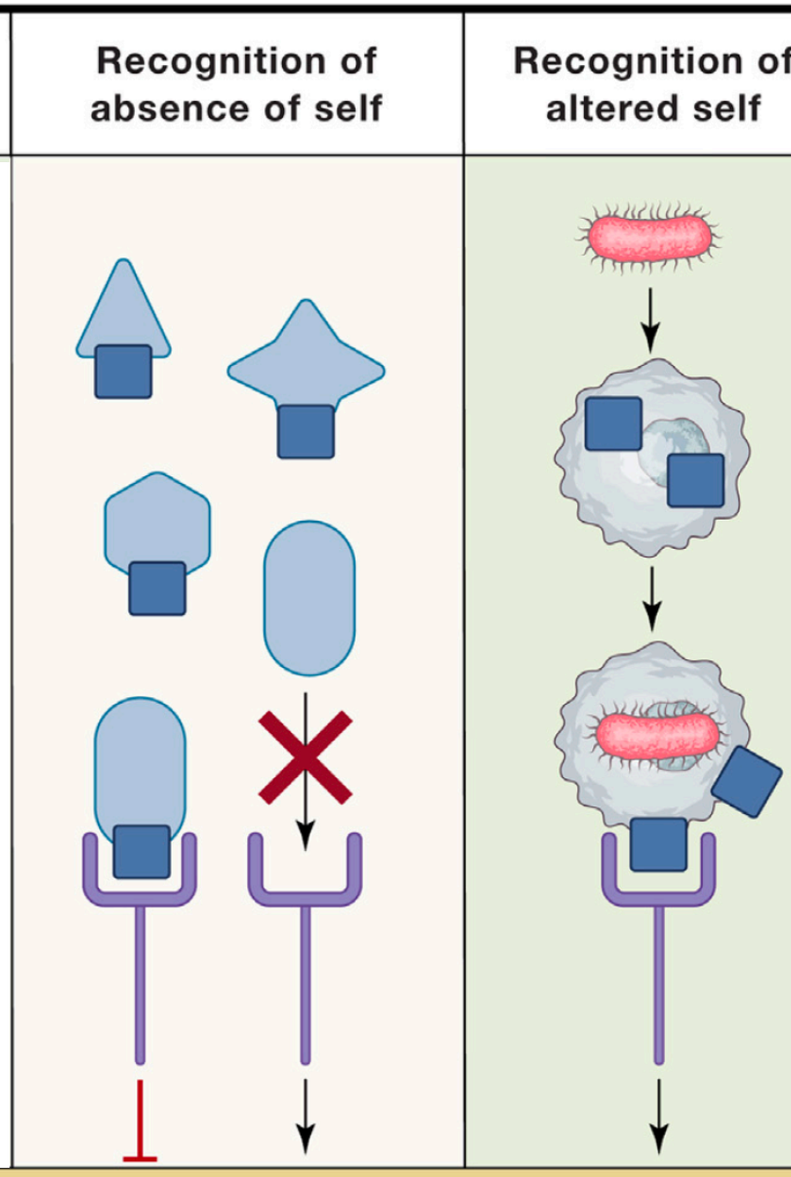
(B) Effector-triggered immunity (ETI)

Host receptors directly sense virulence factors, or more frequently "**guard proteins**" sense the activity of virulence factors that modify host molecules. There are multiple variations on the mechanisms that allow the sensing of microbial effectors. Host guard proteins can be extracellular (*e.g.,* detection of microbial protease activity in Drosophila by Persephone), transmembrane, or intracellular.

Mechanisms of innate sensing, II

(C) Recognition of the absence of self

The immune system is activated when a constitutive signal provided by host cells is not detected by host receptors, indicating material of foreign origin.



(D) Recognition of altered self

Some immune receptors can recognize altered or abnormal self-patterns. This is often a host component located at a place where it is normally absent, such as a normally intracellular molecule present in extracellular spaces.

Immune activation

Microbe or pathogen | Receptors | Microbial molecules | Host molecules

Pradeu et al., 2024

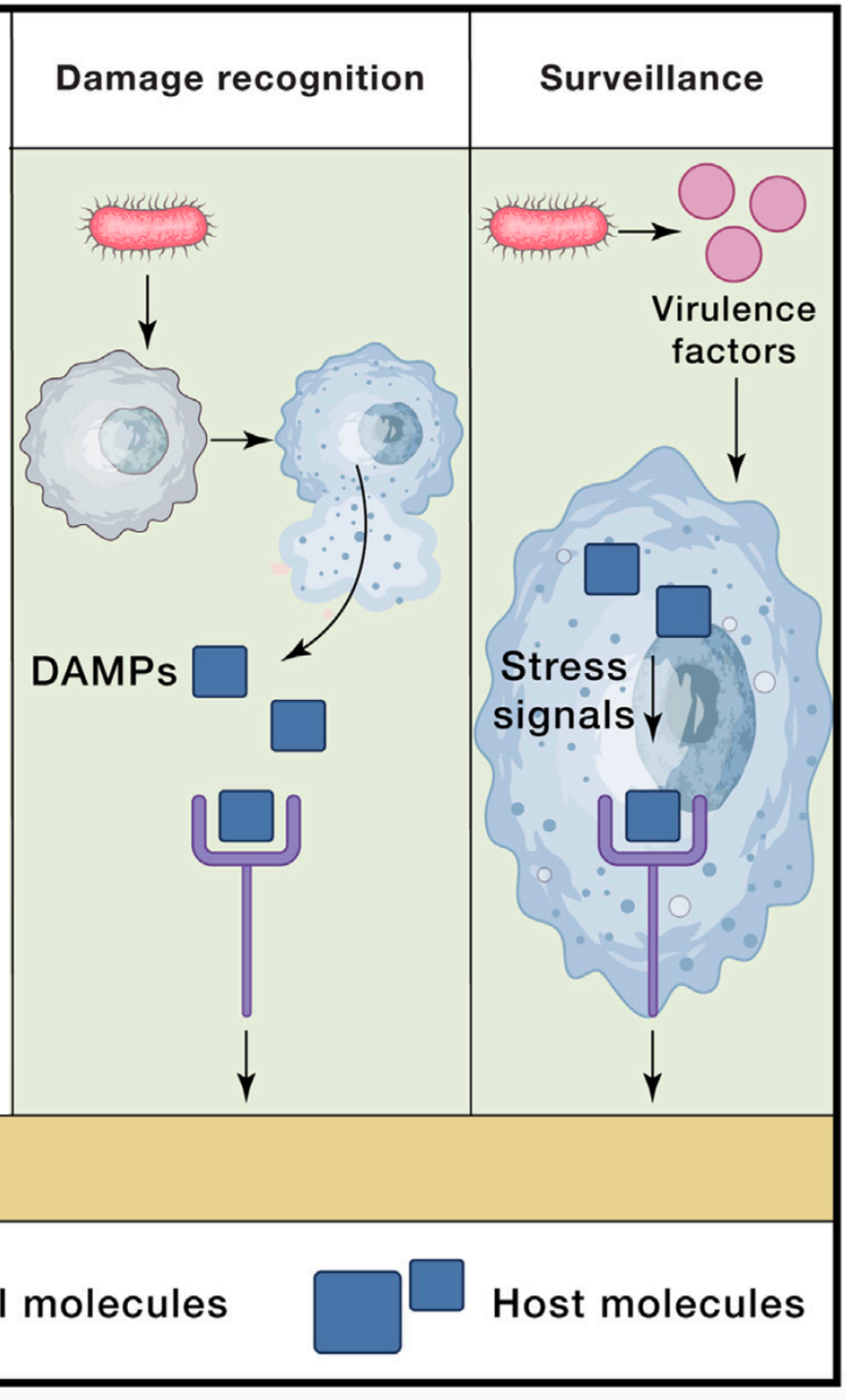
Mechanisms of innate sensing, III

(E) Recognition of damage-associated molecular patterns (DAMPs)

Innate immune responses are triggered by the sensing of host molecules released upon damage to host tissues. **Healthy** living cells do **not** cause **inflammation**, whereas cells that have been **infected, stressed or are on the verge of lytic cell death** have the capacity to **trigger inflammation**

(F) Surveillance

Innate immune responses are triggered by generalist stress pathways that interpret rupture of cellular homeostasis as an indicator of infection.
Sensing mechanisms are either direct (pink background) or indirect via the sensing of activities or damages (green background).



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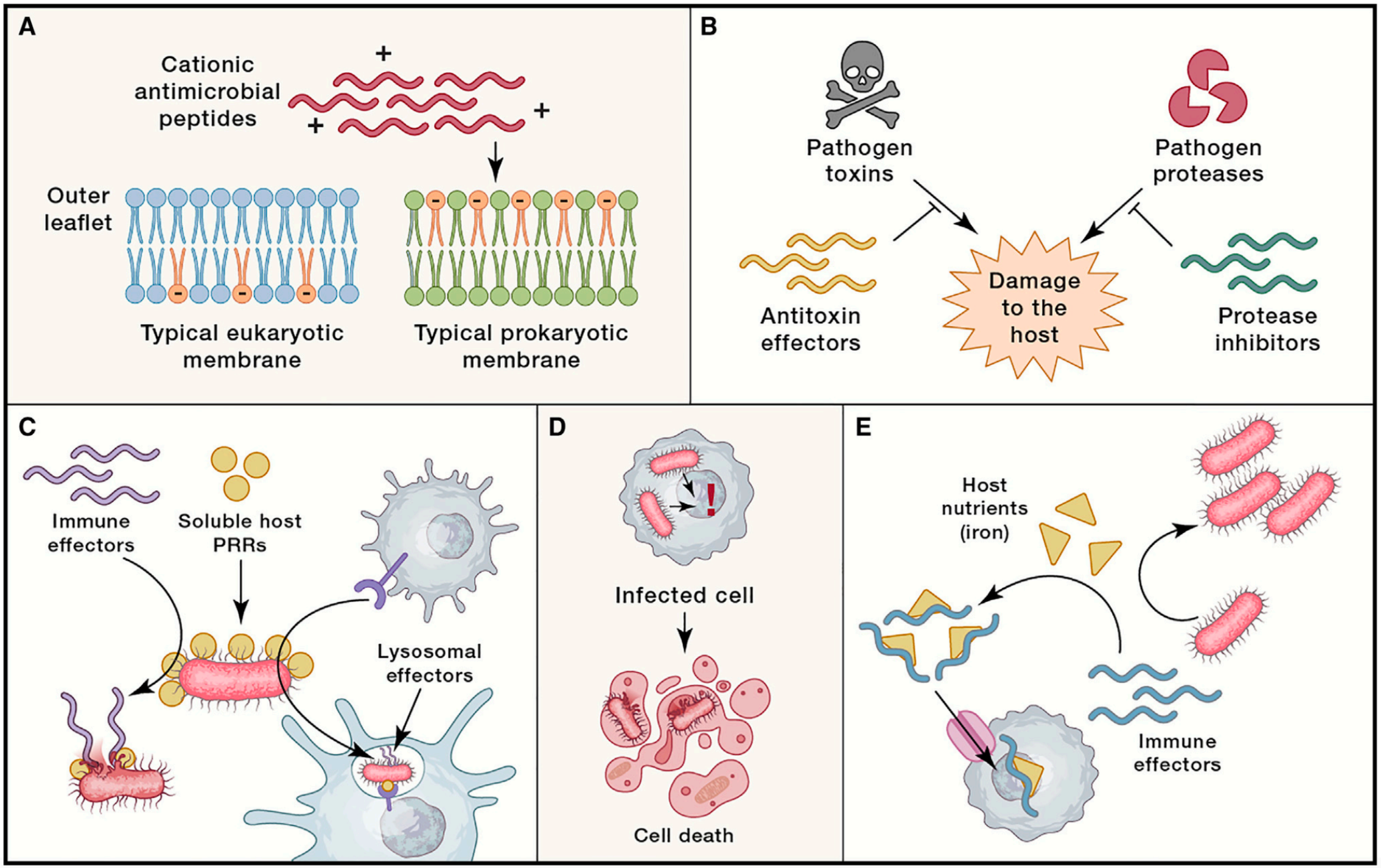
Common principles of innate immune effector mechanisms



Pradeu et al., 2024

Transition from Innate to Adaptive Immune response

Innate immune responses help initiate and shape adaptive immune responses mediated by T and B cells

In a simplified three-signal model:

A. The first signal to activate T cells is provided by **T cell antigen receptor recognition of antigen**

B. The second signal is **costimulation** provided by the **antigen presenting cell (APC)**

C. The third signal is provided by **inflammatory cytokines** derived from innate immune activation, which may act directly on the T cell and/or indirectly by increasing costimulatory molecules on the APC

D. **B cells are activated by antigen** *via T cell-dependent or -independent mechanisms*

Microbes and Humans

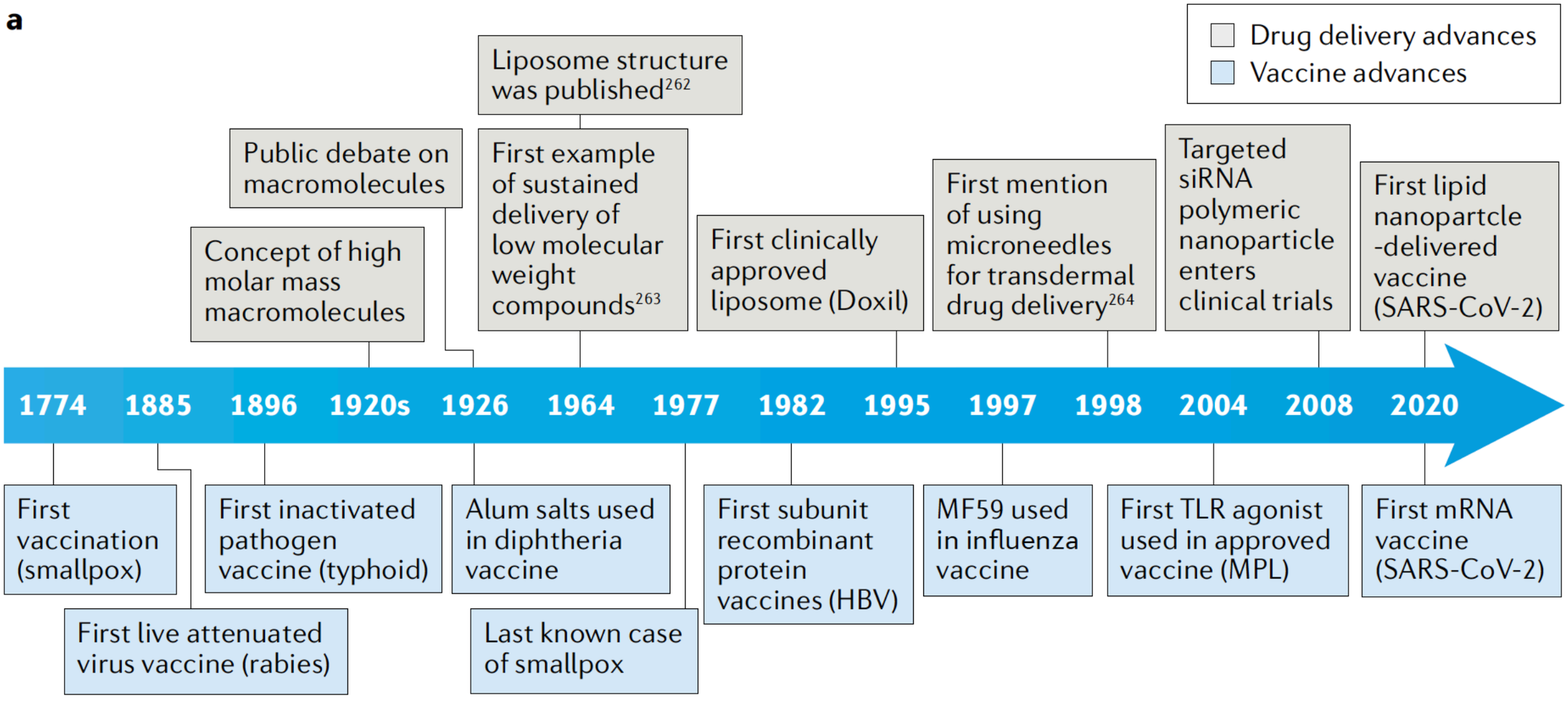
- Providing nutrients
- Fighting off microbial pathogens
- Maintaining the Human ecosystem functioning = healthy homeostasis (—> interaction with immune system)
- Training immune system to recognise the commensals from the pathogens (failure—> sepsis and microbial invasion/disease)
- Training immune system to recognise self from non self (failure—> autoimmune and allergic diseases)

Vaccine

A vaccine is a biological product that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen

To achieve this, the vaccine must contain antigens that are either derived from the pathogen or produced synthetically to represent components of the pathogen

Vaccine timeline



Roth et al., 2022

Vaccine/Pathogen

Tissues at the interface with the outside world (for example, skin, lungs and mucosal sites) are the primary locations of infections, and therefore contain tissue resident immune cells and are constantly patrolled by migratory immune cells.

Lymph nodes downstream of the location of pathogen or vaccine exposure are called draining lymph nodes, and are key sites from the beginning of the immune response throughout the development of mature effector B cells and T cells.

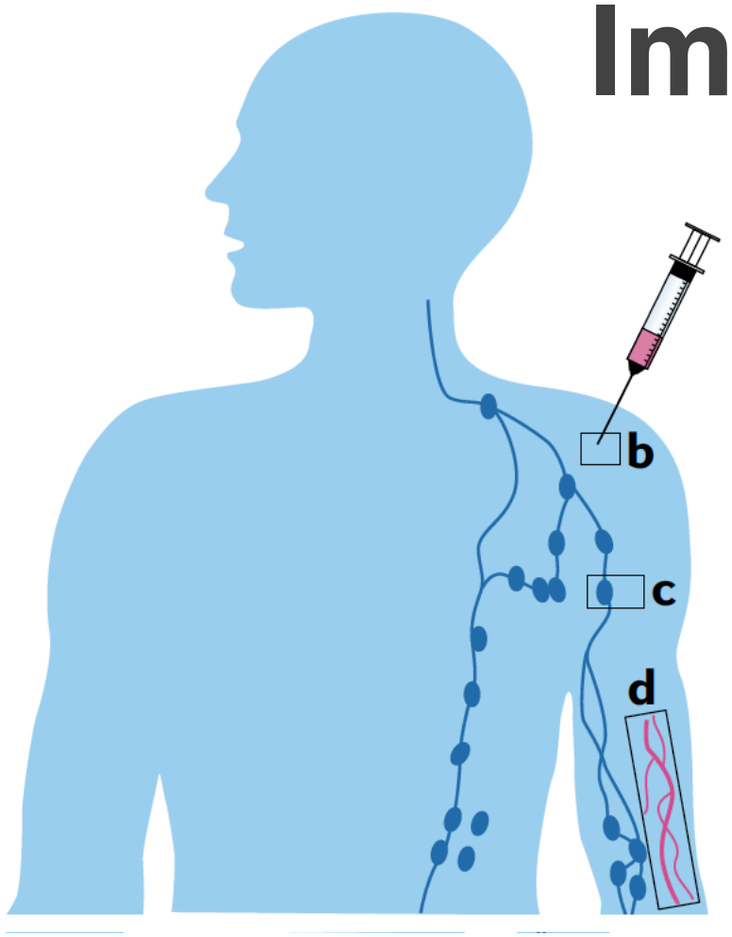
The blood provides an important route for innate immune cells to quickly infiltrate the site of vaccination or infection in the early immune response.

After the immune response is mounted, the blood enables antibodies and memory T cells to reach infected tissue and protect the entire body.

Activation of the innate immune system and migration of key cells and vaccine components to lymph nodes occurs within hours, followed by B cell and T cell maturation within days and weeks.

The long- term memory response remains for months to years following vaccination, providing protection against future infection.

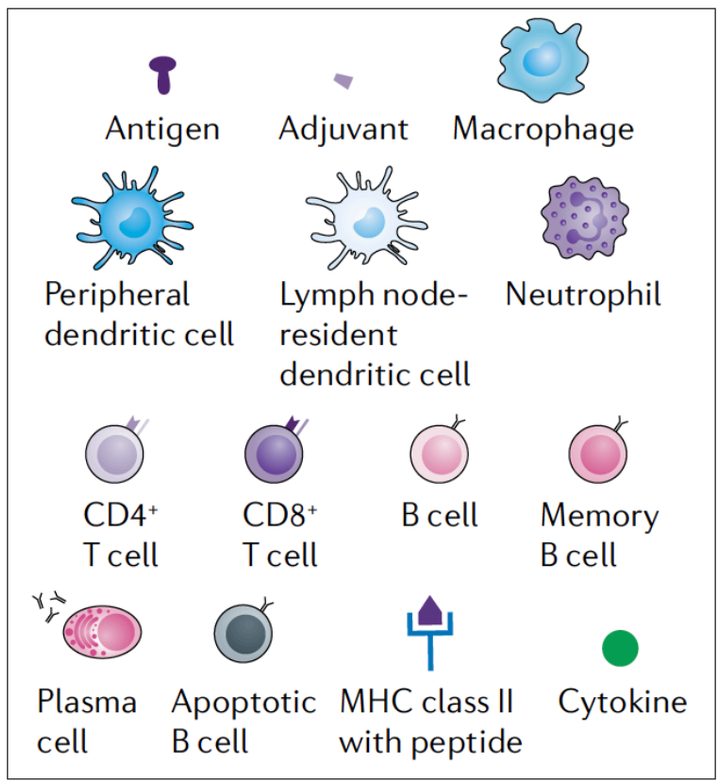
Immune response to vaccine



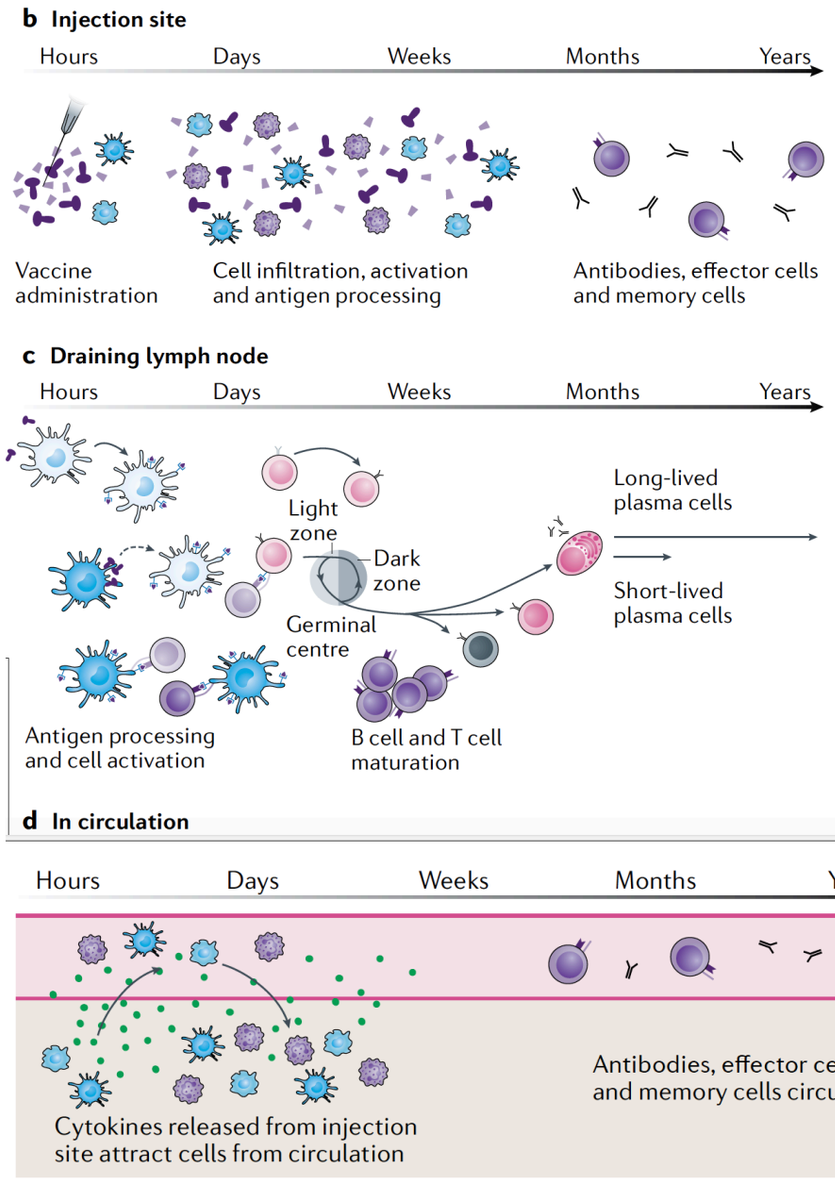
- The vaccine immune response occurs in multiple locations
  — peripheral tissues, lymph nodes and systemic circulation
  — each of which has its own cell composition and function.

- This coordinated action of immune cells requires precise spatial and temporal cues.

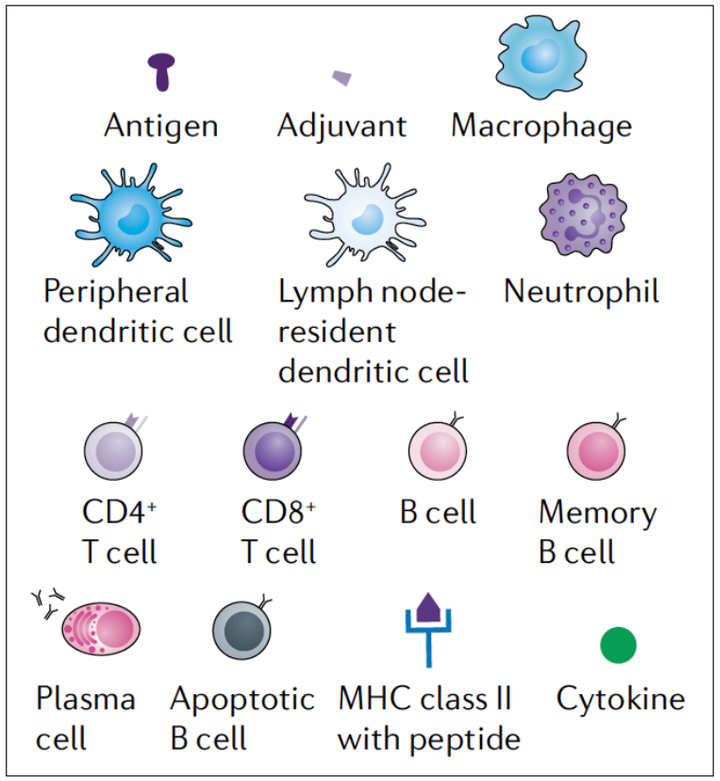
-

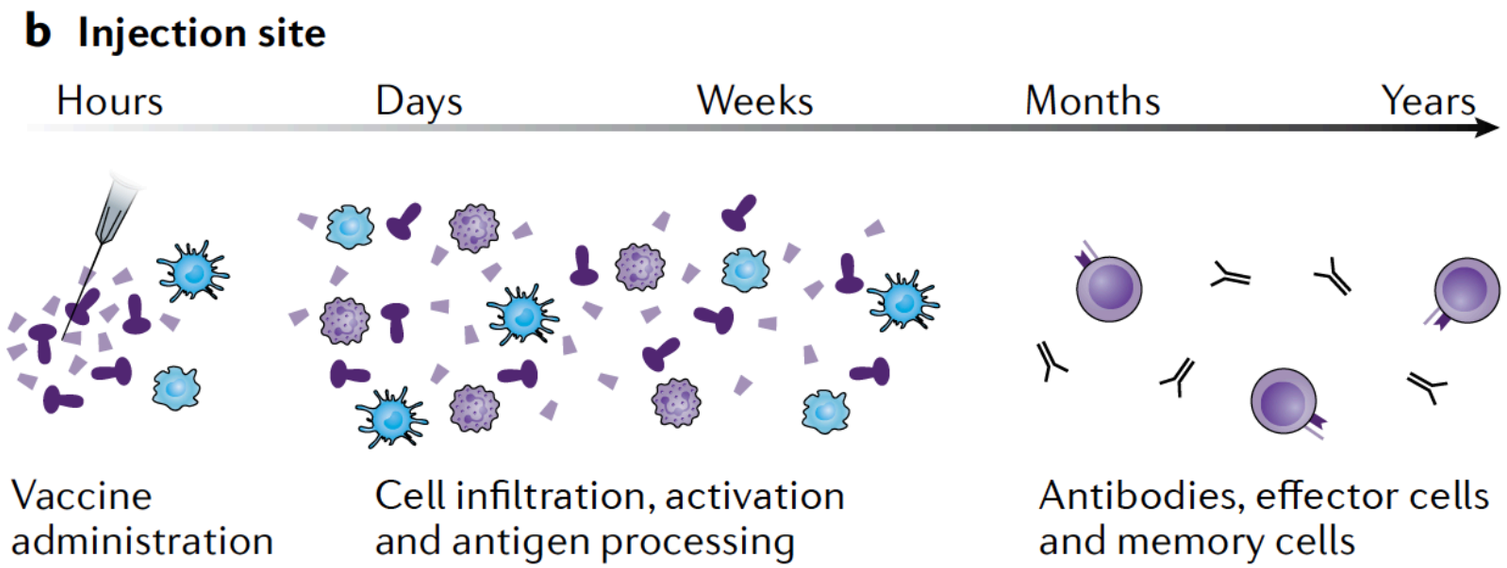


Roth et al., 2022



Immune response to vaccine

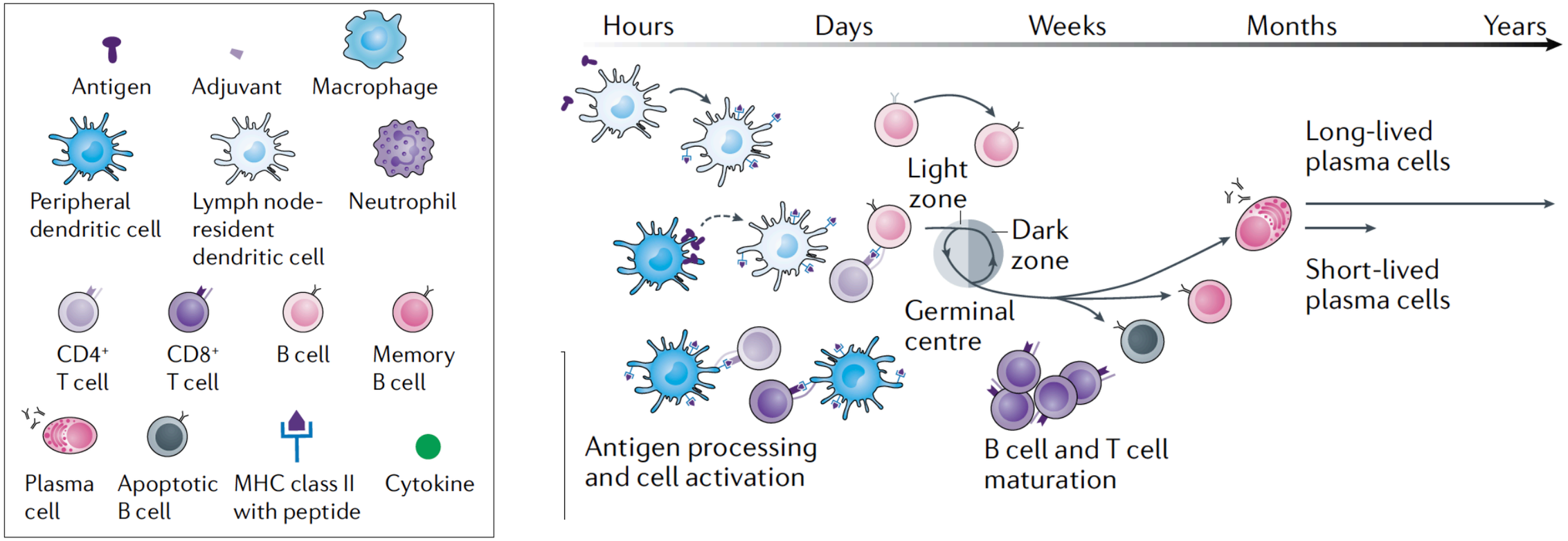




Roth et al., 2022

- At the site of administration, innate immune cells, such as neutrophils and antigen- presenting cells (APCs), first encounter the antigen and adjuvant
- The antigen component of the vaccine is endocytosed and broken down by APCs before being presented on the APC surface major histocompatibility complex (MHC) molecules.
- As innate immune cells become activated, they release cytokines that attract other immune cells from the bloodstream to the site of administration.
- Soluble vaccine components and activated cells enter the lymphatics and travel to local lymph nodes.

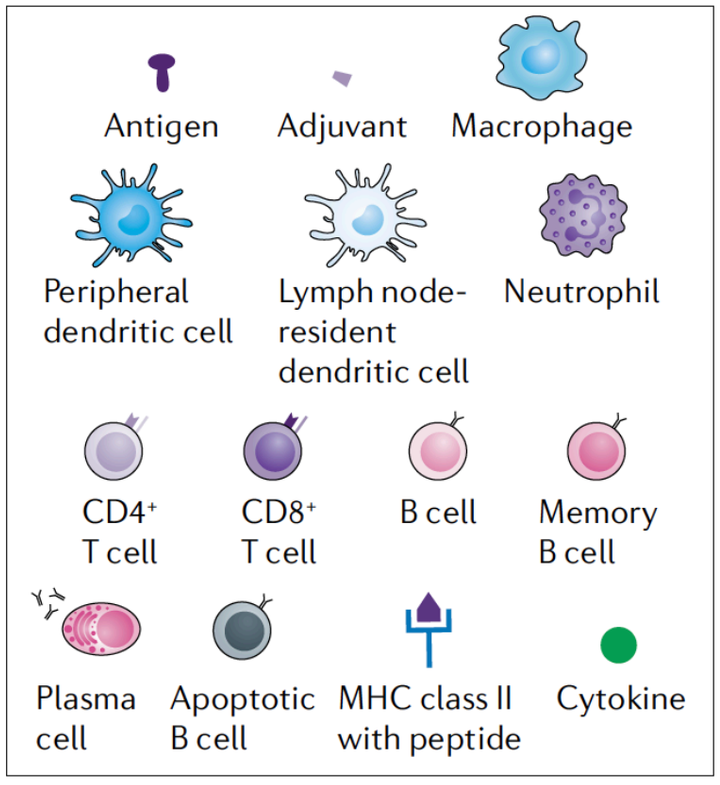
Immune response to vaccine

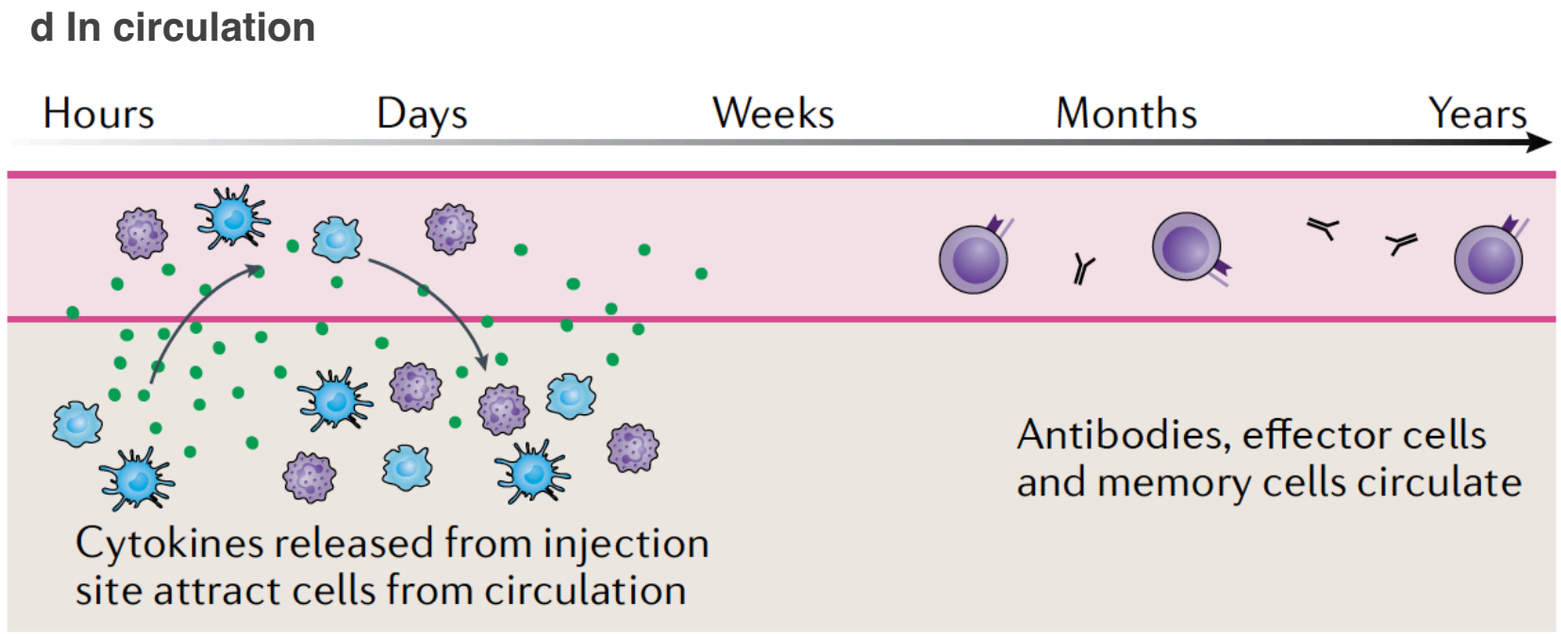


Roth et al., 2022

- Maturation and development of a potent adaptive response continues in lymph nodes downstream of the vaccination site (draining lymph nodes).
- Early in the vaccine response, lymph node- resident phagocytic cells and migratory innate cells arriving from peripheral tissues present antigen and produce inflammatory signals to activate T cells.
- As the immune response develops, sites of B cell development, called germinal centres, form in the B cell zones of the lymph nodes.

Immune response to vaccine

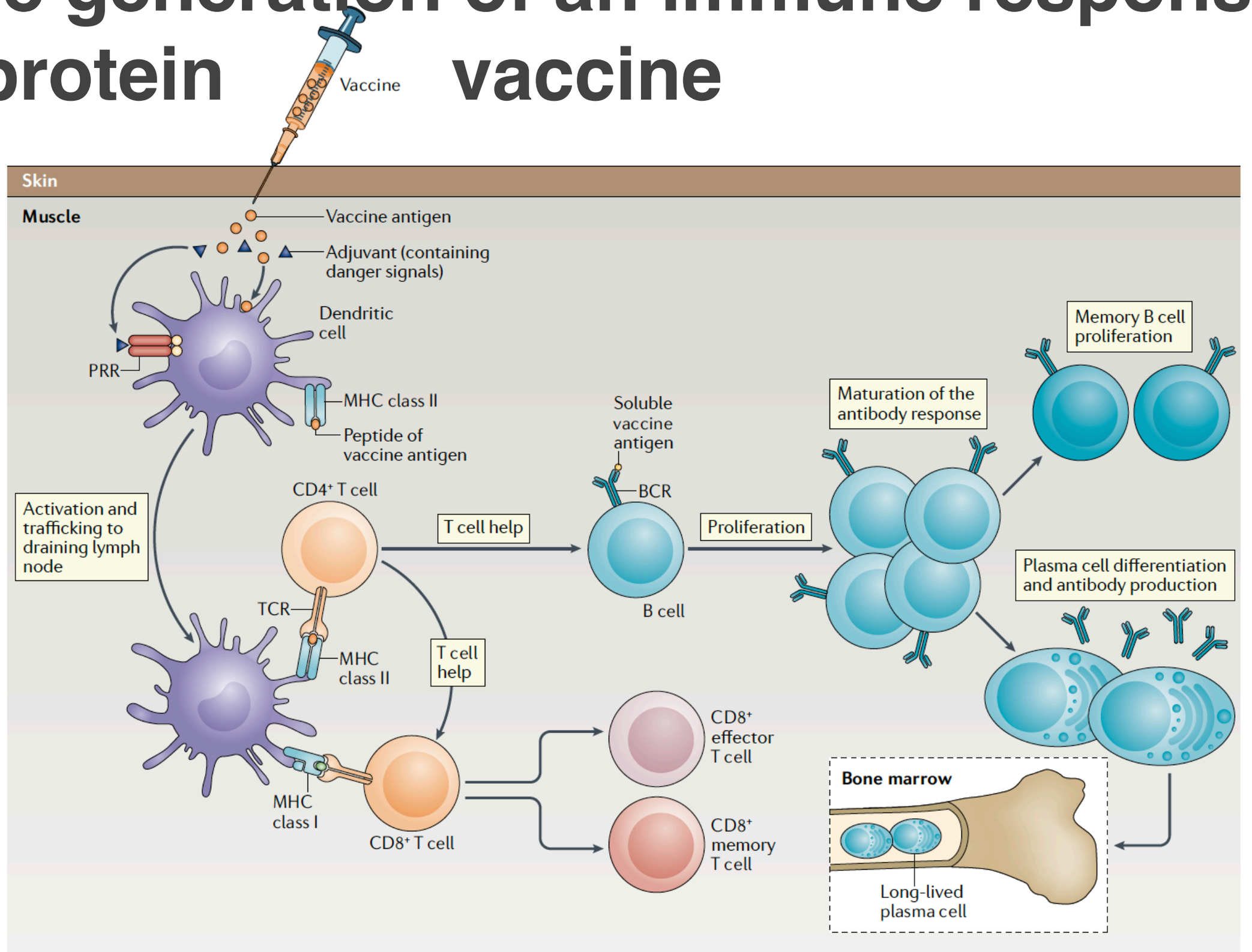




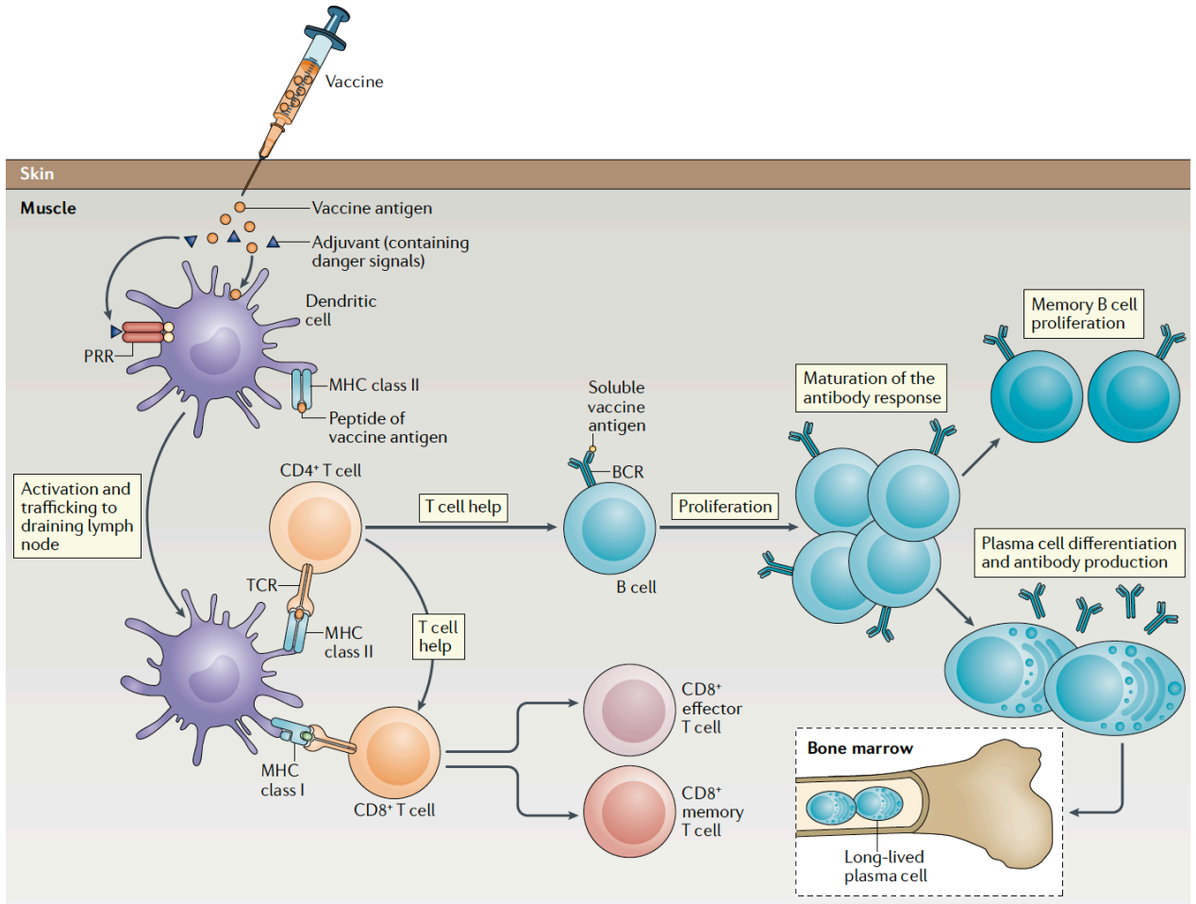
Roth et al., 2022

- Immediately following vaccine administration, local innate cells release cytokines into the circulation to enable a coordinated response thus triggering cell infiltration to the injection site.
- Following vaccination, plasma cells secrete antigen- specific antibodies, which travel through the circulatory system to tissues, where they respond immediately upon pathogen exposure.
- Memory T cells also use the circulatory system to inspect the body for foreign invaders.

The generation of an immune response to a protein vaccine



Pollard & Bijker, 2021



Pollard & Bijker, 2021

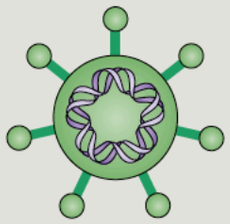
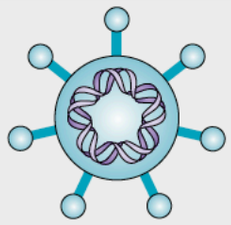
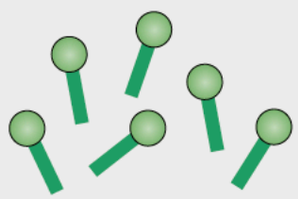
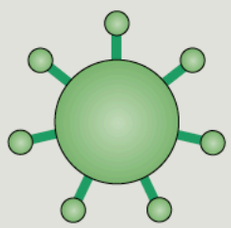
The vaccine is injected into muscle and the protein antigen is taken up by dendritic cells, which are activated through pattern recognition receptors (PRRs) by danger signals in the adjuvant, and then trafficked to the draining lymph node

Here, the presentation of peptides of the vaccine protein antigen by MHC molecules on the dendritic cell activates T cells through their T cell receptor (TCR)

In combination with signalling (by soluble antigen) through the B cell receptor (BCR), the T cells drive B cell development in the lymph node. Here, the T cell-dependent B cell development results in maturation of the antibody response to increase antibody affinity and induce different antibody isotypes

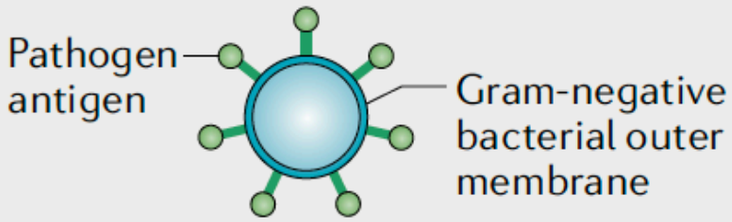
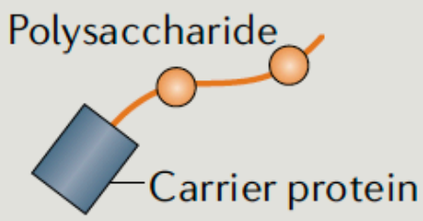
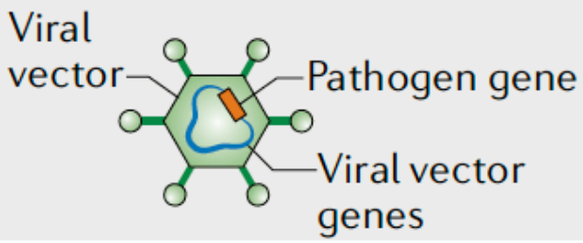
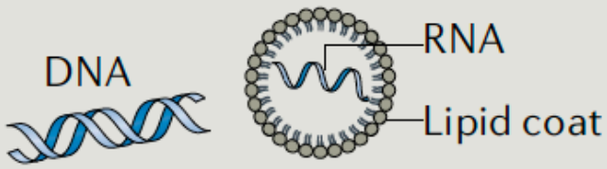
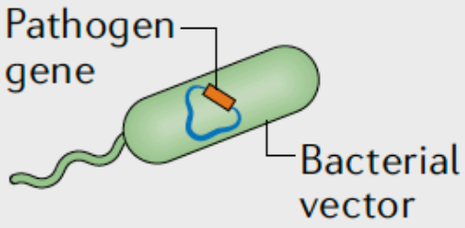
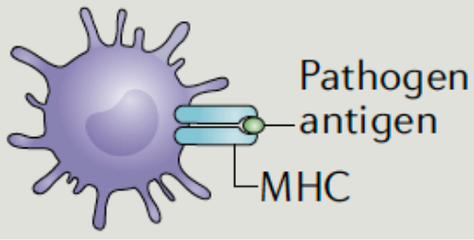
The production of short-lived plasma cells, which actively secrete antibodies specific for the vaccine protein, produces a rapid rise in serum antibody levels over the next 2 weeks

Memory B cells are also produced, which mediate immune memory. Long-lived plasma cells that can continue to produce antibodies for decades travel to reside in bone marrow niches. CD8+ memory T cells can proliferate rapidly when they encounter a pathogen, and CD8+ effector T cells are important for the elimination of infected cells.

Type of vaccine		Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid		Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle		Human papillomavirus	1986 (hepatitis B)

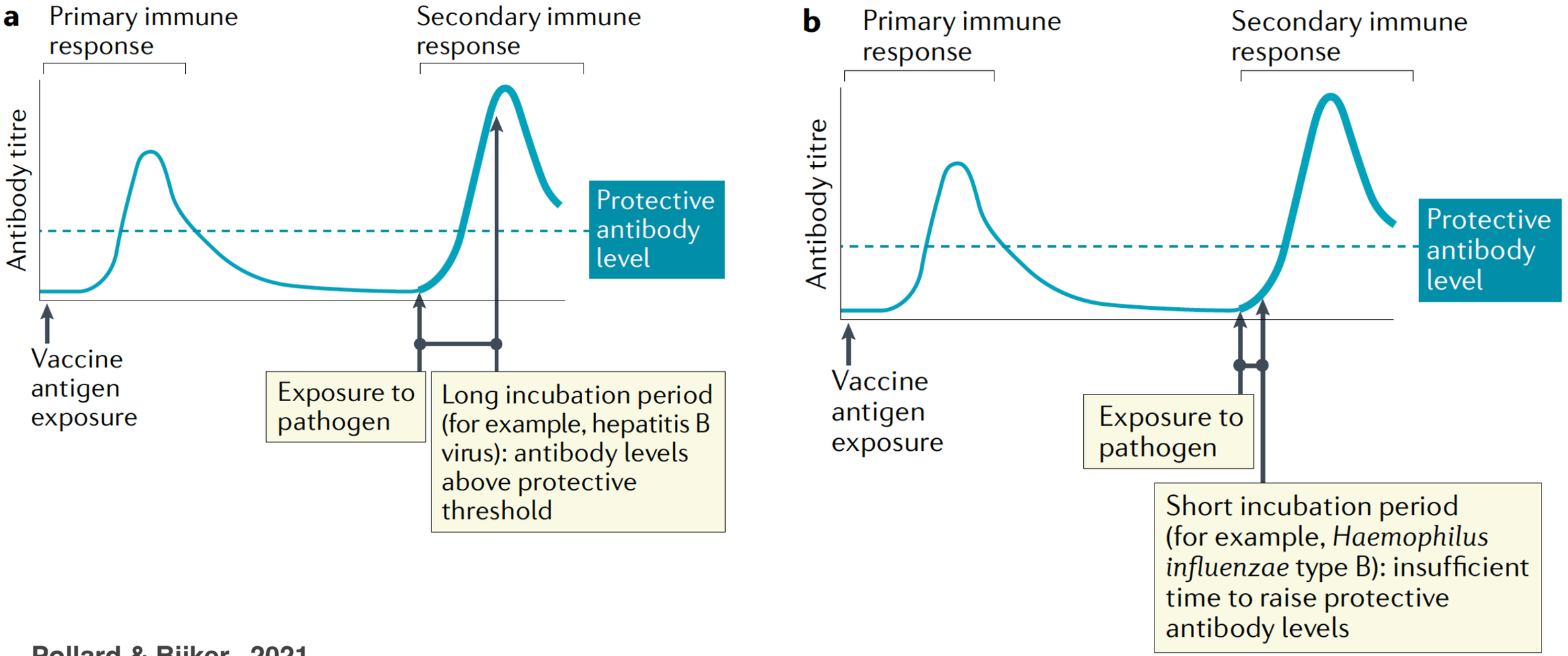
Pollard & Bijker, 2021

BCG, Mycobacterium bovis bacillus Calmette–Guérin.

Outer membrane vesicle		Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored		Experimental	–
Antigen-presenting cell		Experimental	–

Pollard & Bijker, 2021

Immune memory is an important feature of vaccine-induced protection, I

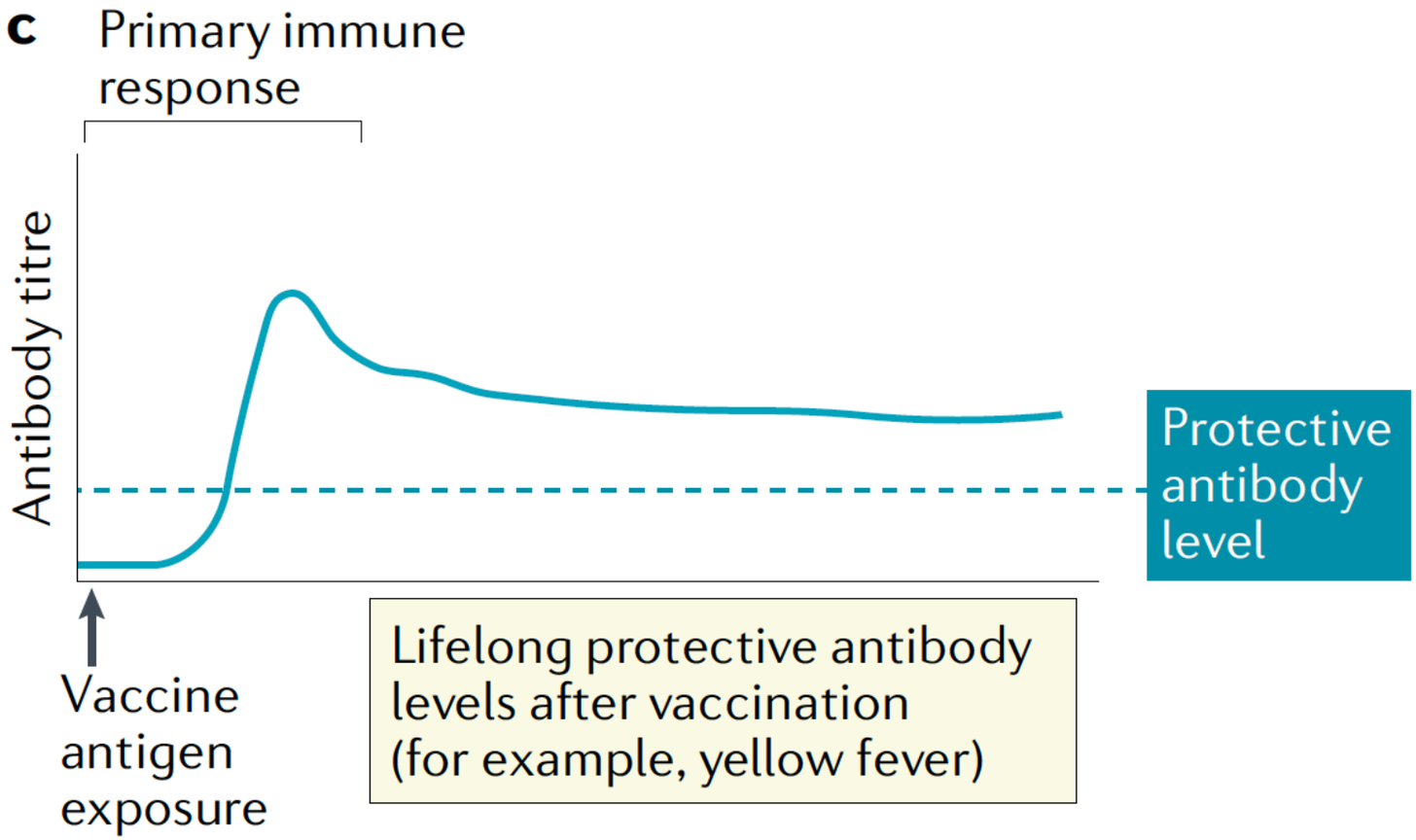


Pollard & Bijker, 2021

Antibody levels in the circulation wane after primary vaccination, often to a level below that required for protection

Whether immune memory can protect against a future pathogen encounter depends on the incubation time of the infection, the quality of the memory response and the level of antibodies induced by memory B cells

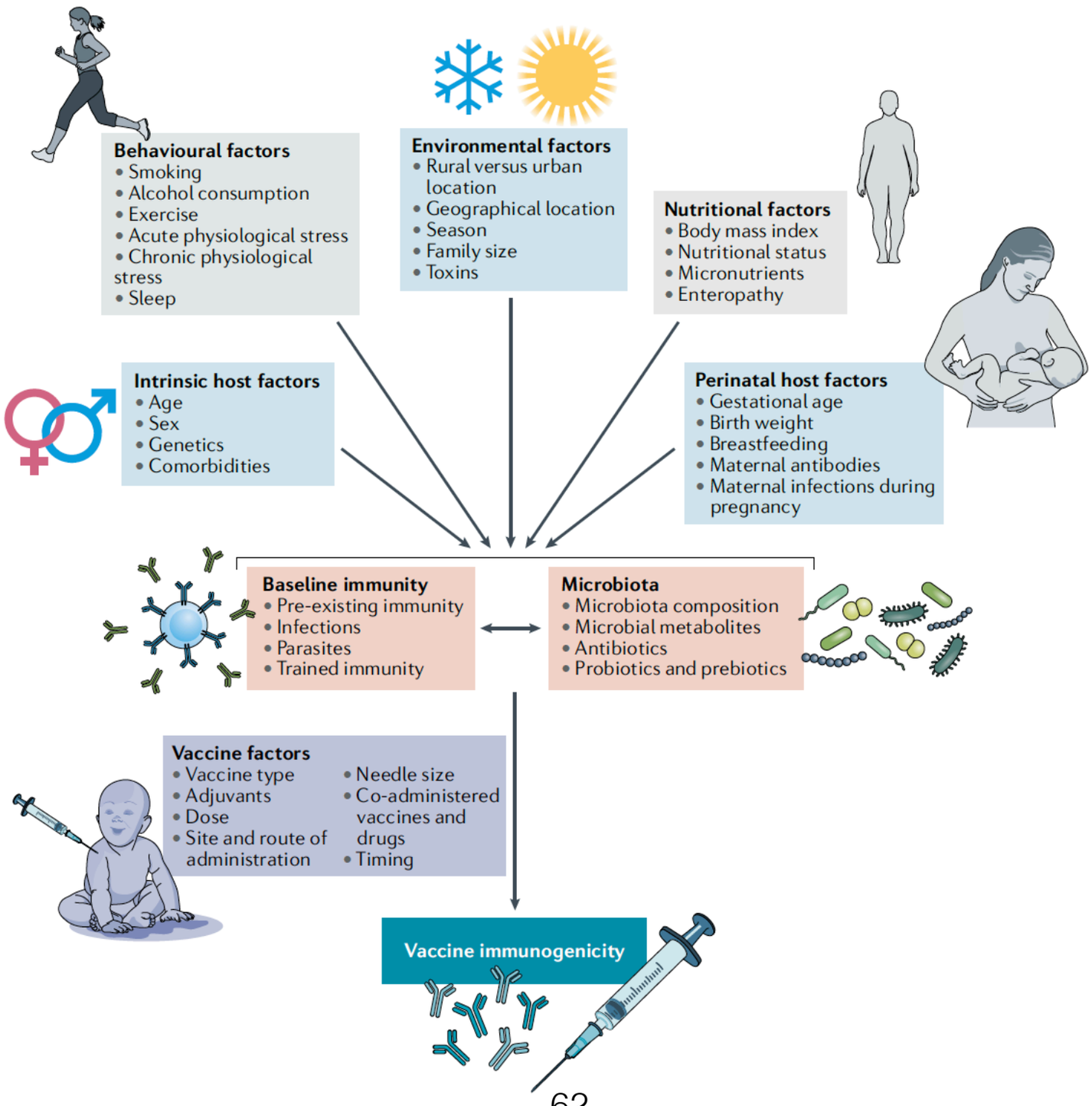
Immune memory is an important feature of vaccine-induced protection, II



Pollard & Bijker, 2021

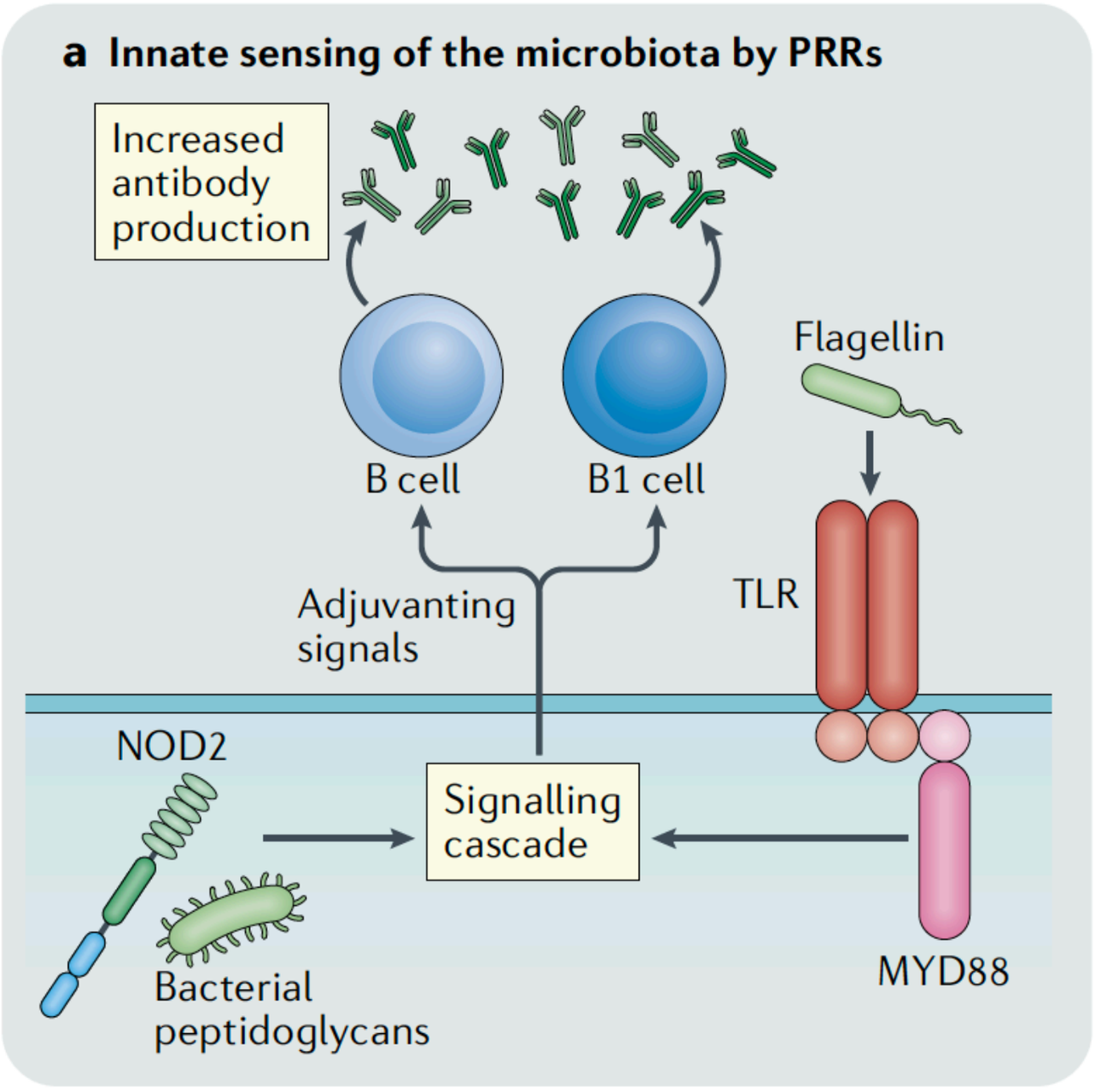
Life long immunity

Factors with the potential to influence vaccine immunogenicity and/or efficacy



Lynn et al., 2022

Microbes-vaccine interactions, I

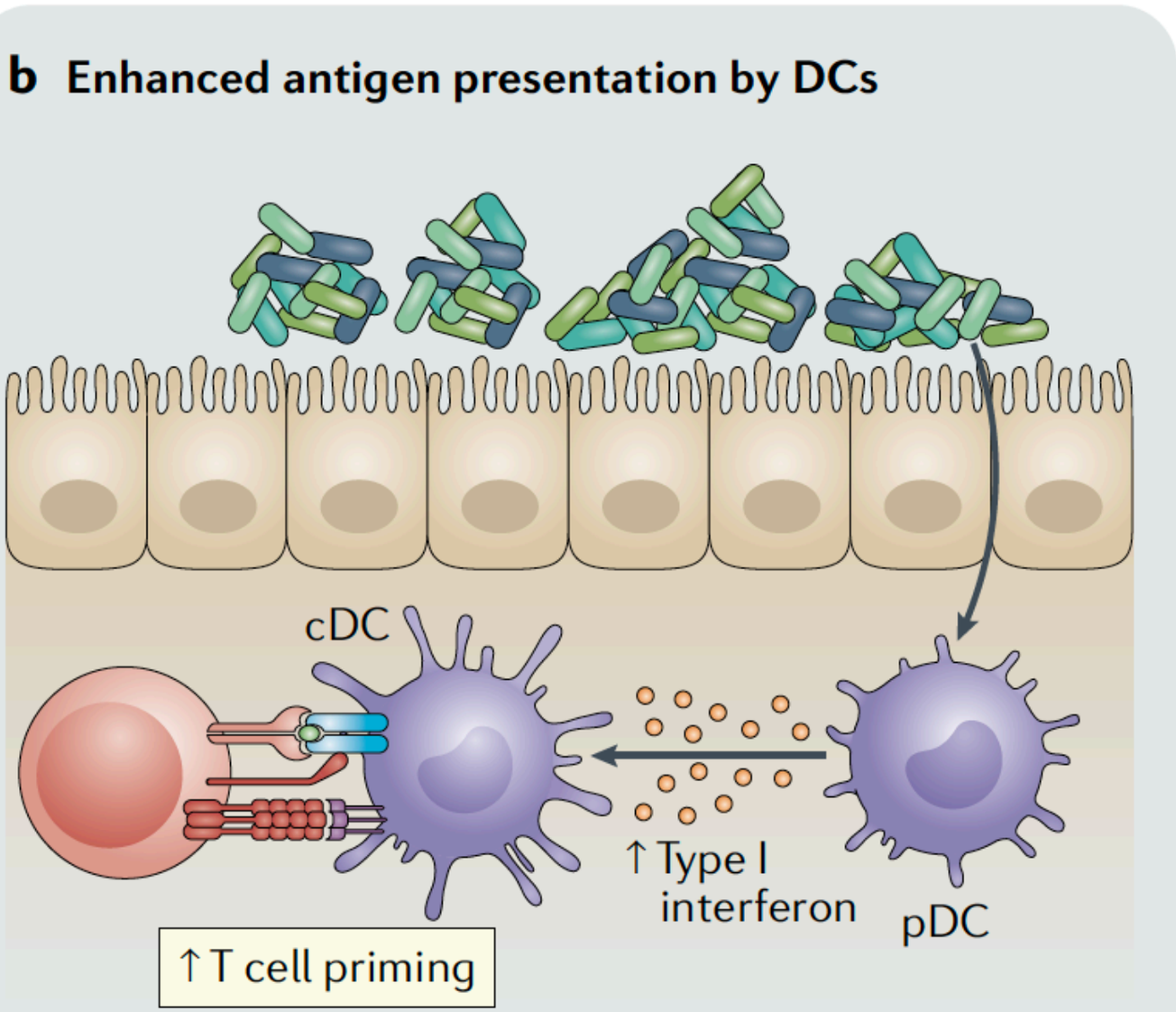


Immunomodulatory molecules produced by the microbiota, such as **flagellin and peptidoglycan**, have been shown in animal models to **modulate vaccine responses by providing natural adjuvants** that are sensed by pattern recognition receptors (PRs), such as Toll-like receptors (TLRs) and NOD2, expressed by antigen-presenting cells.

Other **immunomodulatory** molecules, such as **lipopolysaccharide**, may also similarly modulate responses. PRs expressed by T cells and B cells may also sense these molecules directly.

Lynn et al., 2022

Microbes-vaccine interactions, II

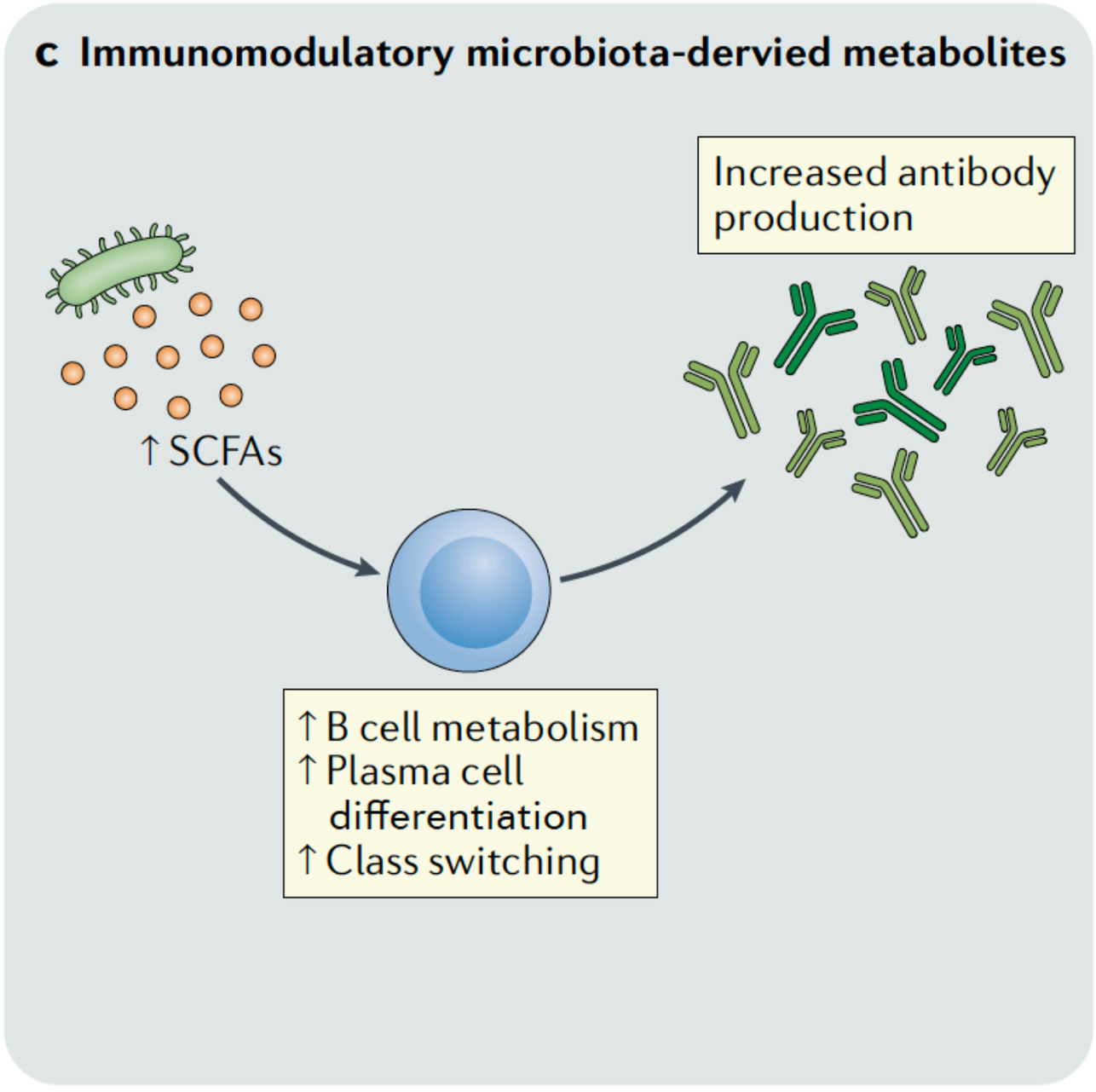


Dendritic cells (DCs) have a crucial role in immune responses to vaccination by presenting vaccine antigens to T cells and secreting immunomodulatory cytokines.

The microbiota regulates the production of type I interferons by plasmacytoid DCs (pDCs), which in turn instruct a specific metabolic and epigenomic state in conventional DCs (cDCs) that enhances T cell priming.

Lynn et al., 2022

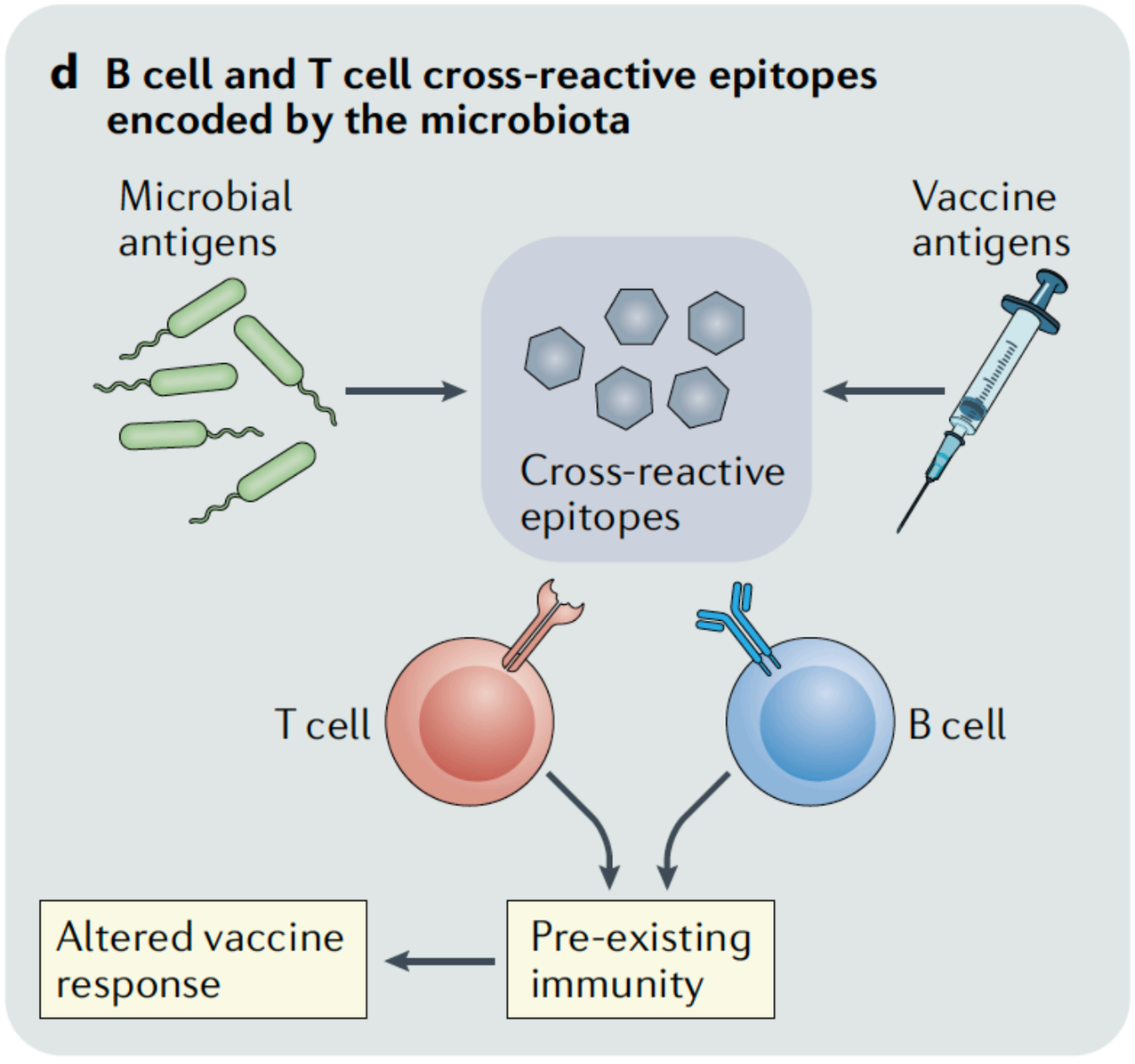
Microbes-vaccine interactions, III



Immunomodulatory metabolites produced by the microbiota, such as short-chain fatty acids (SCFAs), can enhance B cell metabolism to support the energy demands of antibody production and can increase the expression of genes involved in plasma cell differentiation and class switching, potentially altering responses to vaccination.

Lynn et al., 2022

Microbes-vaccine interactions, IV

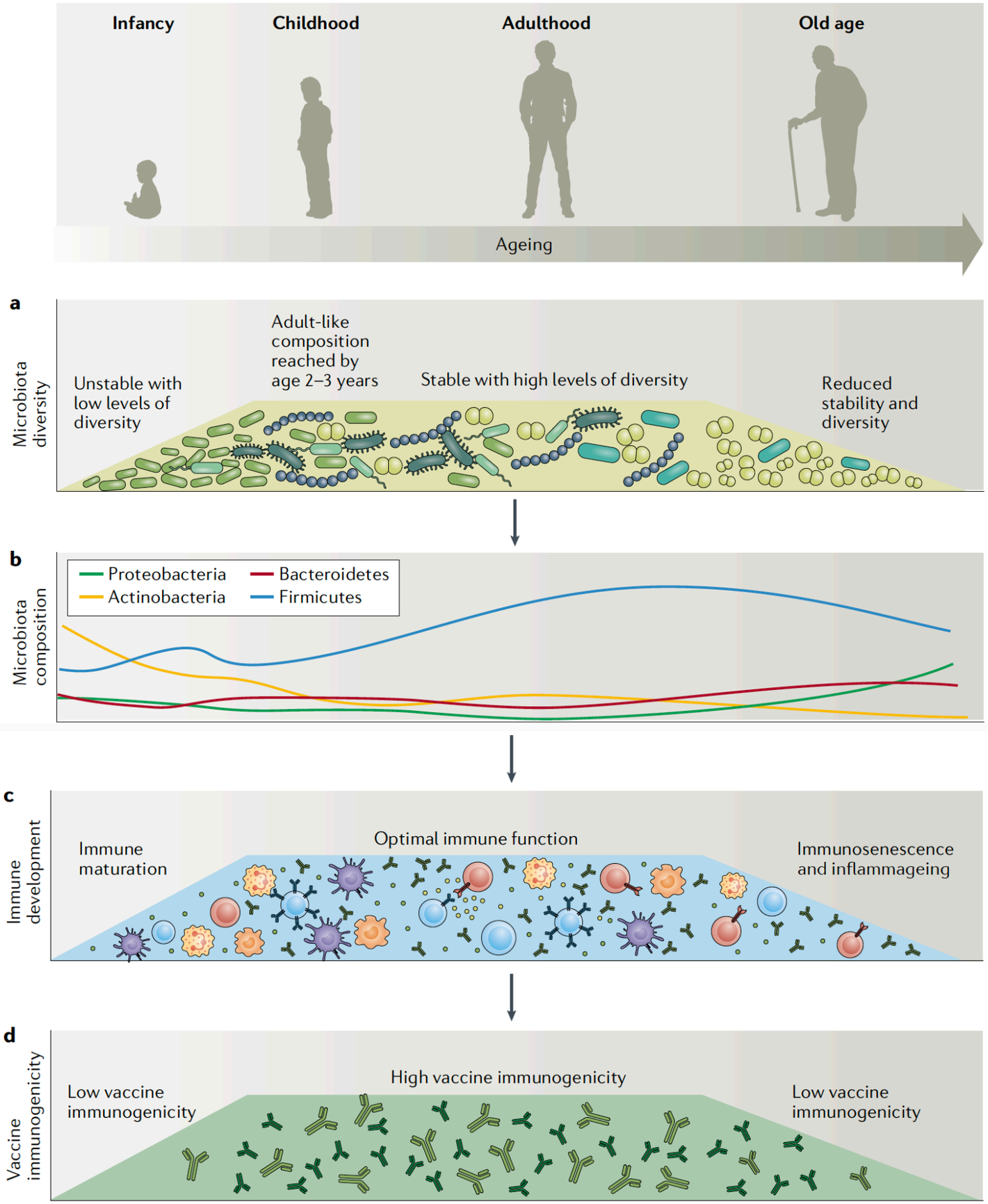


Increasing data suggest that the **microbiota can encode epitopes that are cross-reactive with pathogen-encoded or vaccine-encoded epitopes**.

The presence of cross-reactive B cells or T cells could potentially alter the responses to vaccination.

Lynn et al., 2022

Differences in the gut microbiota of infants and the elderly compared with that of young adults correlate with altered immune status and suboptimal vaccine immunogenicity



Lynn et al., 2022

https://youtu.be/yjAZXIMpw3k?si=ilV45UBzbtb1bIJl

https://vaccinemakers.org/resources/videos-animations

https://youtu.be/gnZEge78_78?si=tTaJxK54Z8o8SXhD

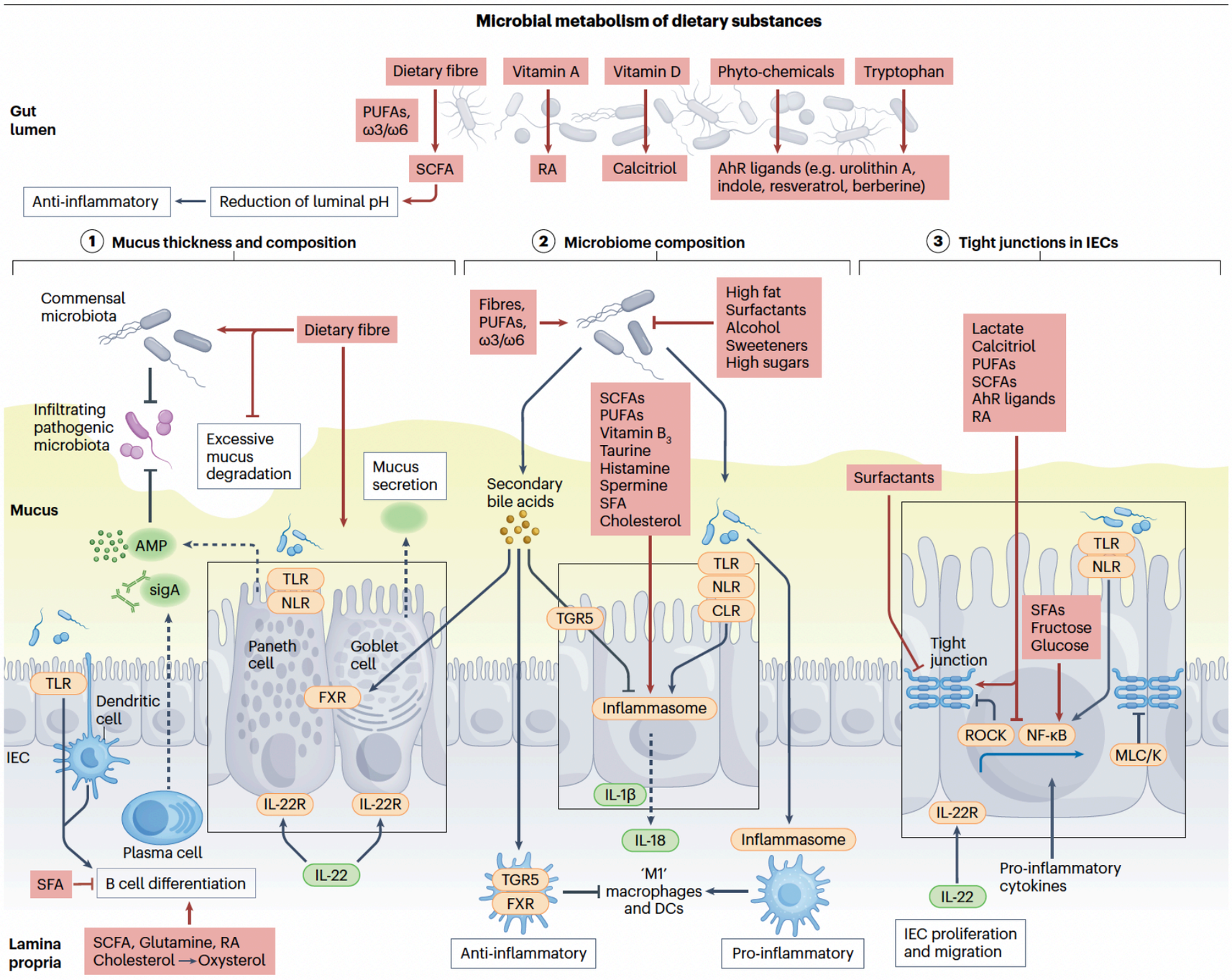
https://youtu.be/CXz6FVqPqHw?si=7rycyijpS5-gBaIW

https://www.vaxpackhero.com/vaccine-heroes/

https://vaccinemakers.org/resources/videos-animations

EXTRA

Dietary orchestration of gut barrier and immunity is linked to the microbiome



Dietary substances and their microbially produced metabolites (in red) modulate intestinal barrier integrity and immunity through various mechanisms involving the resident microbiome.

Sanz et al., 2025

Lexicon

Epitope, portion of a foreign protein, or antigen, that is capable of stimulating an immune response. An epitope is the part of the antigen that binds to a specific antigen receptor

Major histocompatibility complex, MHC
MHC class I and class II molecules are similar in function: they present peptides at the cell surface to CD8+ and CD4+ T cells
MHC are ubiquitous present in all nucleated cells MHC class II molecules are primarily expressed by professional APCs, such as DCs, macrophages and B cells CD4+ T cells

Natural killer (NK) cells are effector lymphocytes of the innate immune system that control several types of tumors and microbial infections by limiting their spread and subsequent tissue damage
NK are classified as group I Innate Lymphocytes (ILCs) and respond quickly to a wide variety of pathological challenges. NK cells are best known for killing virally infected cells, and detecting and controlling early signs of cancer

Lexicon

T cells originate in the bone marrow (like **B cells**) and mature in the thymus. In the thymus, T cells multiply and differentiate into helper, regulatory, or cytotoxic T cells or memory T cells

T CD4+ cells are necessary as **helpers** to promote B cell antibody production and are often required for the generation of **cytotoxic** and memory CD8+ T cell populations

Antibodies are secreted **immunoglobulin** molecules produced mainly by **plasma cells**. The antigen-binding site of the antibody has a unique structure that allows it to bind antigen in a highly specific manner

Antibody is produced by rare populations of terminally differentiated B cells — known as plasmablasts (short lived) and plasma cells (long lived):

IgG: Provides long-term immunity and is the most abundant in blood and extracellular fluid
IgA: Protects mucosal surfaces (e.g., in the respiratory and gastrointestinal tracts)
IgM: The first antibody produced during an initial infection; efficient in forming antigen-antibody complexes
IgE: Involved in allergic responses and defense against parasitic infections
IgD: Plays a role in the activation and regulation of B cells

The Complement

*The complement system was discovered over a century ago by Jules Bordet as a serum-operative key arm of innate immunity that '**complemented' the activity of antibodies during the detection and removal of blood borne pathogens***

Complement is traditionally known as a **serum-effective system**, whereby the **liver expresses and secretes most complement components**, which participate in the **detection** of blood borne pathogens and **drive an inflammatory reaction** to safely remove the microbial or antigenic threat (***e.g.*, opsonisation: bacteria are embellished by proteins that favour phagocytosis or induces direct lytic killing**)

The complement system comprises more than **50 soluble or membrane-bound glycoproteins that engage in multi-tiered protein–protein interactions**, resulting in the **assembly and activation of enzymatic complexes** and the generation of bioactive fragments that initiate **diverse cellular responses** through binding to complement receptors and regulators

Complement function is compartmentalized and operates systemically, locally in the extracellular space, and intracellularly within sub-cellular compartments and organelles

Microbes and Immune System

Immune system does not properly develop in the **absence** of **microbial** stimulation and that early life exposure to a variety of microorganisms is **essential for developing tolerance to beneficial microorganisms and recognizing pathogens as foreign**

Window of opportunity for interactions in order to train the immune system

Thymic development of gut-microbiota-specific T cells

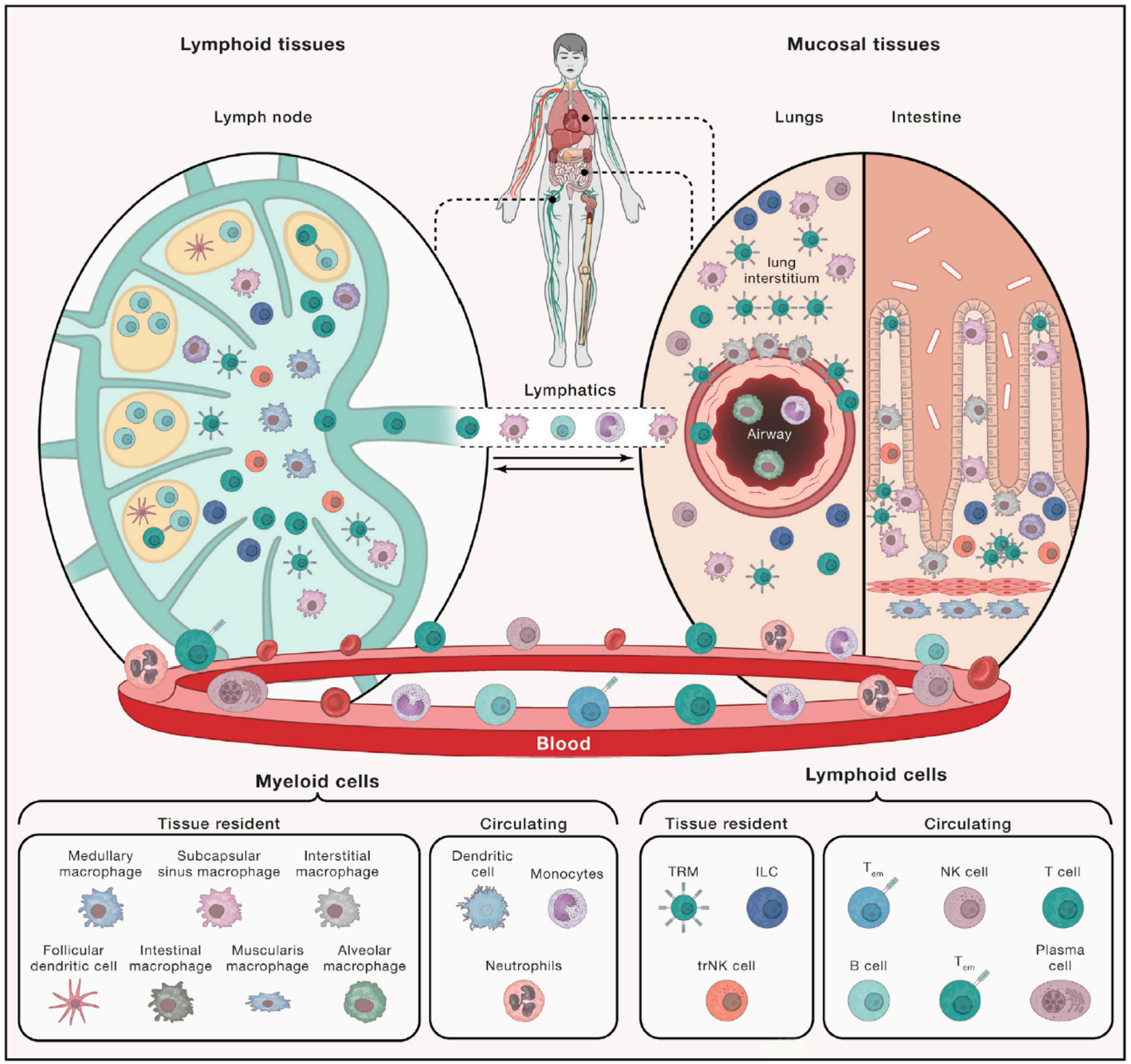
Antigen-specific recognition of intestinal microorganisms by T cells

Local environment shapes the differentiation of effector cells —> unclear how microbiota-specific T cells are educated in the thymus

Intestinal colonization in early life leads to the trafficking of microbial antigens from the intestine to the thymus by intestinal dendritic cells, which then induce the expansion of microbiota-specific T cells. Once in the periphery, microbiota-specific T cells have pathogenic potential or can protect against related pathogens

In this way, the developing microbiota shapes and expands the thymic and peripheral T cell repertoire, allowing for enhanced recognition of intestinal microorganisms and pathogens

Compartmentalization of immune cells in blood and tissue sites



Mucosal sites contain macrophages and **tissue-resident memory T cells TRMs** in the epithelial layers (interstitium) of airways and intestinal villi

In the lymph node, B cells are situated in follicles along with DCs surrounded by T cell areas and distinct macrophage subsets in T cell areas

Germinal centers within follicles are the sites of T-B cell interactions and differentiation of B cells to antibody-secreting cells

The major conduits to circulation (blood and lymphatics) and circulating immune cells

Innate lymphoid cells such as natural killer (NK) cells TRMs predominate in mucosal and exocrine sites, and are also found in lymphoid organs (bone marrow, spleen, lymph node), while circulating memory T cells and naive T cells are in blood and lymphoid sites

Weisberg et al., 2021

Common principles of innate immune effector mechanisms

Immune effectors involved in innate immunity rely on a limited number of mechanisms that revolve around a few principles:

(A) **Destruction of the radically different** (*e.g.*, anti-microbial peptides recognizing negatively charged membrane of bacteria)

(B) **Anti-virulence**

(C) **PRR-assisted elimination** (*e.g.*, complement activation guided by C3b binding to pathogen or phagocytosis of opsonized microbe)

(D) **Suicide of the infected cells**

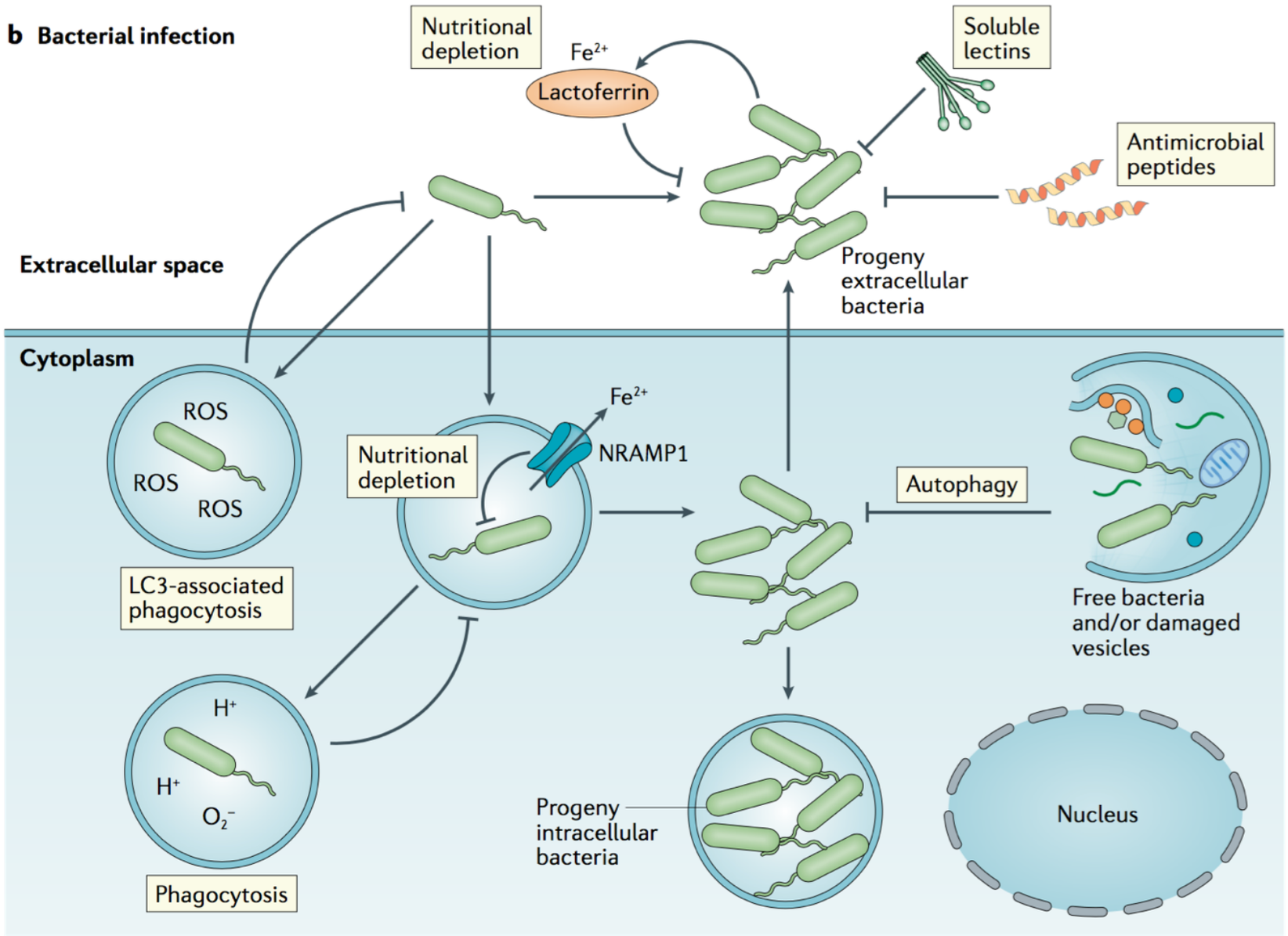
(E) Nutritional immunity

First encounter

Pathogen recognition by extracellular or endosomal receptors

Constitutive innate immune response

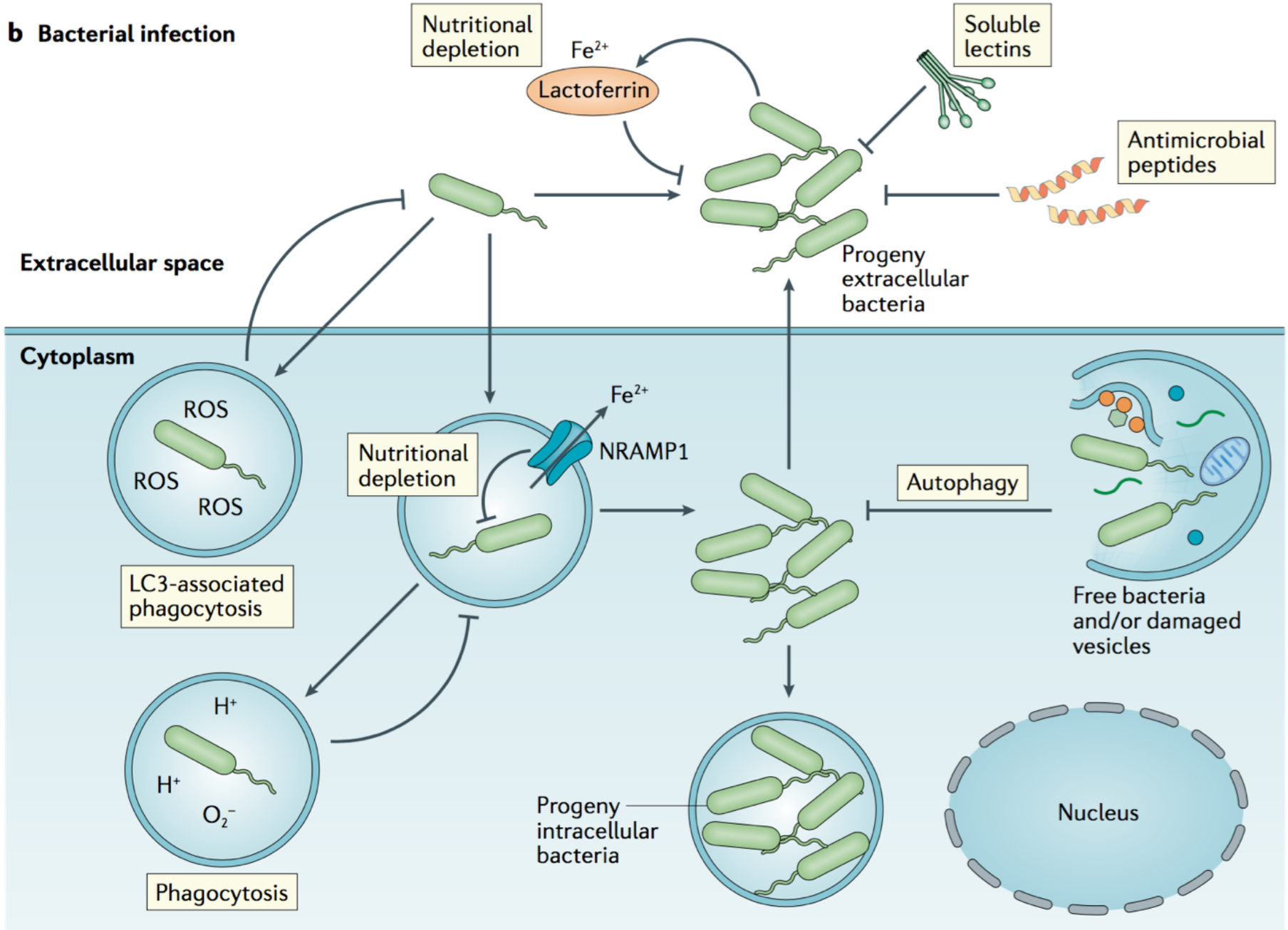
- **Host cell uses bacterial compartmentalization**, **oxidative and nutrient stress**, **antimicrobial peptides**, lysosome-mediate degradation, autophagy, inflammasome activation and pyroptosis to kill the pathogens
- Some intracellular pathogens can control the signalling pathways activated by host receptors, **interact with endocytic pathway, escape** from the phagosome, **inhibit fusion with lysosomes, manipulate vesicular trafficking and avoid autophagosome degradation and inflammasome activation**



Paludan et al., 2021

Targeting microbial replication

Direct inhibition of microbial replication is executed by molecules that interfere with specific steps in the replication cycle of a given microorganism. There are at least six mechanisms of action in this category: restriction factors that directly block a **specific replication step**; **restriction factors that deplete molecules essential for replication; RNA interference (RNAi); antimicrobial peptides; soluble lectins; and metabolite-mediated inhibition of microbial replication**



Paludan et al., 2021

Degenerative mechanisms

The second class of constitutive innate immune mechanisms functions through the **degradation of danger molecules and elimination of unwanted cells**. This class of mechanisms includes **autophagy, phagocytosis, proteasomal degradation and nucleases**. Collectively, degenerative programmes function to continually limit danger signals, allowing for the rapid elimination of unwanted molecules without the activation of energy-consuming amplificative induced immune responses