(1) Hiking concept art. Reprinted from Freepik.com.

CASE 2

Immune Response Summary

Claire Sie

PATH417 2021W2

CASE OVERVIEW

"Suzanne is a 24-year-old avid hiker and excited to visit her friends in Halifax for some hiking in some new scenery. When she arrived on the plane from Vancouver, it was a sunny spring day in Halifax and her friends wanted to show her a great view of the city. Her friends picked her up at the airport and they headed to the nearby Admiral's Cove for a scenic hike to the top of a ridge overlooking the Halifax Harbour. That evening they had a wonderful night out visiting multiple local craft breweries and tasting east coast lobster."

CASE OVERVIEW

"The next morning Suzanne noticed a non-painful bump on the back of her calf, but she was on the way out with friends for another hike, so she did not pay much attention to it. On the hike, as Suzanne was climbing up a steep area, one of Suzanne's friends behind her noticed the back of Suzanne's leg and asked to look at it. It was a tick, and it had embedded its head into the back of Suzanne's leg. Her friend removed the tick and they carried on. Over the next few days, Suzanne developed a ring-like red rash at the site of the tick bite. The rash was hot to the touch and felt like it was burning. Suzanne felt chills and fatigued. Knowing that Lyme disease was in the area, her friend took Suzanne to an Urgent Care Centre (UCC) for assessment. At the UCC, Suzanne head a temperature of 38.0 degrees Celsius, a white blood cell count of 14, and the physician examining her said her rash was a classic "bull's eye" rash caused by *Borrelia burgdorferi* and prescribed her antibiotics for erythema migrans."

(2) Insect icon pack. Reprinted from Freepik.com.

WHAT IS LYME DISEASE?

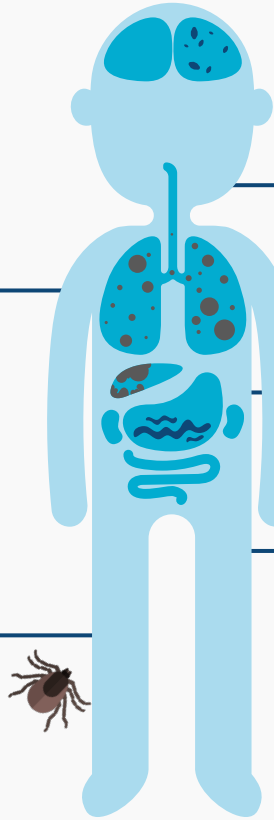
EARLY LOCALIZED INFECTION

IMMUNOLOGICAL SYMPTOMS

Fever, chills, headache, fatigue, muscle and joint pain

ERYTHEMA MIGRANS

Circular/oval-shaped, expanding skin rash at site of tick bite



DISSEMINATED INFECTION

CENTRAL NERVOUS SYSTEM

Meningitis, facial palsy; acute pain caused by spinal nerve inflammation

CARDIOVASCULAR SYSTEM

Heart palpitations or irregular heart beat (Lyme carditis)

JOINTS

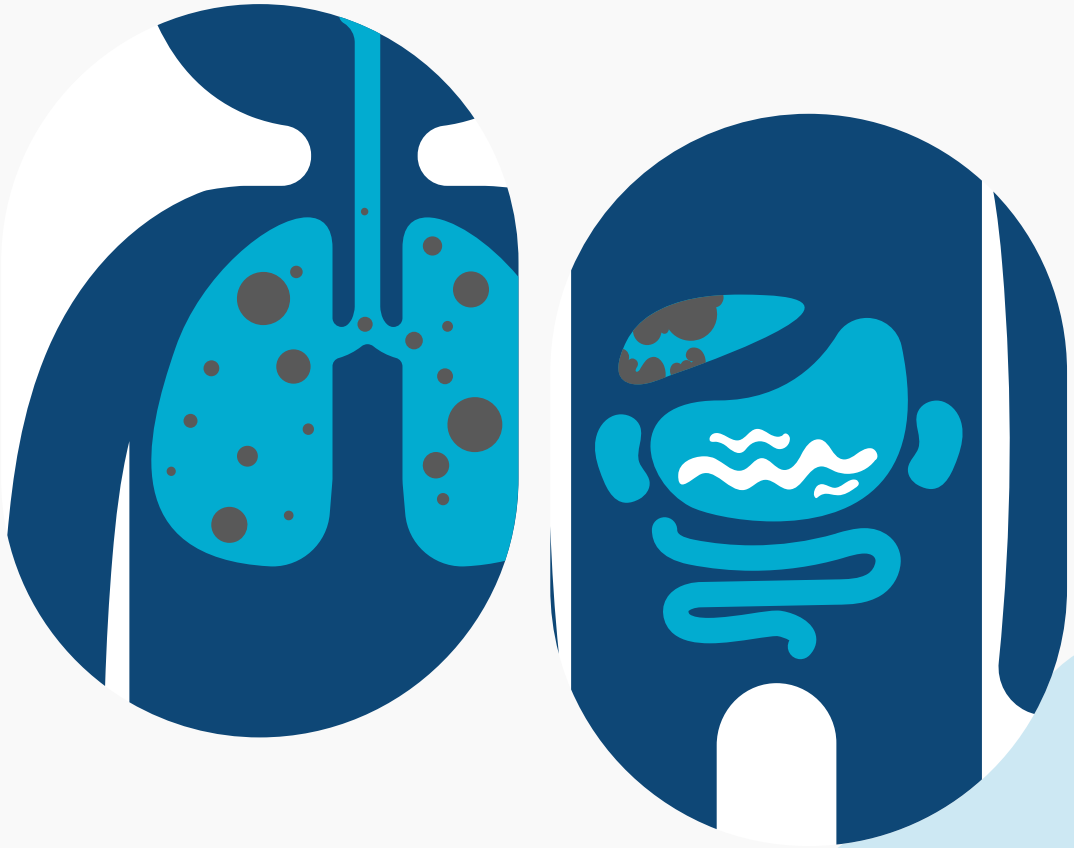
Arthritis; severe joint pain and swelling

(2) Insect icon pack. Reprinted from Freepik.com.

SUZANNE'S SYMPTOMS

Suzanne experiences symptoms associated with early Lyme disease:

- Erythema migrans
- Fever
- Chills
- Fatigue



MAIN CAUSATIVE AGENT: *BORRELIA BURGDORFERI*

Gram-negative, motile and flagellated spirochete

Outer membrane lacks lipopolysaccharide (LPS)

Vector transmission via *Ixodes scapularis* (deer tick) bite

(2) Insect icon pack. Reprinted from Freepik.com.

TABLE OF CONTENTS

01

HOST RESPONSE

What elements of the innate and adaptive (humoral and cellular) immune response are involved in this infection?

HOST IMMUNE RESPONSES

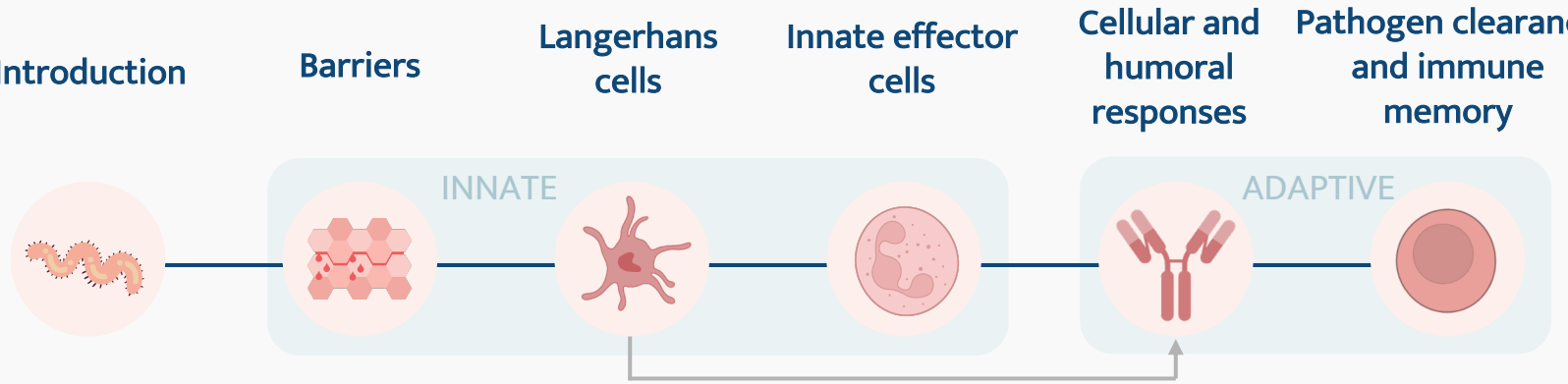
Innate Immune Response

- **Nonspecific**, first-line defense
- **Immediate** activation[1]
- Physical, chemical, cell-mediated defenses[2]

Adaptive Immune Response

- Second-line defense
- **Pathogen-specific** defense systems
  - Humoral (antibody)
  - Cellular

TIMELINE OF INFECTION



Pathogen **transmitted** if tick is attached for 36-48 hours[3]

Pathogen must bypass **physical**, **chemical**, and **anatomical** barriers to establish infection[2]

Pathogen **recognized** by Langerhans cells in the dermis, migration to lymph nodes for antigen presentation[4]

Pathogen **recognized** by neutrophils, macrophages via conserved molecular patterns → **effector functions**[3]

Lymphocytes **activated** by antigen presenting cells, secrete **antibodies** and **cytokines**[4]

Memory cells remain after clearance, enabling **efficient activation** of immune response upon re-infection

Immune cell icons from Biorender.com

INNATE IMMUNE RESPONSE

1 Physical Barriers

Skin and mucous membranes **bypassed**

- Pathogen introduced to bloodstream via tick bite

2 Inflammation

Mast cells release **histamine** and **inflammatory mediators**[4]

- Blood vessel dilation, increased blood flow and vascular permeability

3 Complement

Complement proteins migrate from blood to tissues

- Complement pathway activation

4 TLR-1/2

Recognition of *B. burgdorferi* surface proteins[5,6]

- Triggers production and secretion of **inflammatory cytokines**[7]

5 Effector cells

Recruited by inflammatory cytokines (**chemotaxis** and **extravasation**)[8]

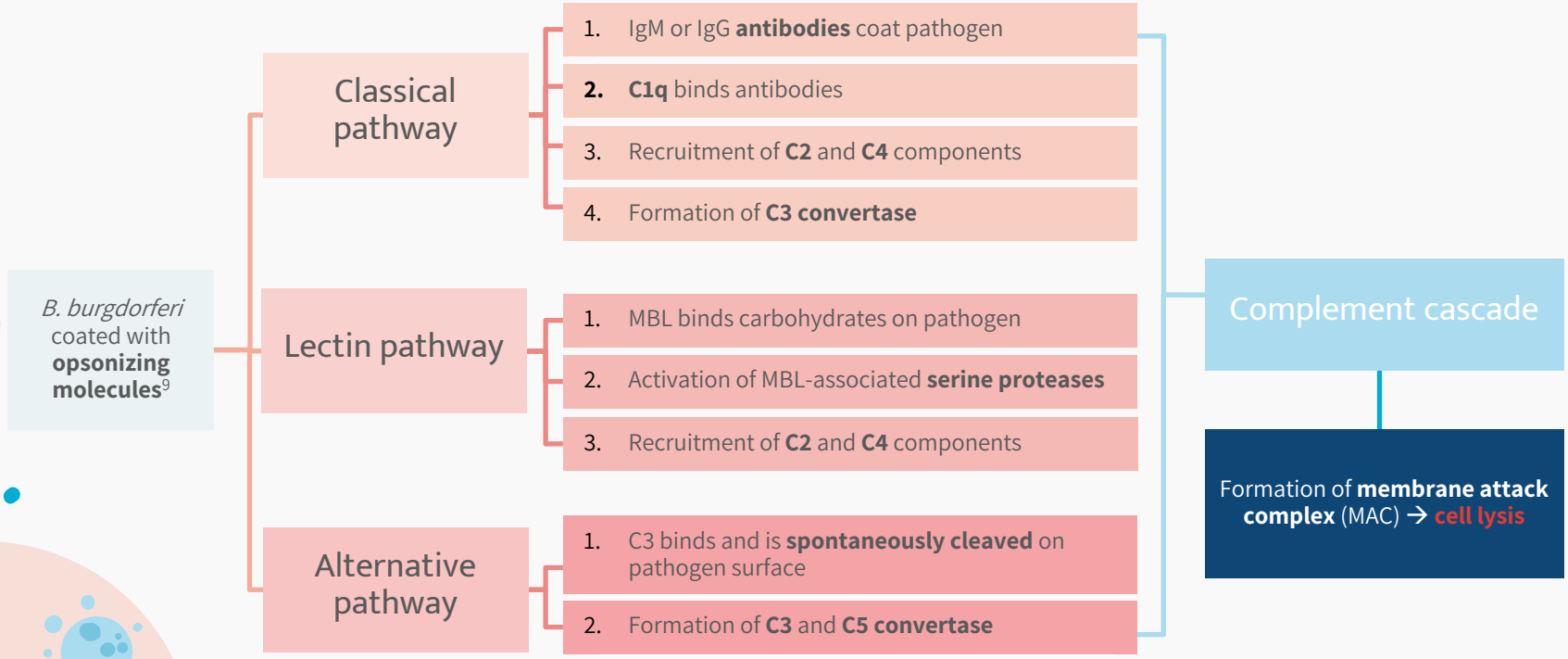
- Macrophages, granulocytes mediate **phagocytic killing** of pathogen

6 Downstream...

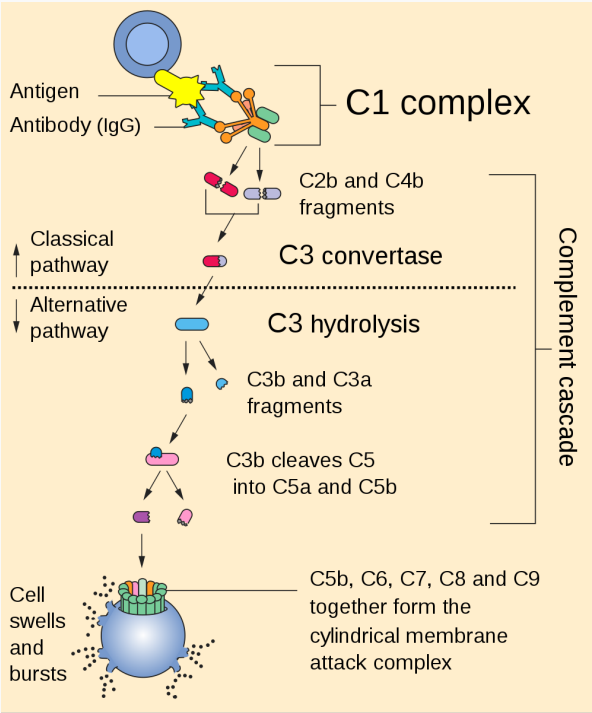
Dendritic cells engulf and kill pathogens

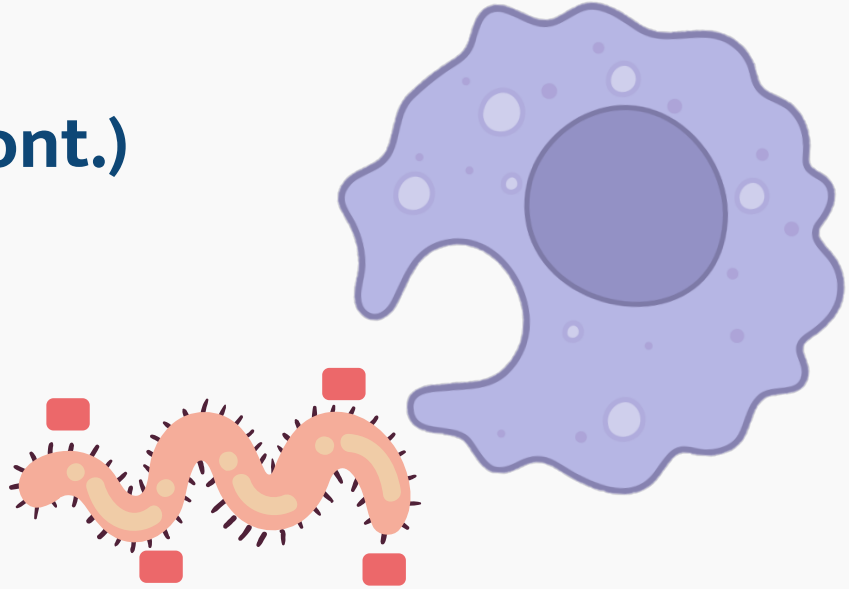
- Migration to lymph nodes for **antigen presentation** (bridge to adaptive immunity)

OVERVIEW OF THE COMPLEMENT SYSTEM[5]



COMPLEMENT SYSTEM (cont.)





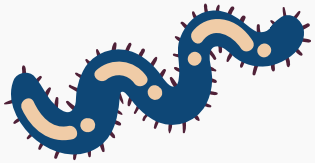
Opsonized *B. burgdorferi* can also be **recognized by complement receptors** CR1, CR2, and CR3 on phagocytic cells, inducing **engulfment**[5]

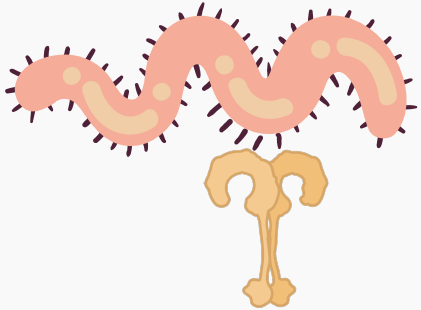
(3) Diagram of the classical and alternative complement activation pathways. Reprinted from Wikimedia commons.

Immune cell icons from Biorender.com

PATHOGEN-ASSOCIATED RECOGNITION RECEPTOR RECOGNITION

- **Pathogen-Associated Molecular Patterns** (PAMPs) are found on *B. burgdorferi*'s cell surface
  - **Surface lipoproteins** – Outer surface proteins A, B, C (OspA, OspB, OspC)[10]
  - **Peptidoglycan**[6]
  - Cell surface **triacylated lipid element**





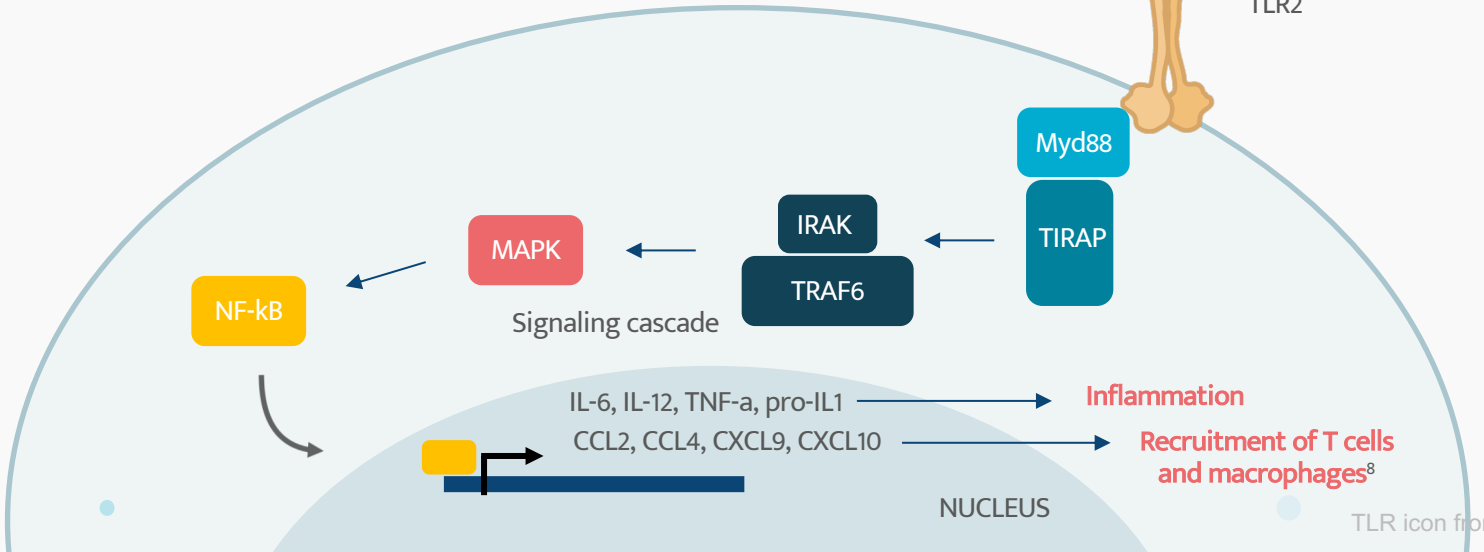
*not to scale

- PAMPs are recognized by **Pattern Recognition Receptors** (PRRs) expressed on innate effector cells, trigger production of cytokines/chemokines[5]
  - **Toll-Like Receptors** (TLR2, TLR1)[5,6]
  - **Nucleotide-binding oligomerization domain** (NOD)—like receptors (NOD1 and NOD2)

TLR icon from Biorender.com

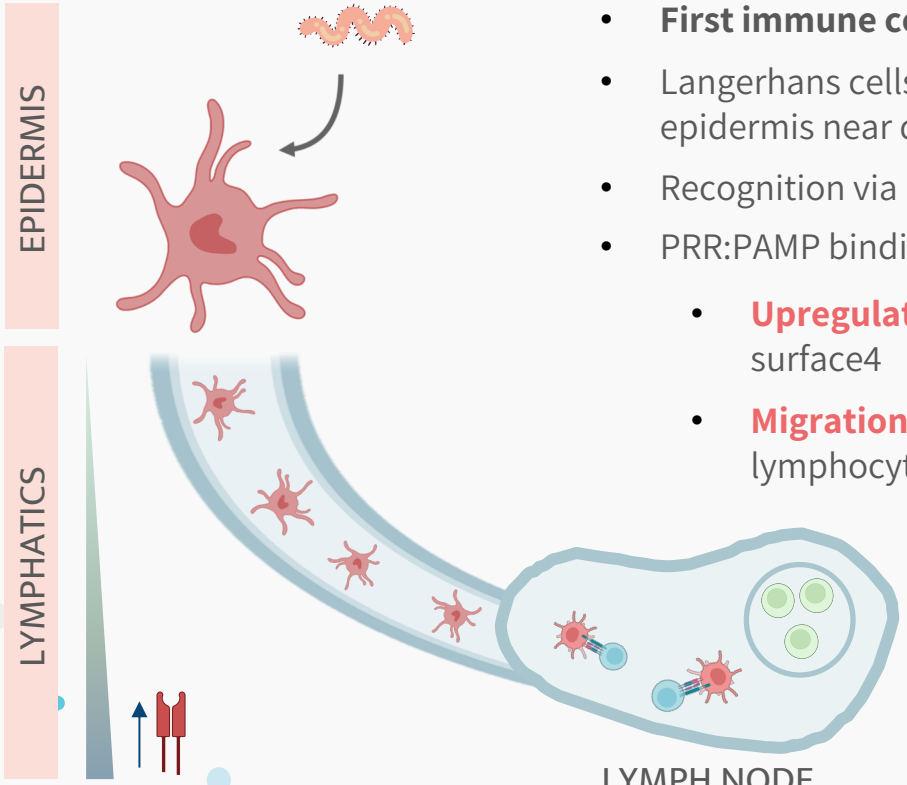
TLR2 SIGNALING PATHWAY[6]

1. **PAMP** (peptidoglycan) binding to **TLR2**
2. **Myd88** recruited by Toll-interleukin 1 receptor (TIR) domain-containing adapter protein (**TIRAP**) to cell membrane
3. Signaling cascade
   - Recruitment of **IRAK** kinases, **TRAF6**
   - Activation of **MAP** kinases and **NF-kB**
4. Activate transcription of **pro-inflammatory cytokines** and **chemokines**



TLR icon from Biorender.com

LANGERHANS CELLS: INITIAL RECOGNITION

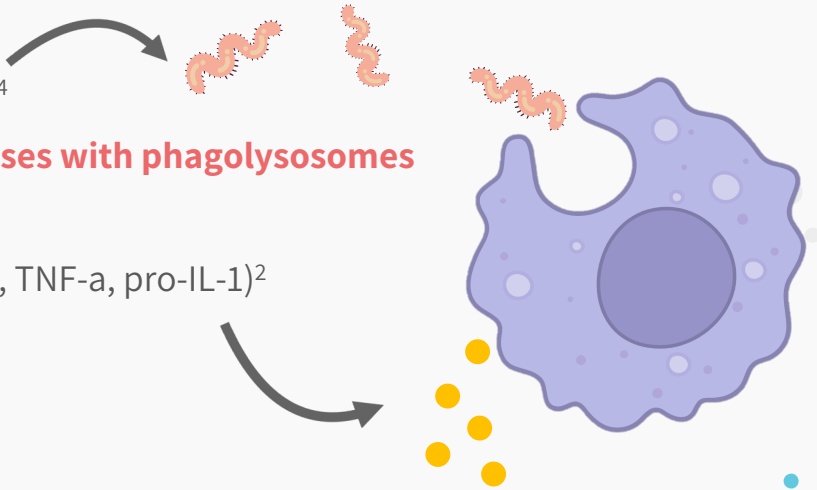


- **First immune cells** encountered by *B. burgdorferi*
- Langerhans cells are **tissue resident macrophages** found in epidermis near dermal interface[11]
- Recognition via **PRRs**
- PRR:PAMP binding leads to:
  - **Upregulation of MHC class II** molecules at cell surface surface4
  - **Migration to lymph nodes** for antigen presentation to lymphocytes[4]

Immune cell icons from Biorender.com

PHAGOCYTIC EFFECTOR CELLS OF INNATE IMMUNITY

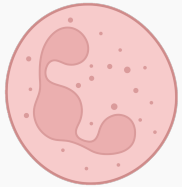
- **Engulf pathogens** and participate in **inflammatory response**[12]
- [2]Composed of:
    - **Granulocytes** – neutrophils, eosinophils, basophils, mast cells
    - **Macrophages**
    - **Dendritic cells**
- PRR engagement triggers **phagocytosis** of pathogen[14]
- Once engulfed, compartment containing pathogen **fuses with phagolysosomes**
    - Very low pH compartment to kill bacteria
- Most can release **inflammatory cytokines** (IL-6, IL-12, TNF-a, pro-IL-1)[2]



Immune cell icons from Biorender.com

THE ROLE OF MACROPHAGES AND NEUTROPHILS

Both are capable of killing via fusion of vesicle containing pathogen to a **phagolysosome**



MACROPHAGES

- Secretes **leukotrienes**
- Capable of O_2-dependent and O_2-independent killing[12]
    - **O_2-dependent**: Reactive oxygen species
    - **O_2-independent**: proteases and lysozymes
- Also serves as an antigen-presenting cell (APC)
- Releases and stimulates cytokine production

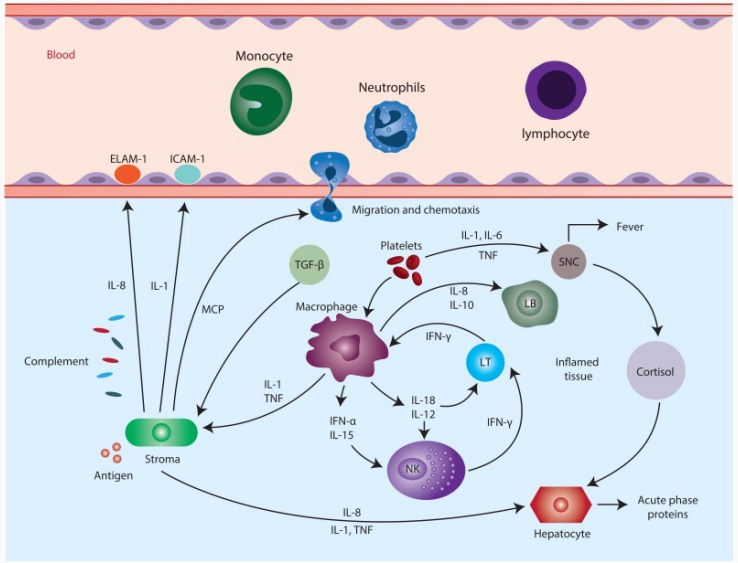
NEUTROPHILS

- Recruited to site of infection via leukotrienes
- Releases:
    - Antimicrobial peptides
    - Reactive oxygen species
    - **Neutrophil extracellular traps** (NETs) to trap and destroy pathogens[2]

OTHER EFFECTOR CELLS OF INNATE IMMUNITY

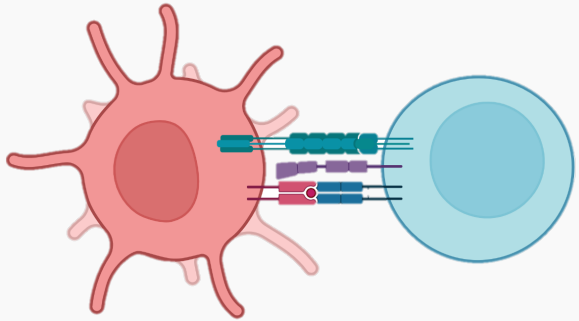
- Epithelial and endothelial cells
- Natural killer cells
- Innate lymphoid cells
- Platelets
- Mast cells

- Many of these cells secrete **antimicrobial peptides** (AMP) and **reactive oxygen species** (ROS)[2]
    - AMPs - cathelicidin, defensins[2]
    - ROS - nitric oxide



(4) Effector mechanism of innate immune response. Reprinted from Aristizabal & Gonzales.

BRIDGING THE INNATE AND ADAPTIVE RESPONSES



Both are capable of processing and presenting a pathogen-derived antigen on cell surface MHC molecules

DENDRITIC CELLS

- Highly efficient **antigen-presenting cell** (APC)
- Phagocytoses pathogen, becomes **activated**
  - Antigen processing and presentation on MHC class I or class II molecules[4]
  - **Migrates to lymph node** to present to and activate CD4+ and CD8+ T cells[4]

MACROPHAGES

- Highly efficient phagocytic cell
- Less efficient APC than dendritic cell
- Mainly **stays at site of infection** to initiate localized inflammatory response

Immune cell icons from Biorender.com

CELL-MEDIATED ADAPTIVE IMMUNE RESPONSE

B. burgdorferi infection triggers **differentiation** of CD4+ T cells

CD4 T helper 1 cells (Th1)

Th1

Release **effector molecules** (interferon and TNF-a) to activate phagocytes[15]

CD4 T helper 17 cells (Th17)[15]

Th17

Release **IL-17A**

Recruitment of **neutrophils**

Release **TNF-a**

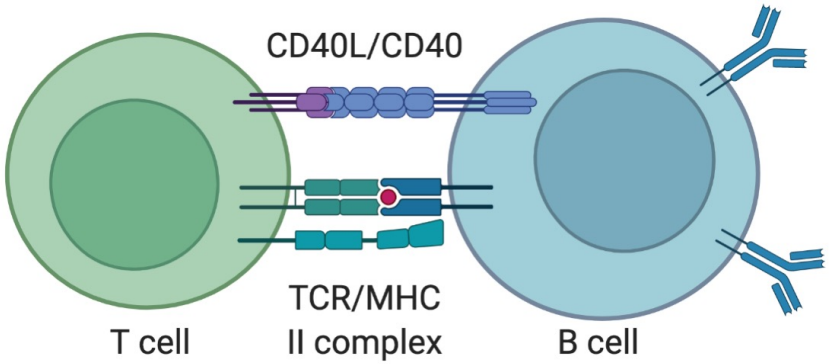
Secrete **reactive oxygen species** and nitric oxide

Release **IL-22**

Stimulate tissue cells to produce **antimicrobial peptides**

HUMORAL ADAPTIVE IMMUNE RESPONSE

- CD4 T helper cells activate B cells
- Activated B cells produce **pathogen-specific antibodies**
- Antibodies can **bind**, **neutralize**, and **opsonize** *B. burgdorferi* for phagocytosis[16]

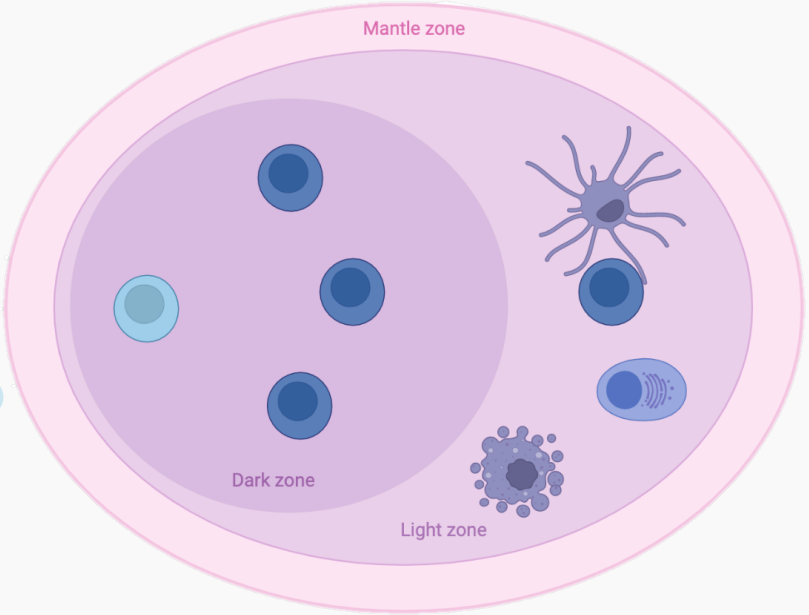


During infection, **high levels** of *B. burgdorferi*-specific **antibodies** are produced

➢ **Reduction** of *B. burgdorferi* from tissues

Immune cell icons from Biorender.com

GERMINAL CENTERS



- Where B cells undergo **proliferation**, **class-switching**, **affinity maturation**, **memory cell formation**[17]
- **Transient** germinal center formation seen in *B. burgdorferi* infection
    - **Unable to sustain** B cell maturation and development into memory cells[18]
    - May contribute to **persistence of pathogen** and **susceptibility to reinfection**

Germinal center icon from Biorender.com

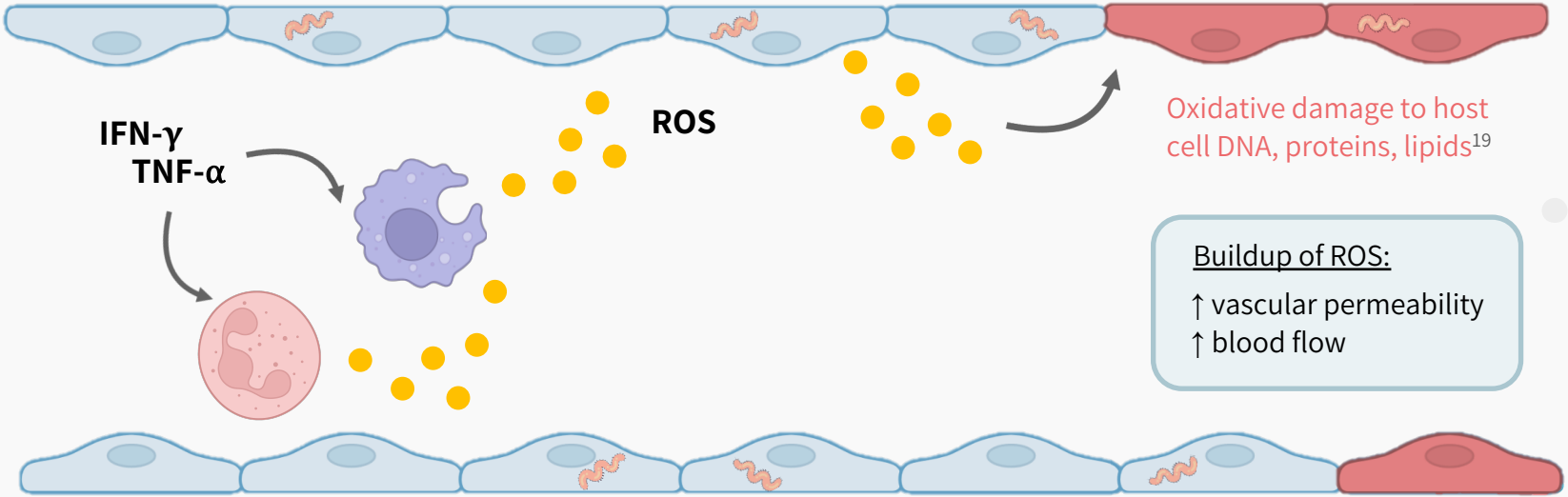
02

HOST DAMAGE

What damage ensues to the host from the immune response?

TISSUE DAMAGE

Oxidative stress can be caused by production of **reactive oxygen species** (ROS) during inflammatory response[2]



Immune cell icons from Biorender.com

ERYTHEMA MIGRANS

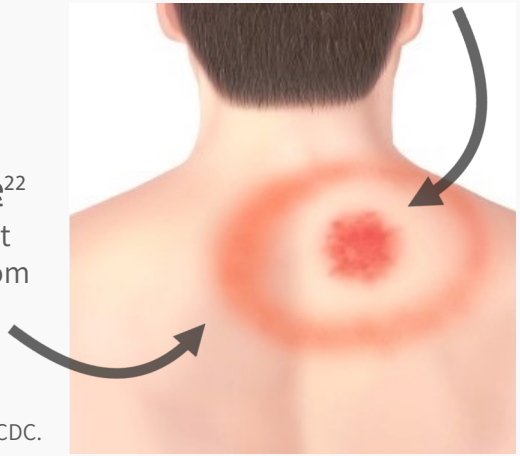
- Begins at **site of tick bite** after 3-30 days[20]
- Caused by innate immune response:
    - Release of **host enzymes** → digestion of extracellular matrix proteins facilitates bacterial dissemination
    - Release of **inflammatory cytokines**
    - **Rapid macrophage clearance** from infection site
- Untreated infections can persist and spread to secondary infection sites

Stationary central rash[21]

Innate response against **tick salivary proteins**

Expanding outer circle[22]

Immune response against **pathogen** as it **spreads** from point of entry

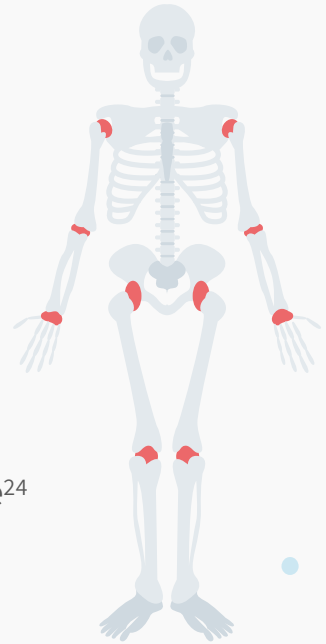


(5) Stereotypical appearance of erythema migrans rash. Reprinted from CDC.

CHRONIC INFLAMMATION

Lyme arthritis

Caused by chronic inflammation from *B. burgdorferi* penetration into **joint tissue**



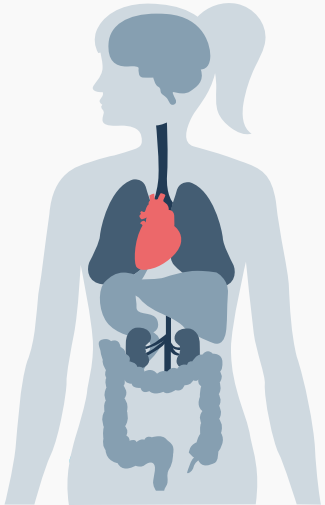
- Typically occurs after several months of **persistent infection**
  - Persistently high levels of **IL-6** can lead to chronic inflammatory disease[24]

- Innate and adaptive immune responses contribute to damage
  - Inflammation = **high metabolic burden**, damage to host cells and tissues[23]
  - Pathogen infiltrates synovial tissue
  - **Recruitment of mononuclear cells** → accumulation of neutrophils, complement, cytokines[25]

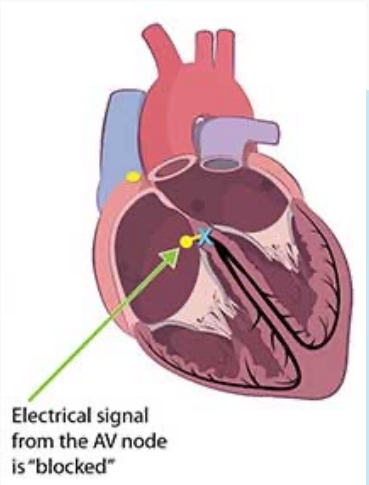
EFFECTS ON CARDIOVASCULAR SYSTEM

Lyme carditis

Caused by inflammatory response to *B. burgdorferi* infection of the peri/myocardium, leading to tissue damage[26,27]



- **Disruption of normal electrical signaling** from atrioventricular node → interference with coordination of heartbeat[27]
- **Heart block** - impairment of electrical signal controlling contraction of heart chambers[26]
- Symptoms:
  - Shortness of breath
  - Fainting
  - Chest pains
  - Light-headedness
  - Palpitations



(6) Diagram of third-degree heart block. Reprinted from CDC.

EFFECTS ON NERVOUS SYSTEM

1 LYMPHOCYTIC MENINGITIS

- Pathogen binds to endothelium and infiltrates central nervous system → **inflammatory cascade**
- Damage to meningeal lining → **lymphocyte infiltration**[29]
- Formation of **neuronal lesions** from accumulating lymphocytes and plasma cells[30]
- Symptoms: fever, headaches, light sensitivity, stiff neck[31]

2 RADICULONEURITIS

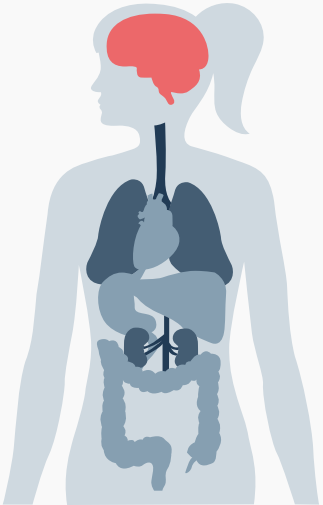
- Damage to **peripheral nerves**[31]
- Symptoms: numbness, tingling, pain, limb weakness

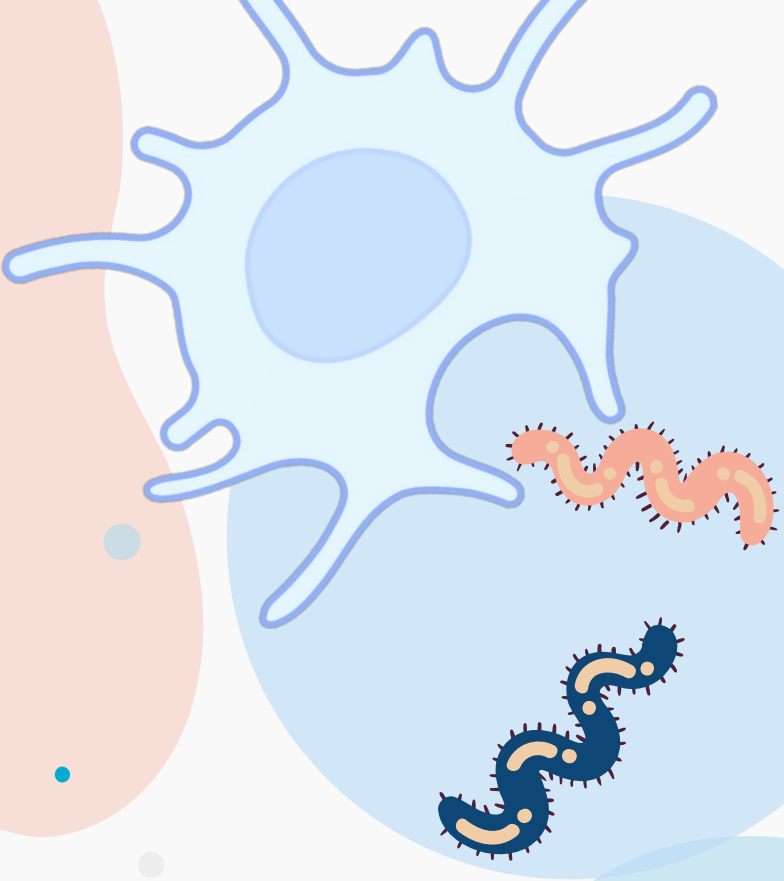
3 CRANIAL NEURITIS

- Damage to **cranial nerves**[31]
- Symptoms: facial palsy

"Classic Triad"

Three nervous tissue pathologies associated with prolonged *B. burgdorferi* infection[28,30,32]





03

BACTERIAL EVASION

How does the bacteria attempt to evade these host response elements?

Dendritic cell icon from Biorender.com

COMPONENTS OF TICK SALIVA[33]

SALP15[34]

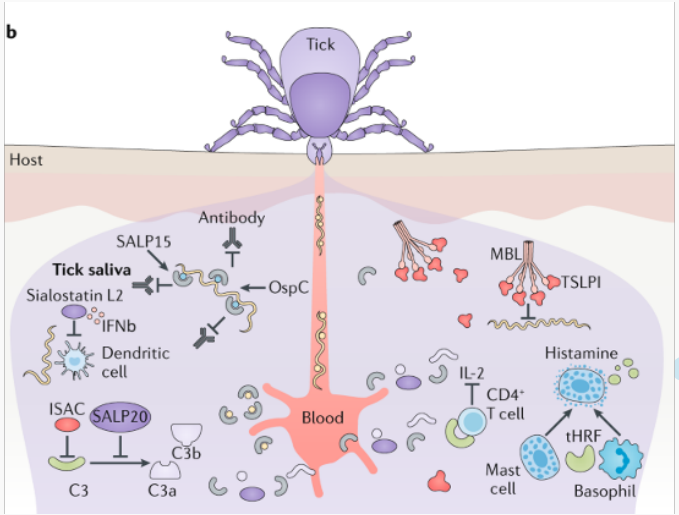
- Inhibits antibody-mediated, **classical** complement pathway
- Binds **OspC** on pathogen
- Inhibits formation of **membrane attack complex** (MAC)[35]

SALP20[34]

- Inhibits **alternative** complement pathway
- Binds and deactivates C3 convertase[33]

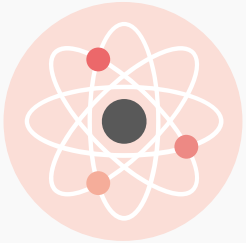
Tick Salivary Lectin Pathway Inhibitor (TSLPI)[34]

- Inhibits **lectin** complement pathway
- Obstructs mannose-binding lectin (MBL)-dependent C4 activation[33]



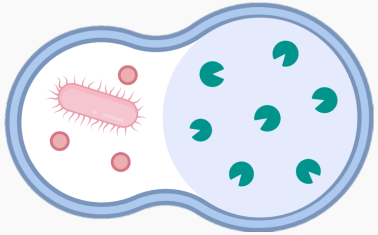
(7) Immunoregulatory components of tick saliva. Reprinted from Kurokawa et al..

RESISTANCE TO ROS and AMPs



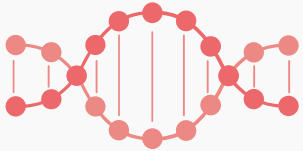
Lactoferrin

- Iron-binding transport protein
- *B. burgdorferi* **does not require iron** as a cofactor for survival → uses manganese[36]



Lysosomes

- *B. burgdorferi* has **limited susceptibility** to lysosomal-mediated killing

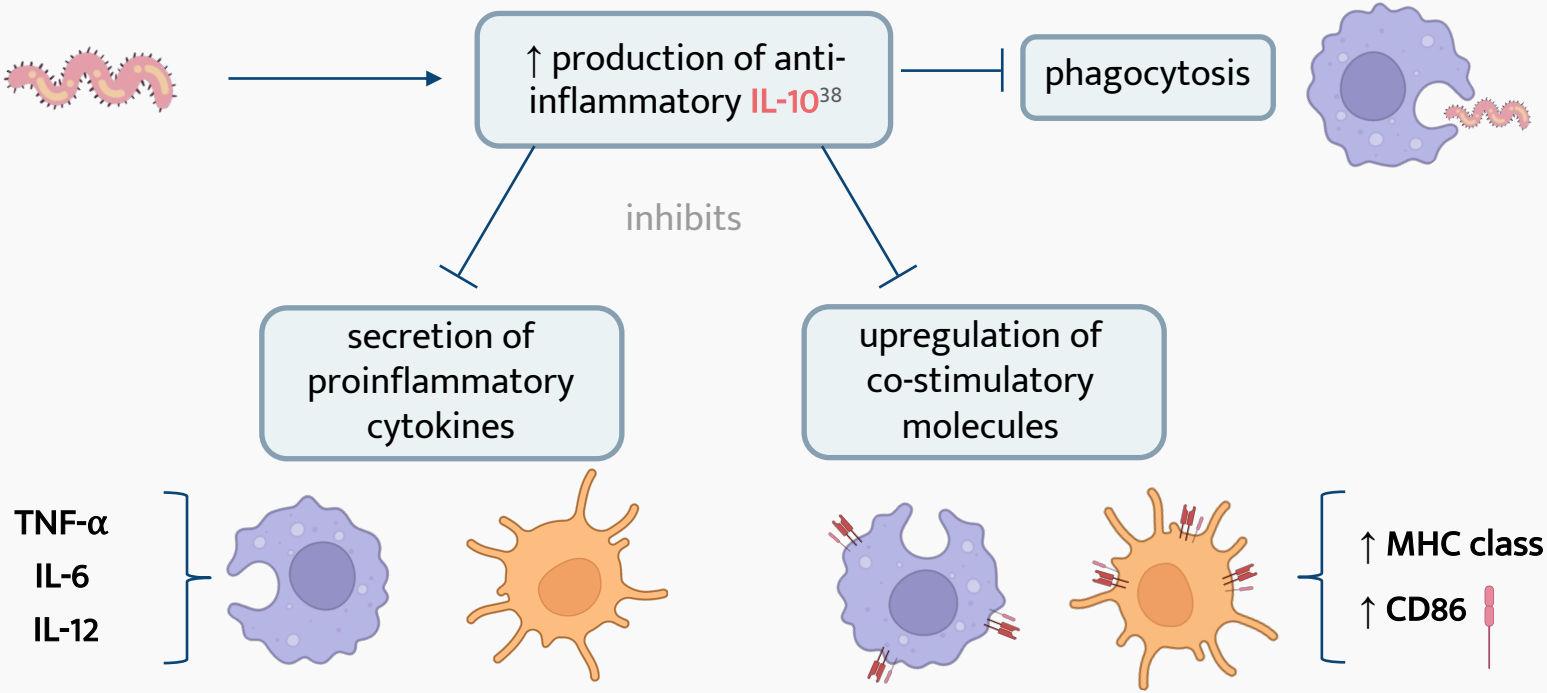


ROS and RNS

- ROS and RNS cause oxidative damage to DNA, proteins, tissues
- *B. burgdorferi* encodes genes for **DNA repair enzymes**, ribonuclease, transport proteins[17,37]

Phagolysosome icon from Biorender.com

EVASION OF PHAGOCYTOSIS



EVASION OF COMPLEMENT

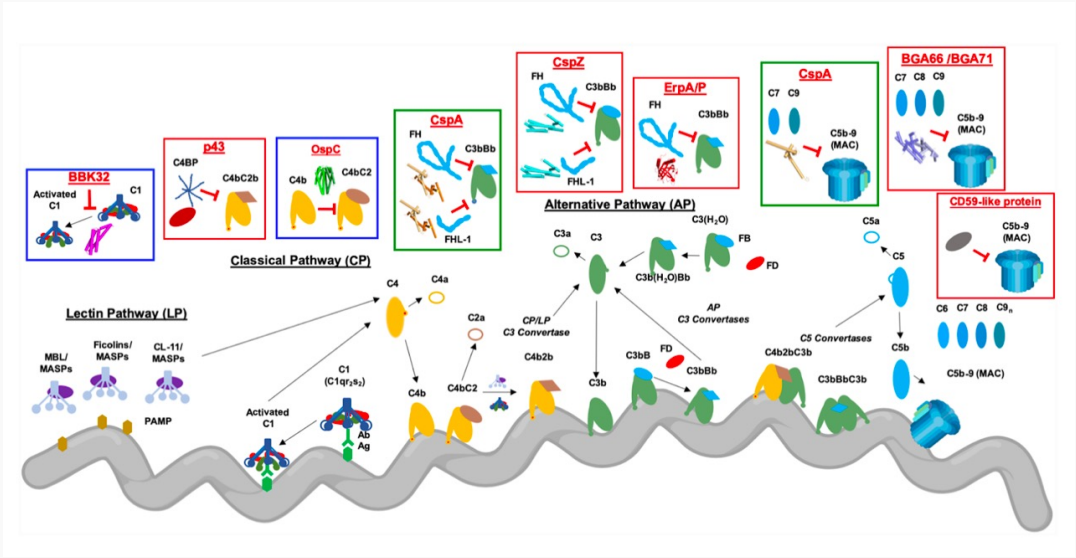
PROBLEM:

Complement is **abundant in blood** and causes opsonization, phagocytosis, and lysis of invading pathogens

SOLUTION:

B. burgdorferi **outer surface proteins** can inhibit complement activation, amplification, and terminal steps[39,40]

EVASION OF COMPLEMENT (cont)



BBK32 prevents formation of C1 complex, inhibiting early stage of classical pathway[39]

P43 recruits C4b-binding protein, downregulating classical and lectin pathway[39]

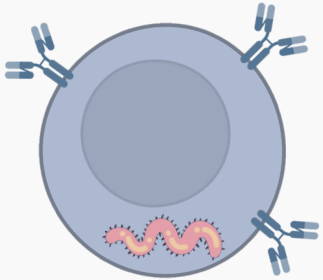
OspC prevents formation of C3 convertase, inhibiting activation of both classical and lectin pathways[40]

CspA and **CspZ** bind factor H and factor H-like protein, preventing complement-mediated opsonization[41]

CspA prevents formation of membrane attack complexes (MACs) and subsequent lysis[40]

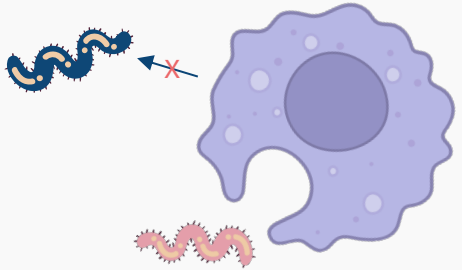
(8) Complement evasion mechanisms by *B. burgdorferi*. Reprinted from Skare & Garcia

EVASION OF ADAPTIVE IMMUNE RESPONSE



Infiltration of B cells

- *B. burgdorferi* may be able to infiltrate B cells[42]
- **Prevent** B cells from **recruitment** and **proliferation**
- Persistence within secondary infection sites[42]



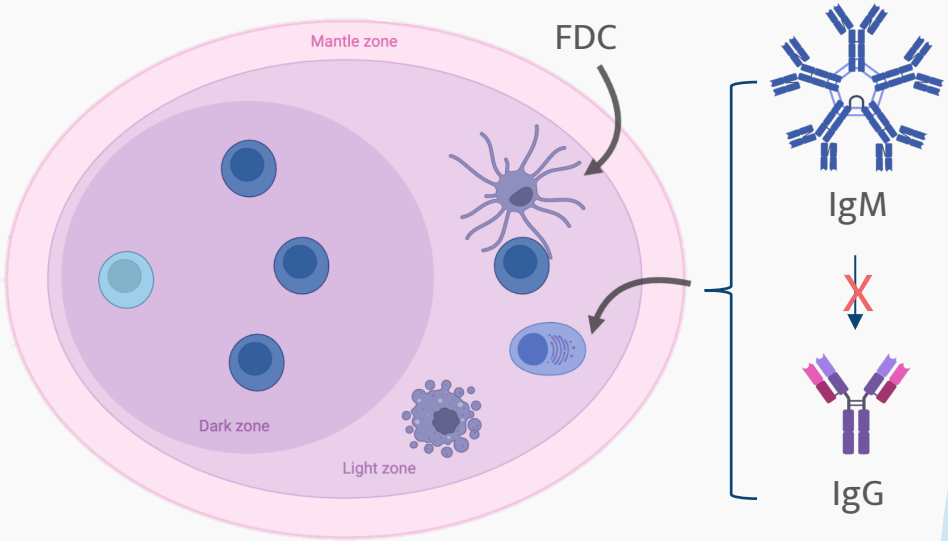
Antigenic variation

- **Altered surface molecule expression** to avoid recognition by host immune system
- Via random segmental **recombination** of genes (vlsE, OspC)[42]
- **Downregulation of OspC** expression after initial colonization prevents strong antibody response[42,43]

EVASION OF ADAPTIVE IMMUNE RESPONSE (cont)

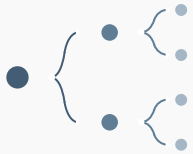
Defective germinal centers

- Serum IgM antibodies remain high during infection (**minimal class switching to IgG**)
- **Lack of sustained germinal center formation**[33]
- Due to **decline in Tfh levels** and **follicular DC mislocalization**[33,44]
- Pathogen thought to interfere with antigen presentation on FDCs via complement[39,40]



Class switching occurs in the Light zone of germinal centers

OTHER MECHANISMS OF EVASION



IMMUNOSPRESSION

- Exploitation of IFN pathways[45]
- Inhibition of **T cell function**

BREAKDOWN OF CONNECTIVE TISSUES

- Promotes **motility** and **invasion** into skin[46]

EXPRESSION OF ADHESINS

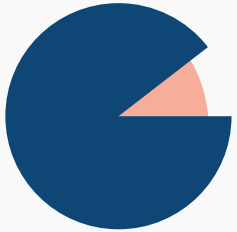
- Virulence factor **BBK32** allows bacteria to halt and enter vasculature[42]
- Promotes **invasion** of bloodstream

04

OUTCOME

Is the bacteria completely removed? Does the patient recover fully? Is these immunity to future infections from this particular bacteria?

POST-LYME DISEASE SYNDROME (PLDS)



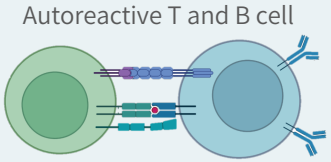
15%

of patients have persistent symptoms even after oral antibiotic treatment[47]

- Lyme disease symptoms **persist after antibiotic treatment**: joint and muscle aches, cognitive dysfunction, fatigue

May be due to:

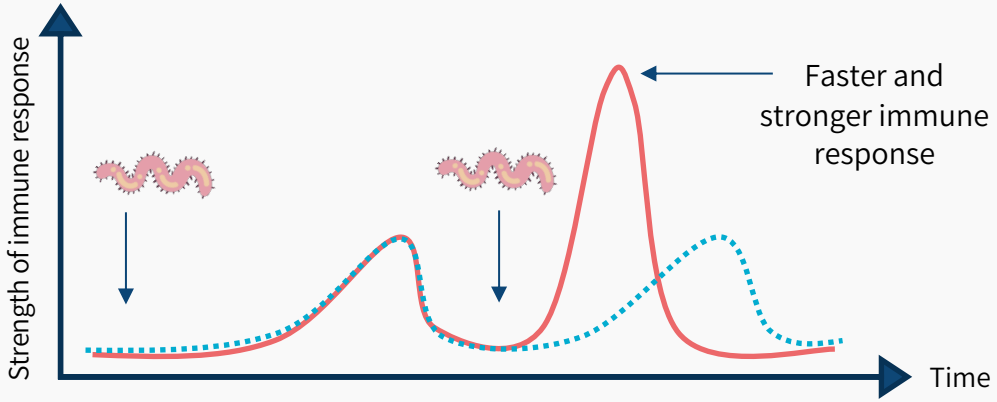
Hidden reservoirs of *B. burgdorferi* persisting in host[48]



Initial *B. burgdorferi* infection triggering **auto immune responses**[48]

- **No known treatment**
- Prolonged dosage of antibiotics can damage organs and disrupt normal host microbiota[49]

IMMUNE MEMORY



Classic immunological memory

Suggested immunological memory during *B. burgdorferi* infection

- Immune memory is **strain-specific** → develops against surface proteins (e.g. OspA)[50]
- **Antigenic variation** allows *B. burgdorferi* to evade antigen-specific memory immune responses[51]
  - Reinfection by same strain possible → suggests **initial infection does not produce long-term protective immunity**[52]
- May be due to host being **unable to form sustained germinal centers** for formation of memory B cells and class switching → lower levels of IgG and memory B cells can render host unable to resolve subsequent infections[53]

RELAPSE

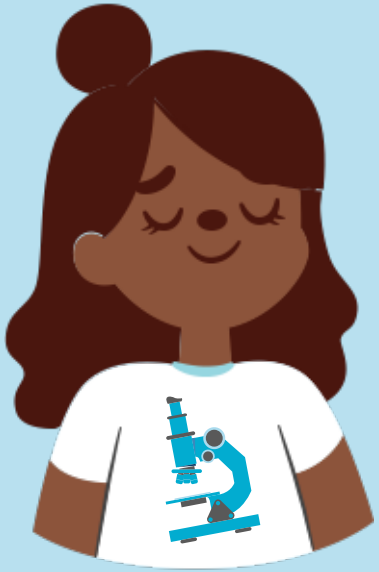
Reinfection

- Typically occurs during **spring/summer**
- Tick bite (punctum) present
- Can occur **years after** initial infection[55]

Symptoms of *B. burgdorferi* infection following an initial infection[54]

Relapse

- Independent of seasonality[54]
- Tick bite (punctum) **absent**
- Occurs when **treatment** of *B. burgdorferi* infection is **delayed or absent**
- **Within 1 year** of initial infection[54]



SUZANNE'S CASE

Since Suzanne was treated within days of the initial infection, she is expected to make a full recovery – a happy ending to an eventful vacation!

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IMAGE SOURCES

Immune cell icons were sourced from Biorender.com.

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