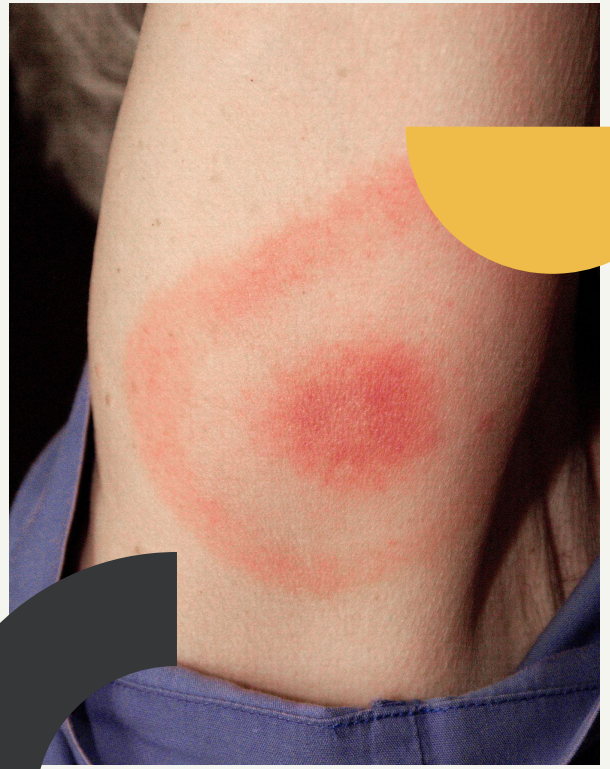
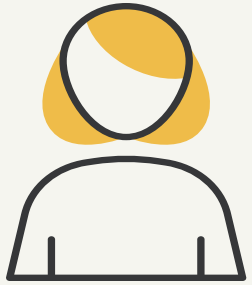
HOST IMMUNE RESPONSE - LYME DISEASE

Yisa Yu



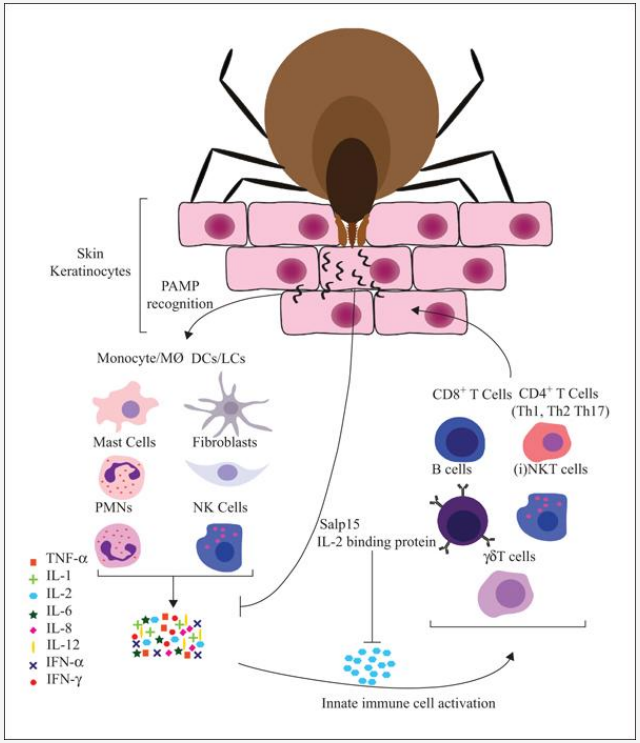
PATIENT OVERVIEW



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. 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.**

Host Response

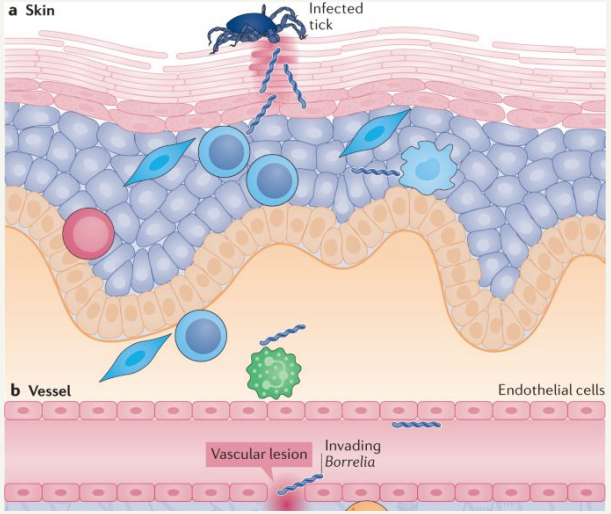
- Innate Immune Response + Adaptive (Humoral and Cellular) Immune Response
- Innate immune system is the first line of defense and involves:
  - Langerhans cells (LCs)
  - Effector cells
  - Pathogen associated molecular patterns (PAMP) recognition
  - Complement system
  - Mannose binding lectin (MBL) protein
  - Reactive oxygen species (ROS)
  - Antimicrobial peptides (AMPs)
  - Extracellular traps
  - Inflammation
- Erythema migrans develops
- Fevers, headaches, malaise, arthralgia, swollen lymph nodes may be observed as early symptoms



INNATE IMMUNE RESPONSE

Innate Immune Response

- Physical barriers
  - Tight junctions in the skin
  - Epithelial and mucous membrane surfaces
  - Mucus
- Anatomical barriers
- Chemical barriers
  - Secretion of AMPs
  - Soluble mediators
- Signalling transduction system
  - Complement cascade
- Innate cells
  - Macrophages
  - Dendritic cells
  - Granulocytes
  - Natural killer cells

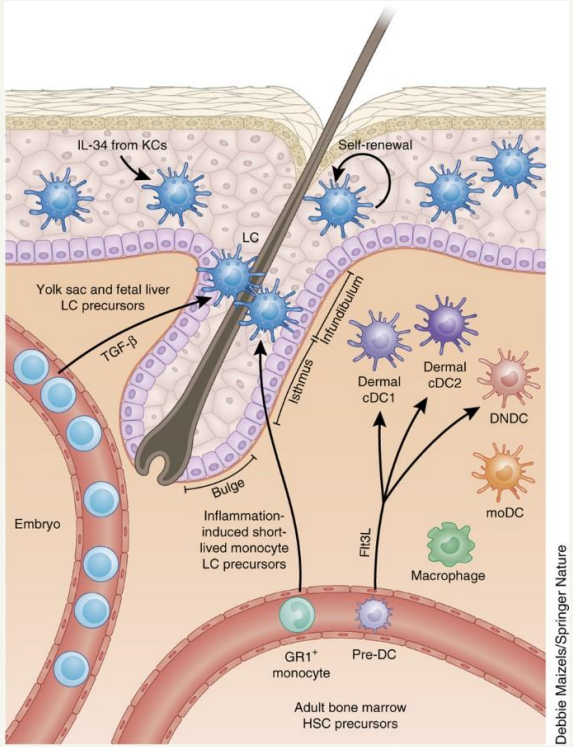


<u>In Suzanne's case:</u>

- Physical barrier of the skin has been breached
- Bacteria entered the dermis and into bloodstream, as well as infecting endothelial cells

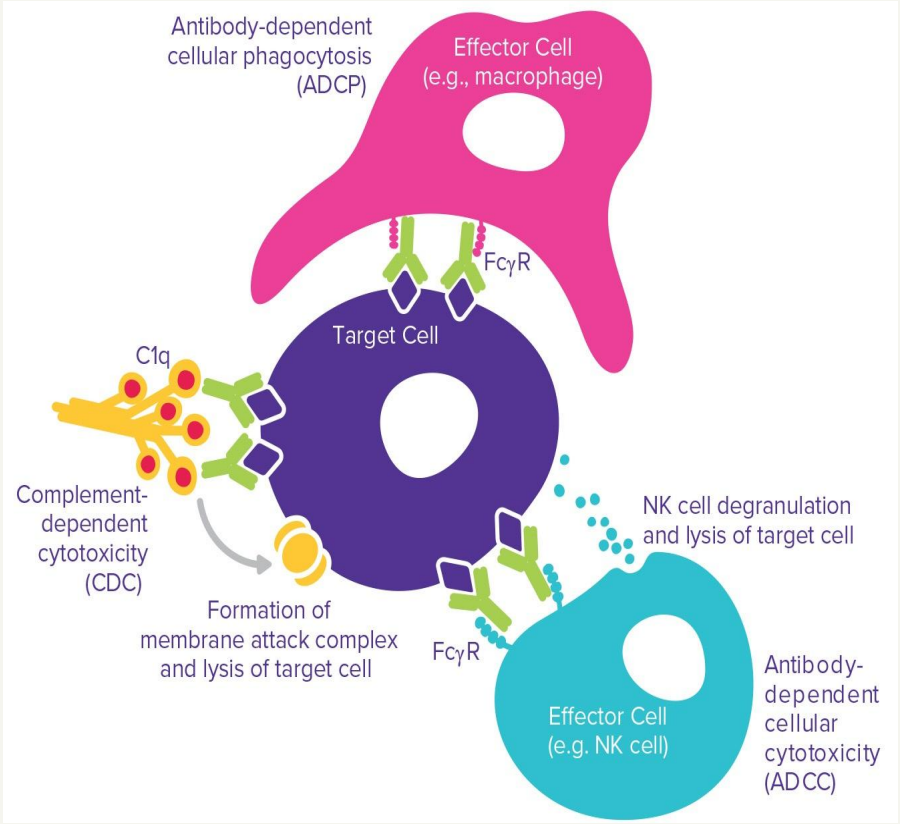
Langerhans cells (LCs)

- First immune cells encountered by Borrelia burgdorferi
- found in the epidermis near the dermal interface and express pattern recognition receptors (PRRs) that allow them to recognize pathogens encountered near the skin surface
- leads to the upregulation of MHC class II and migration to lymph nodes to present antigens to lymphocytes



Debbie Maizels/Springer Nature

Effector Cells

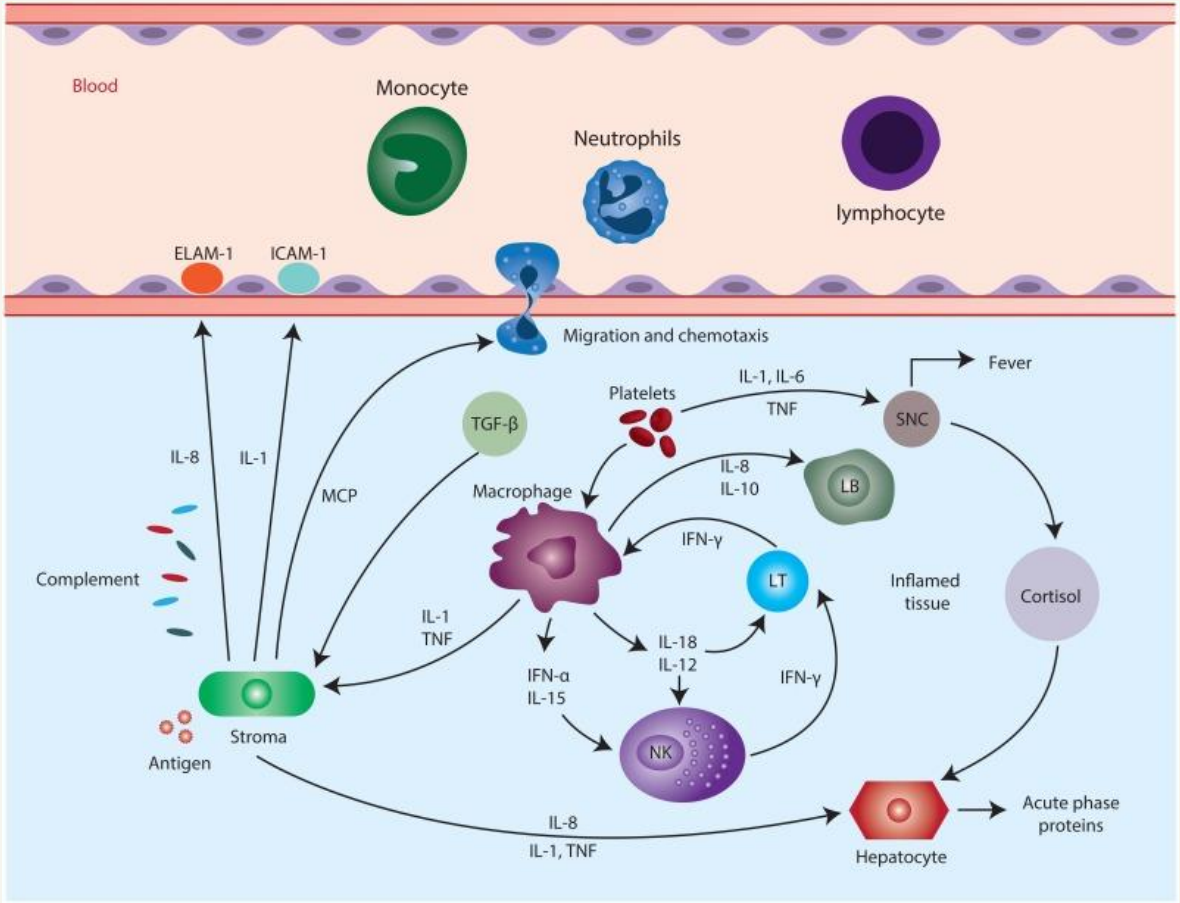


- Includes **phagocytic cells**, **epithelial and endothelial cells**, **natural killer cells**, **innate lymphoid cells** and **platelets**
- Majority of cell components have **PRRs** on cell surface and release **cytokines**
- **Antigen presenting cells** (eg. dendritic cells, macrophages) contain **pattern-recognition receptors** (eg. Toll-like receptors, nucleotide-binding oligomerization domain-like receptors) that involve in recognizing B. burgdorferi

Effector mechanism

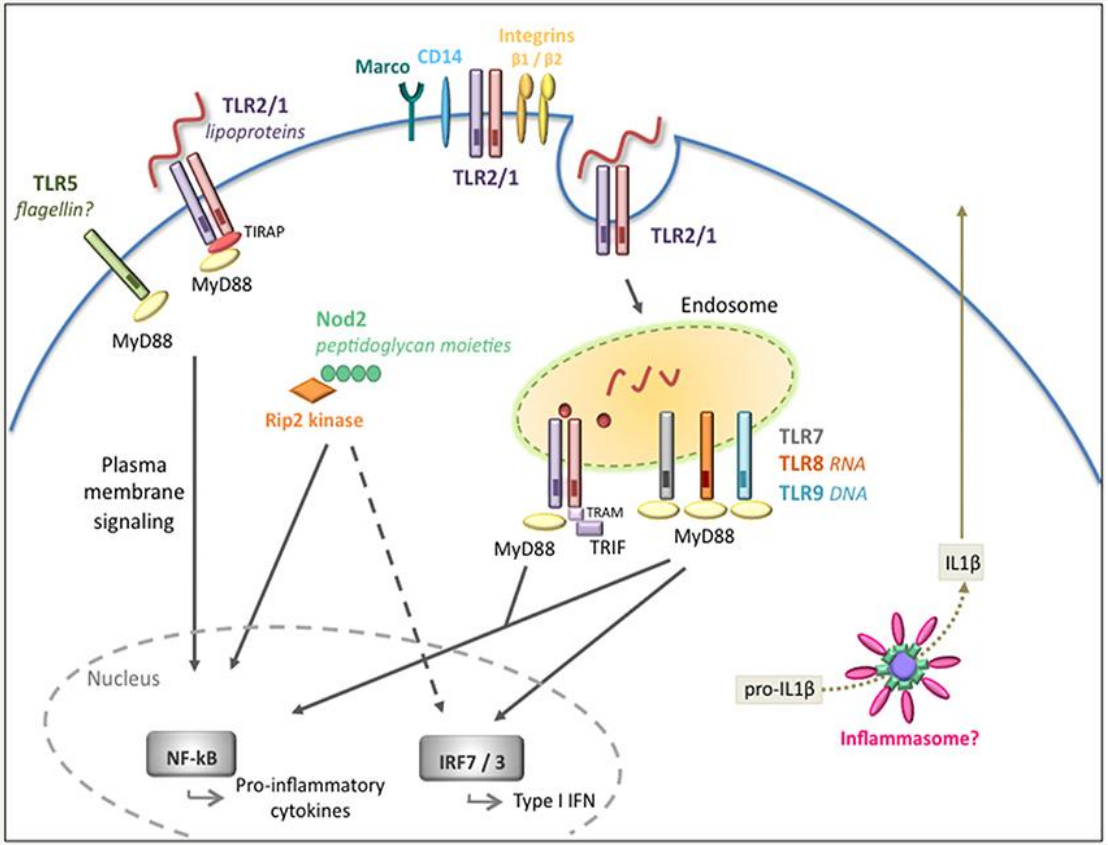
Neutrophils	➔ recruited by the leukotrienes and migrate to the site of infection within 4 hours of infection ➔ engaged when their PRRs recognize bacteria and initiate phagocytosis ➔ can phagocytose microbes in their proximity and fuse with lysosomes to form phagolysosomes, which become acidified and kill the bacteria
Macrophages	➔ have both an oxygen-dependent and oxygen-independent microbicidal action ➔ an present antigens and activate lymphocytes, then release and stimulate cytokine production ➔ produce extracellular matrix proteins and matrix metalloproteinases (MMP) which regulate the immune response and aid tissue remodelling once the inflammatory process has ended
Dendritic cells	➔ transport and carry antigens from peripheral lymphatic nodes to primary lymphatic nodes ➔ antigen processing and presentation via MHC class II molecules ➔ Can phagocytose pathogens
Natural killer cells	➔ immunoglobulin-like receptor (KIR) and CD94-NKG2A inhibitory receptors identify the MHC class I molecules ➔ Express PRRs and cytokines to support T cell differentiation, stimulate macrophage function, promote leukocyte to migrate to the site of infection
Mast cells	➔ release a variety of cytokines that enhance the inflammatory process ➔ have Fc receptors that engage when IgE binds the bacterial antigen ➔ release cytokines to increase vascular permeability, fluid accumulation and recruit more innate immune cells

Effector mechanism



PAMPs recognition

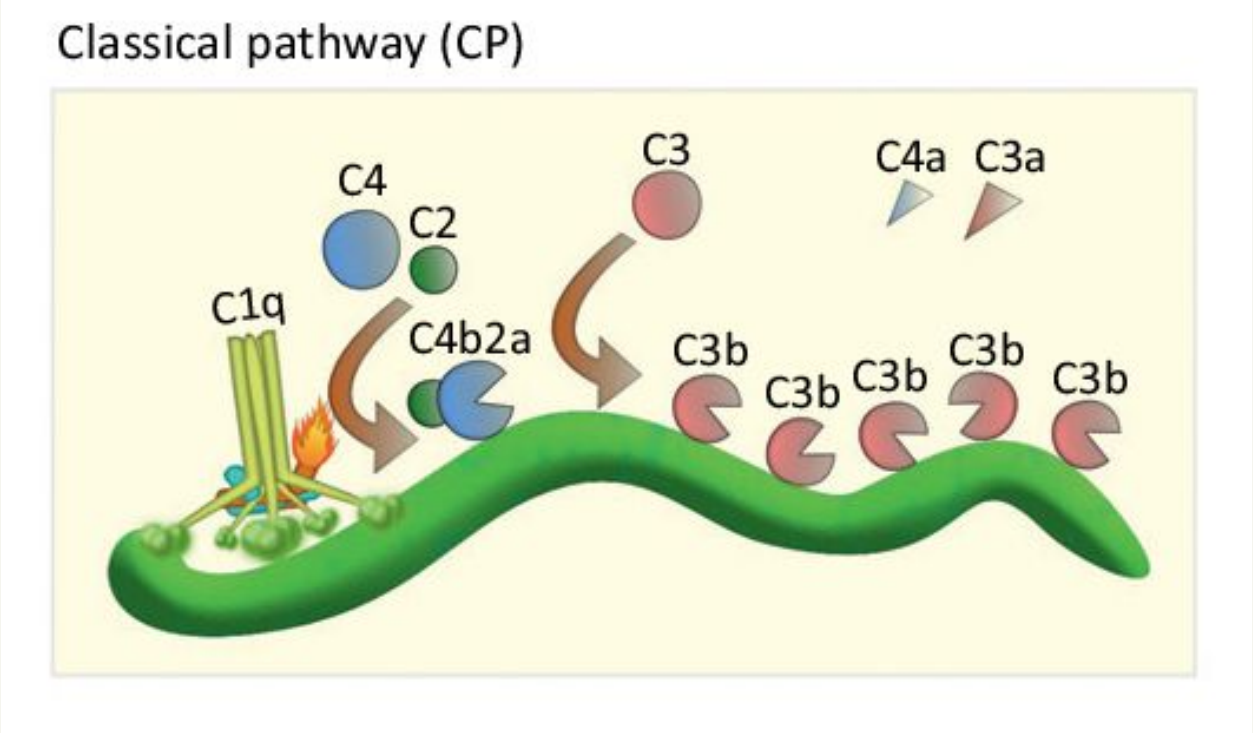
- Through **Toll Like Receptors (TLR)**, **Nucleotide Oligomerization Domain (NOD)-like receptors (NLRs)**, and **C-type lectins (CTLs)**
- Major PAMPs of B. burgdorferi: **OspA**, **OspB** and **OspC**
- **TLR2** can form **heterodimers** with **TLR1** and recognize *B. burgdorferi* **triacylated lipid element** on its cell surface localized lipopeptides
- **TLR4** is secondary in the recognition of *B. burgdorferi* as it requires a certain polysaccharide in order to be activated
- **CD14** is the **co-receptor** for TLR4 and has been known to exhibit its own pathogen-recognizing capacity



Complement System

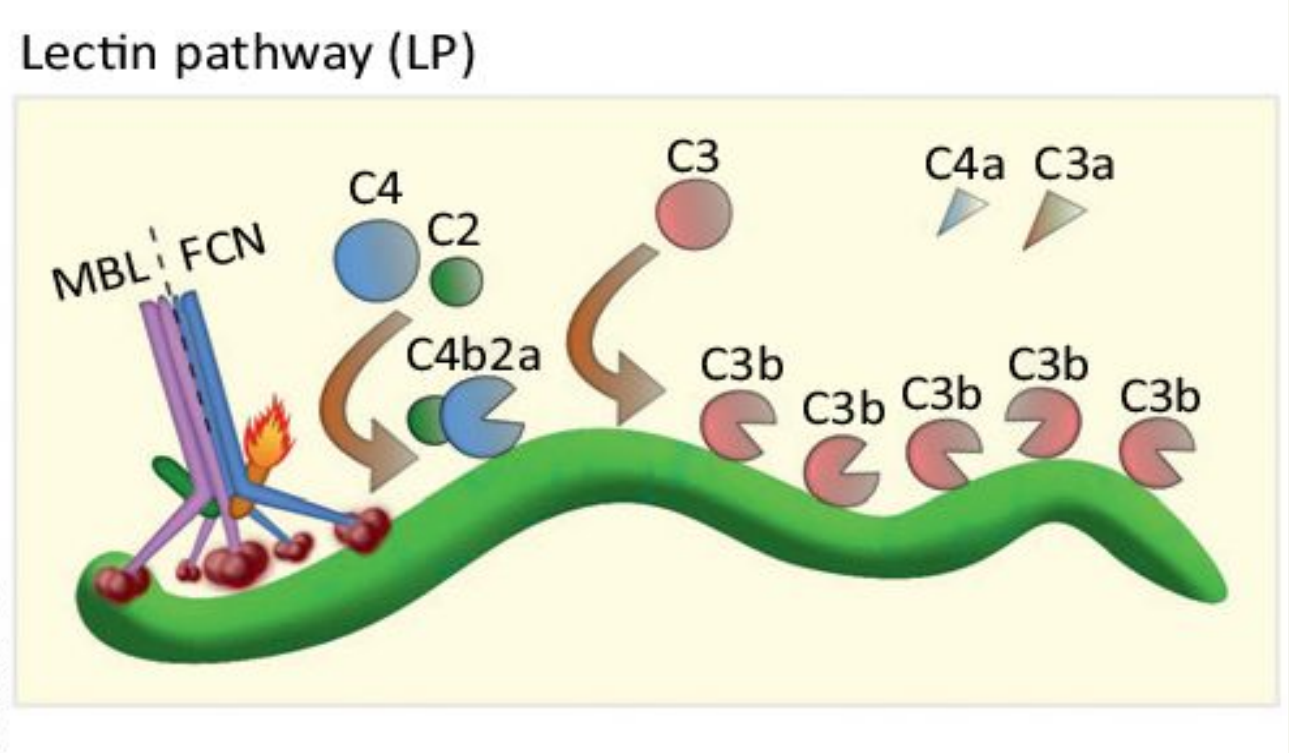
- Induces immune response to invading pathogens, regulate cytokine synthesis, and assist in the removal of immune complexes and dead cells
- Can be activated via 3 pathways:
  - The classical pathway
  - The lectin pathway
  - The alternative pathway
- All 3 pathways result in the formation of membrane attack complex (MAC), leading to cell lysis
- Opsonized Borrelia is then recognized by complement receptor CR1, CR2 and CR3 on phagocytic cells, leading to its destruction.

The Classical Pathway



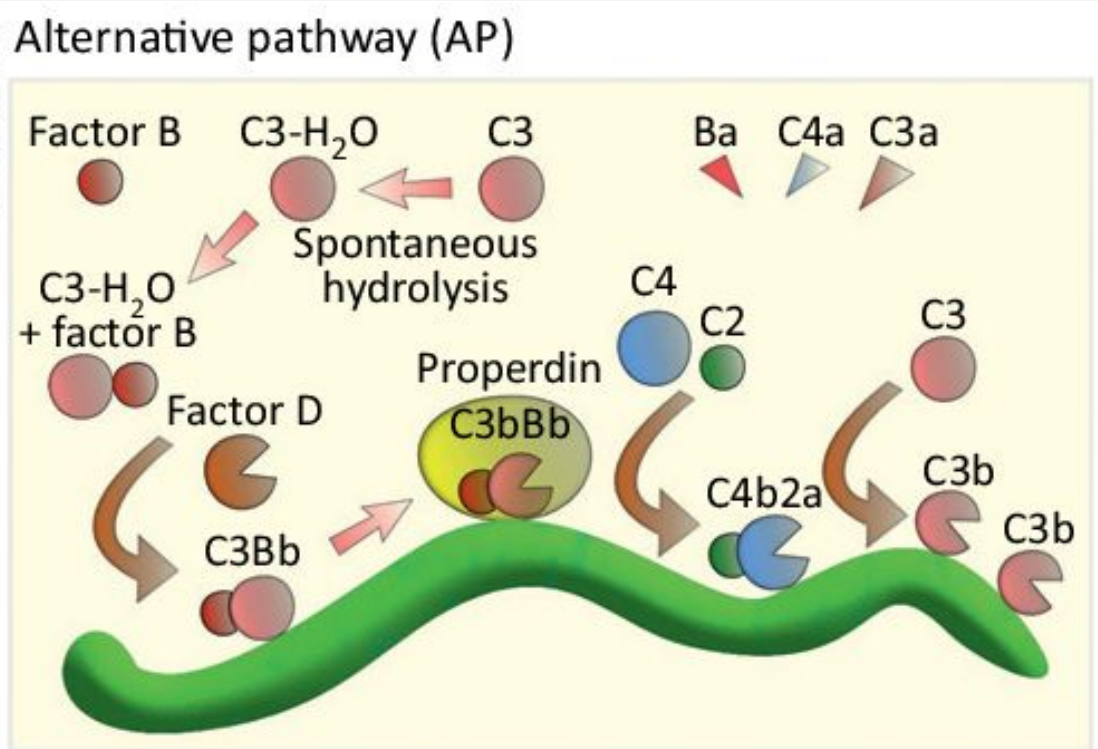
C1q, a complement factor, binds to antibodies (such as IgM or IgG) on the bacterial surface, activating the complement cascade and ultimately the complement components C2 and C4 via the classical pathway

The Lectin Pathway



initiated by lectin binding to carbohydrates on *B. burgdorferi* surface

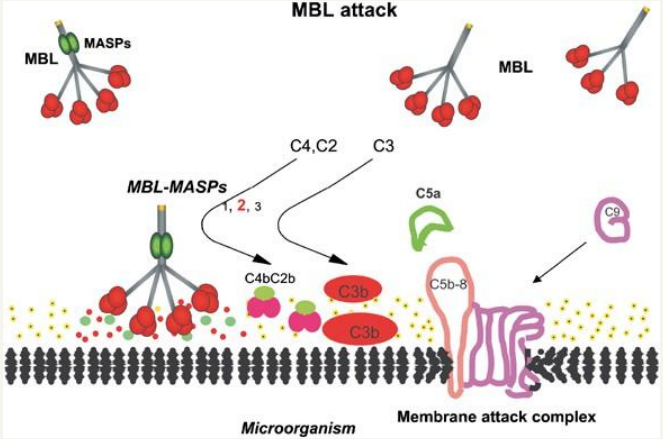
The Alternative Pathway



initiated by the spontaneous activation of C3 on the bacterial surface

Mannose-binding lectin (MBL) protein

- Largely produced in the liver and released into bloodstream
- can identify carbohydrates that function as opsonins and bind and activate complement factors such C1q, increasing the inflammatory response
- Form complexes with MASPs (made up of 2 genes and 5 gene products), and MBL binding to carbohydrate ligands cause conformational changes in the associated MASP, which boost proteolytic activity



Reactive Oxygen Species (ROS)

- Generated by activation of the enzymatic complex nicotinamide adenine dinucleotide phosphate oxidase (NOX2) and include:
  - Superoxide anion
  - Hydrogen peroxide
  - Hydroxyl radical
  - Peroxynitrite
  - Hypocholorous acid
- Nitric oxide generation by inducible nitric oxide synthase (iNOS) is one of the most important microbicidal strategies used by phagocytic cells against a variety of pathogens

Antimicrobial peptides (AMPs)

- Innate and epithelial cells, including keratinocytes, release AMPs, which are host defence peptides
- engaged in a variety of cell activities, including cell migration, proliferation, differentiation, cytokine production, angiogenesis, and wound healing
- Neutrophils and epithelial cells both produce cathelicidin, also known as LL-37, and Gram-negative and Gram-positive bacteria, fungi, and viruses are all susceptible to this AMP
- Defensins include α- and β-defensins

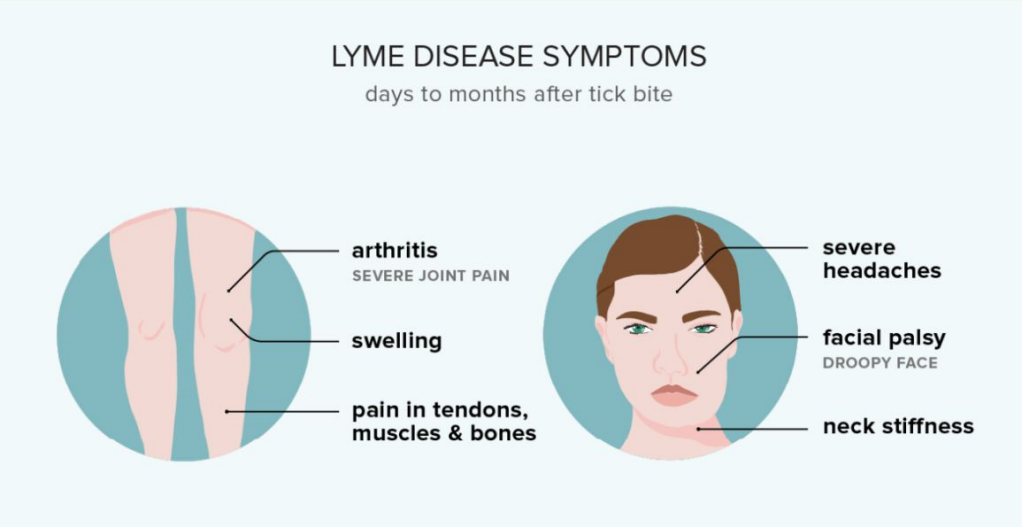
Neutrophils	Paneth cells in GI tract	Keratinocytes
Store α-defensins (hαD-1, -2, -3, -4)	Synthesize HαD-5 and -6	Generate B-defensins (hD-1, -2, -3)

Extracellular traps

- Extracellular DNA traps are involved with viral processes, allergy and autoimmune illnesses, and are part of innate immunity
- Referred to as NETs, EETs, METs, MCETs
- Made up by:
  - DNA
  - Histones
  - Contents of intracellular granules (eg. elastase, myeloperoxidase (MPO), cathelicidins, tryptase, cationic proteins, and major basic protein)
- Triggered by:
  - granulocyte/macrophage-colony stimulating factor (GM-CSF)
  - Interferons
  - IL-8
  - C5a
  - LPS

Inflammation

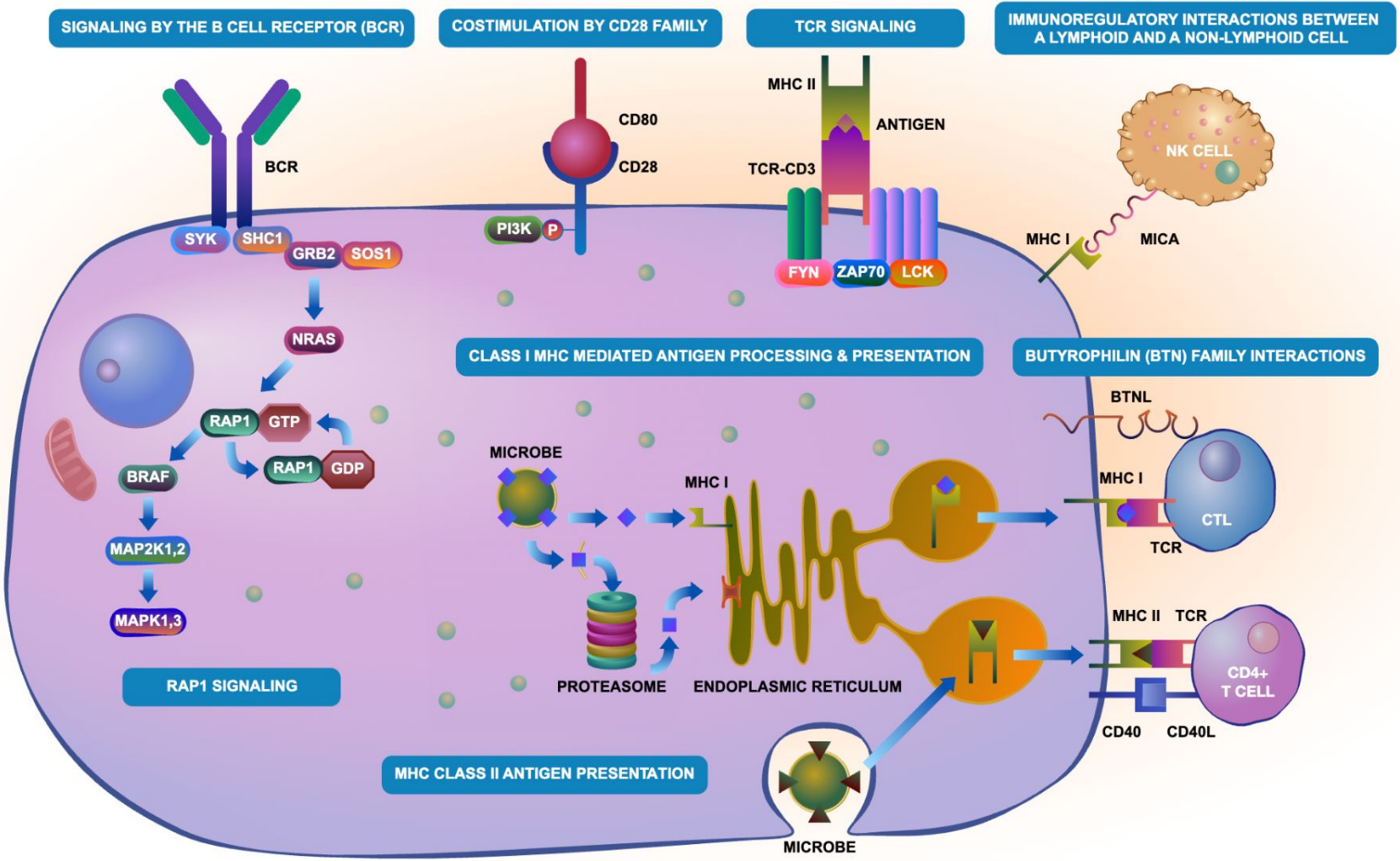
- Indications
  - Redness
  - Swelling
  - Heat
  - Pain
  - Loss of tissue function
- Blood flow and vascular permeability both rise
- Endothelial cell retraction causes vascular permeability, which allows leukocytes to pass through and plasmatic proteins including complement, coagulation factors, and antibodies such as IgG to pass through.



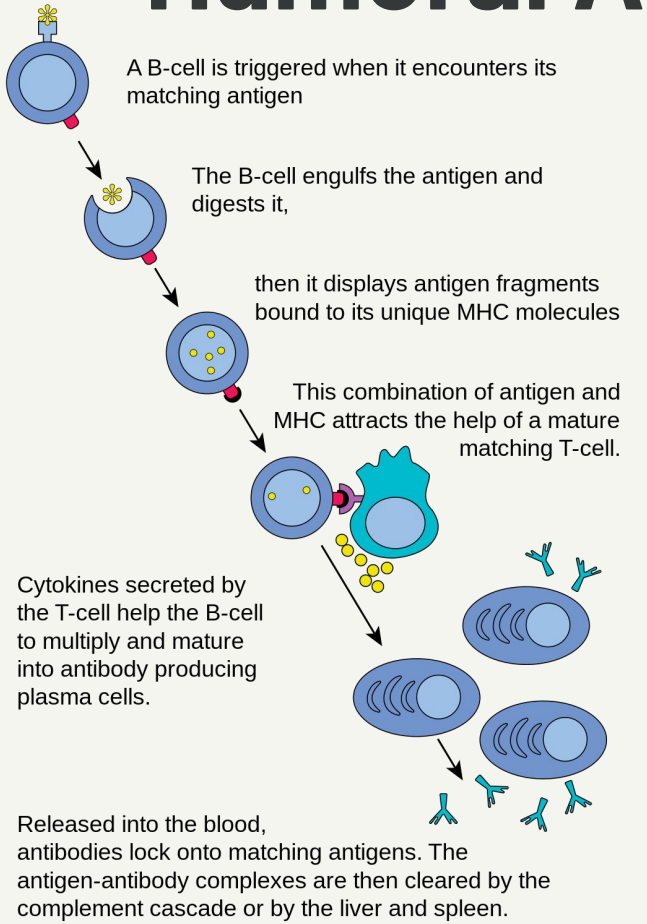
In Suzanne's case:

- Inflammation is the cause of Suzanne's rash feeling:
  - "Hot to touch"
  - "burning"

ADAPTIVE IMMUNE RESPONSE

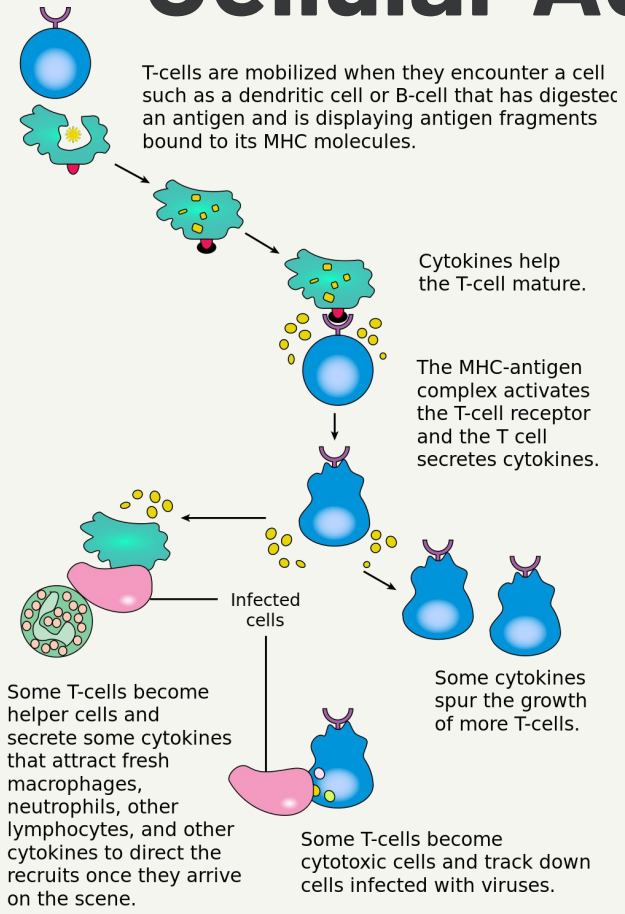

SIGNALING BY THE B CELL RECEPTOR (BCR)
BCR
SYK
SHC1
GRB2
SOS1
NRAS
RAP1
GTP
RAP1
GDP
BRAF
MAP2K1,2
MAPK1,3
RAP1 SIGNALING
COSTIMULATION BY CD28 FAMILY
CD80
CD28
PI3K
P
TCR SIGNALING
MHC II
ANTIGEN
TCR-CD3
FYN
ZAP70
LCK
IMMUNOREGULATORY INTERACTIONS BETWEEN A LYMPHOID AND A NON-LYMPHOID CELL
NK CELL
MHC I
MICA
CLASS I MHC MEDIATED ANTIGEN PROCESSING & PRESENTATION
MICROBE
MHC I
PROTEASOME
ENDOPLASMIC RETICULUM
BUTYROPHILIN (BTN) FAMILY INTERACTIONS
BTNL
MHC I
CTL
TCR
MHC II
TCR
CD4+ T CELL
CD40
CD40L
MHC CLASS II ANTIGEN PRESENTATION
MICROBE

Humoral Adaptive Response



- IgM and IgG antibodies respond to *B. burgdorferi* antigens such as OspA, OspC and flagellar antigen B
- High levels of *B. burgdorferi* antigen-specific antibodies are produced to prevent reinfection with the same *B. burgdorferi* strains
- CD4 T follicular helper cells (Tfh) along with follicular dendritic cells (FDCs) are essential for the formation of germinal centers, which is where B cells undergo:
    - Proliferation
    - Class-switching
    - affinity maturation
    - production of long-lived memory cells
- IgG does not appear to contribute significantly to the long-term Ab responses
    - contributes to the persistence of *B. burgdorferi* in the host as well as host susceptibility to reinfection

Cellular Adaptive Response

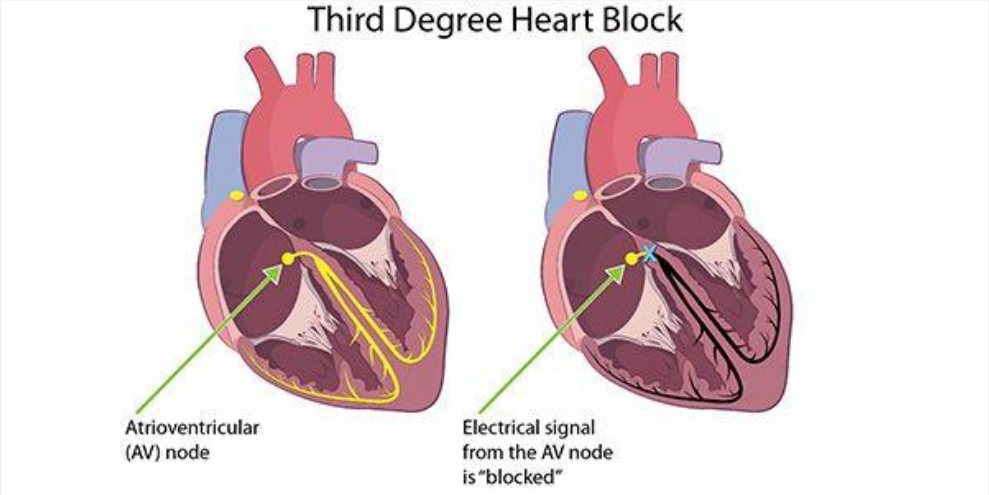


- Infection with *B. burgdorferi* causes CD4+ T cells to develop into T Helper 1 (TH1) cells, which generate IFN and TNF
- the induction of TH1 cells is mediated by IL-12 production by DCs
- When infected with *B. burgdorferi*, CD4+ T cells differentiate into T Helper 17 (TH17) cells in the absence of external IFN
- TH17 release Inflammatory cytokines such as IL-17A, IL-22, and TNF
- The combination of IL-17A and TNF can then cause macrophages to produce and release NO and ROS
- Many of the pro-inflammatory cytokines produced are responsible for Suzanne's symptoms, including her fever

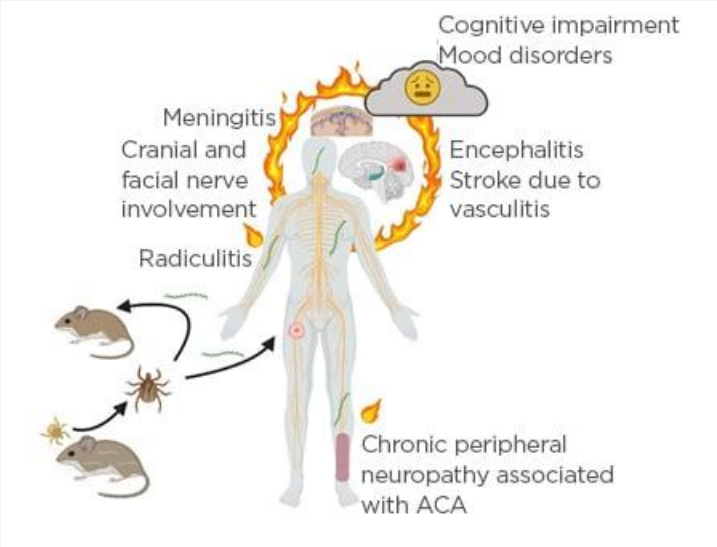
HOST DAMAGES FROM IMMUNE RESPONSE

Effects on the Cardiovascular System

- disrupt the normal electrical signaling of the heart at the atrioventricular level, leading to defects in the coordination of heart contractions
- Mild heart block can occur
- Symptoms:
  - Shortness of breath
  - Fainting
  - Chest pains
  - Lightheadedness
  - Palpitation
- production of reactive oxygen species (ROS) causes oxidative stress
  - induce changes in blood consistency
  - harm to adjacent host cells
  - induce oxidative damage to host cell DNA, proteins, and lipids



Effects on the Nervous System

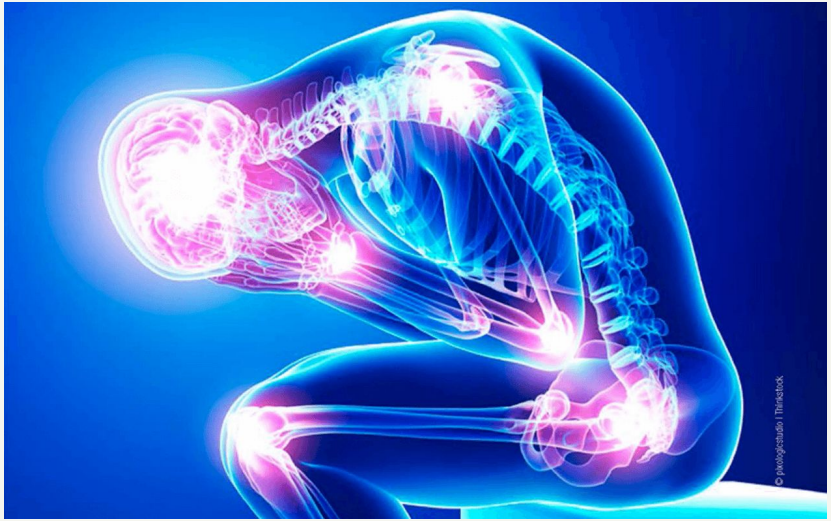


Affected regions	Cranial nerves	Peripheral nerves	Central nervous system
symptoms	Facial palsy	radiculoneuritis (numbness, tingling, pain, or weakness)	fever, headaches, light sensitivity, and a stiff neck

- May result in:
  - Slower thinking
  - difficulty with concentration
  - difficulty with remembering
- “Classic triad”
  - lymphocytic meningitis
  - Radiculoneuritis
  - cranial neuritis
- meningeal lining or brain parenchyma can be damaged due to the inflammation of peripheral nerves
- lymphocytes can then infiltrate:
  - the dorsal root ganglia
  - nerve roots
  - gray matter of the central nervous system components
  - the brain and the spinal cord

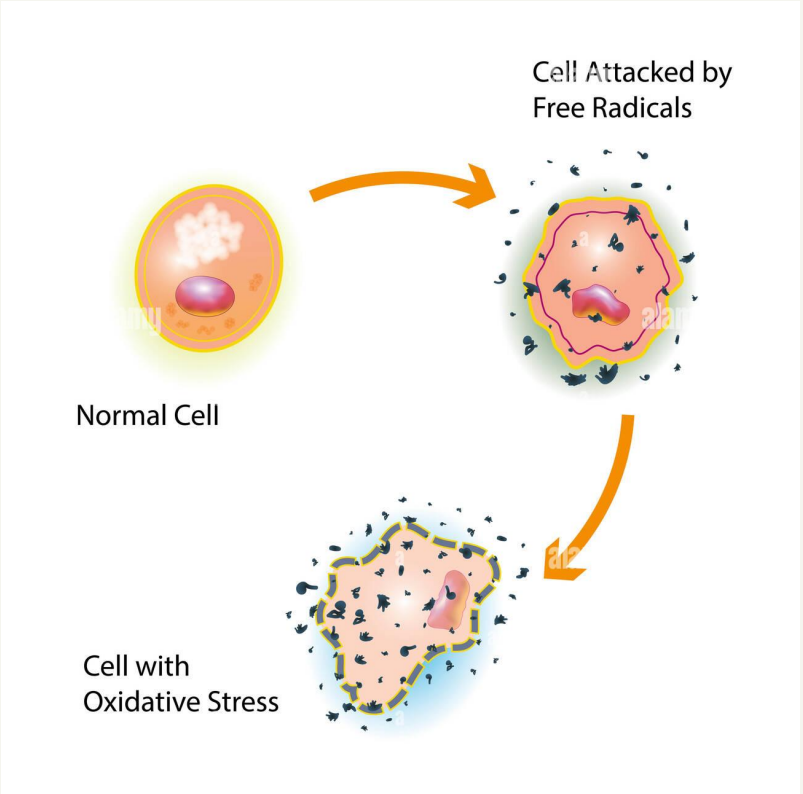
Chronic Inflammation

- Lyme arthritis develops when *B. burgdorferi* penetrates joint tissue and causes inflammation
- sometimes referred to as slow, long-term inflammation that lasts for several months to years
- increased vascular permeability of blood vessels and increased blood flow to the site of inflammation
- requires a large amount of metabolic energy
- frequently leads in damage and destruction of host tissues

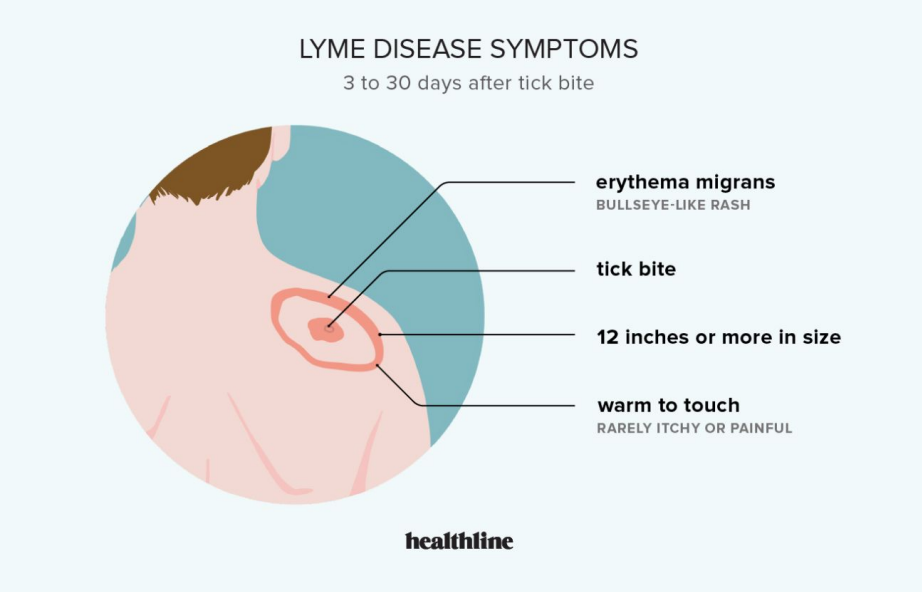


Oxidative Stress

- Caused by production of reactive oxygen species (ROS) by neutrophils and macrophages
- induce changes in blood consistency as well as harm to adjacent host cells
- induce oxidative damage to host cell DNA, proteins, and lipids, which can lead to inflammation and cell death
- the immunological response to infection causes oxidative stress-mediated endothelial injury, which can lead to endothelial cell death



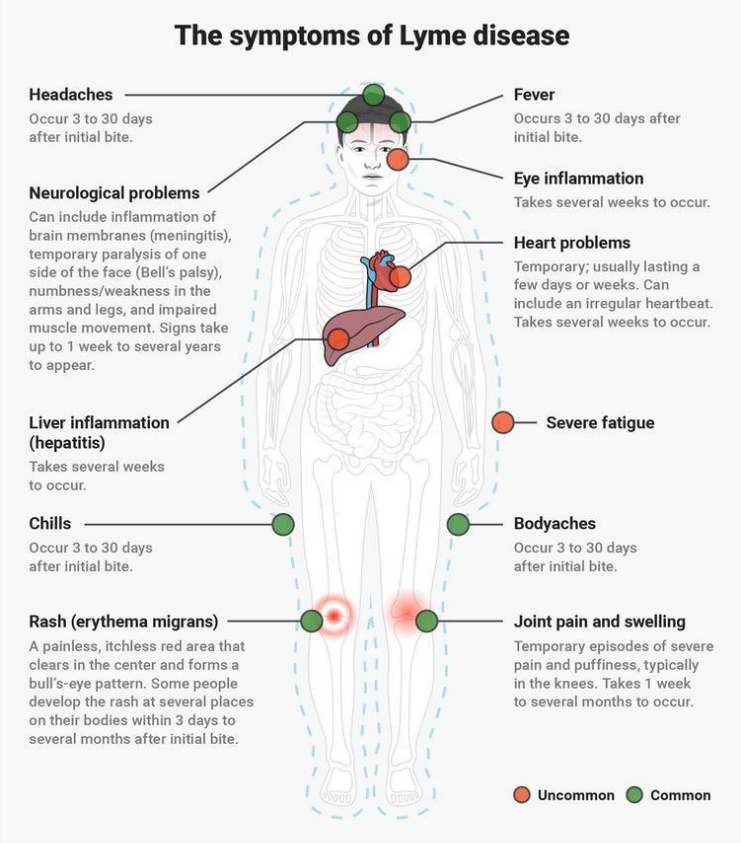
Rash and skin/organ damage



- the immune response towards the salivary proteins of the tick causes the central rash
- As the bacteria spread outwards from the point of entry, the rash expands, developing the outer circle observed in erythema migrans
- The bullseye pattern is produced due to rapid macrophage clearance from the infection site
- Slower macrophage clearance from the tissues would lead to a more homogenous rash

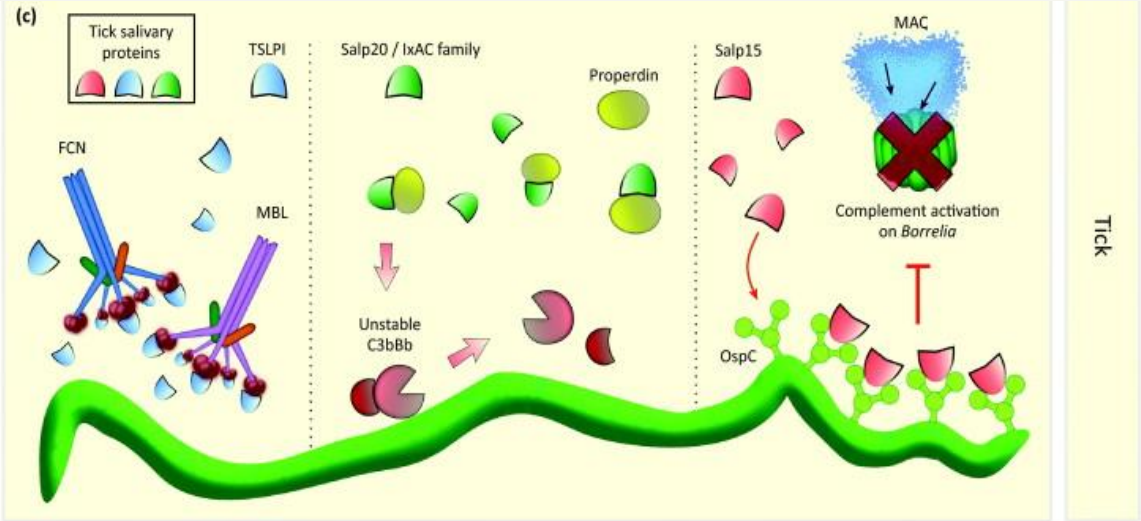
Rash and skin/organ damage

- infection can spread to joints, the heart, and the nervous system if left untreated
- The final and most severe stage of Lyme disease is characterized by arthritis at the lower joints, which can be accompanied by carditis and neuropathy
- the patient may experience joint swelling and/or pain most commonly in:
    - Knees
    - Shoulder
    - Ankle
    - Elbow
    - Jaw
    - Wrist
    - Hip
- The bacteria invasion leads to the recruitment of mononuclear cells into the infected joint tissue, as well as host matrix metalloproteinases



BACTERIAL EVASION

Bacterial evasion - Ticks



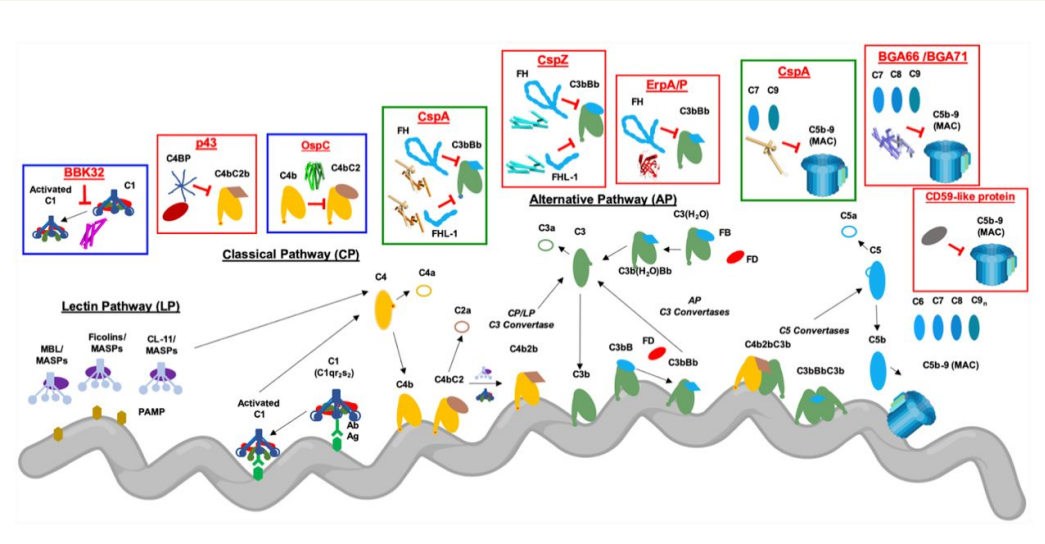
- Salp15
  - a tick salivary protein
  - binds to OspC
  - protect the bacterium from antibody-mediated killing
  - inhibit a portion of the membrane attack complex (MAC)
- Salp20
  - inhibit the complement alternative pathway
  - dissociate C3 convertase components by binding and dissociating C3BbP

- Tick Salivary Lectin Pathway Inhibitor (TSLPI)
  - reduces complement-mediated killing
  - interferes with the complement lectin pathway cascade through obstruction of the mannose-binding lectin (MBL)-dependent C4 activation
  - results in impaired neutrophil phagocytosis and chemotaxis
  - diminished lysis of *B. burgdorferi*

B. burgdorferi - host response evasion

- has resistance to antimicrobial proteins and a limited susceptibility to lysosomes because it does not require iron for survival
- can interfere with phagocyte activities by causing an increased production of anti-inflammatory interleukin IL-10
    - IL-10 suppresses the secretion of proinflammatory cytokines TNFα, IL-6, and IL-12
    - leads to suppression of phagocytosis by macrophages
    - Leads to a decrease in the production of proinflammatory mediators and co-stimulatory molecules
- encodes genes that provide resistance to ROS and RNS for important proteins such as DNA repair enzymes, ribonuclease, and transport proteins
- uses a manganese cofactor rather than iron so that DNA damage is less likely to occur

B. burgdorferi - Complement Inhibition



- **BBK32** binds to **C1r** and traps C1 in a zymogen state, preventing **C1 complex formation**
- **OspC** binds **C4b** and interferes with the activation of both the **classical pathway** and **lectin pathway**
- Bacterial **P43** recruits **C4b-binding protein (C4BP)**, downregulating the **classical pathway** and **lectin pathway**
- **CspA** and **CspZ** bind **factor H (FH)** and **factor H-like protein 1 (FHL-1)**, which are negative regulators that inhibit activation of the **alternative complement pathway**
- **CspA** binds **C7** and **C9** and blocks C9 polymerization

B. burgdorferi – host response evasion

B. burgdorferi may be able to infiltrate B cells and prevent them from recruitment and proliferation so that the pathogen is able to persist for a longer period of time in these secondary sites it travels to

B. burgdorferi escapes the host adaptive immune response through antigenic variation

- ➔ achieves this through random segmental recombination of genes at the vls locus
- ➔ downregulated after infection is established to avoid antibody targeting

B cell functionality is not optimal in *B. burgdorferi* infections

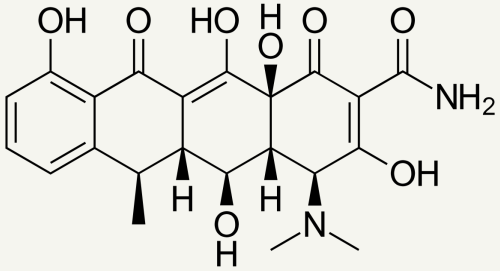
- ➔ serum IgM levels remain high throughout infection and IgG levels are lower than expected
- ➔ Defect T-dependent germinal centers are formed due to Tfh level decline and follicular dendritic cell mislocalization

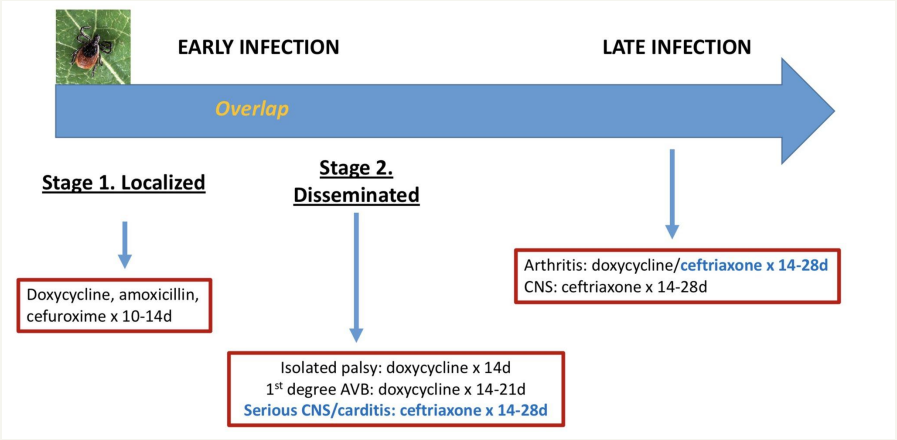
B. burgdorferi inhibits C3 and C4 formation through inhibiting C3 proconvertase and C1 complex activities

- ➔ C3 and C4 are unable to be deposited on FDCs, which interferes with FDC antigen presentation to B cells, leading to the premature collapse of germinal centers before it can function properly

INFECTION OUTCOMES

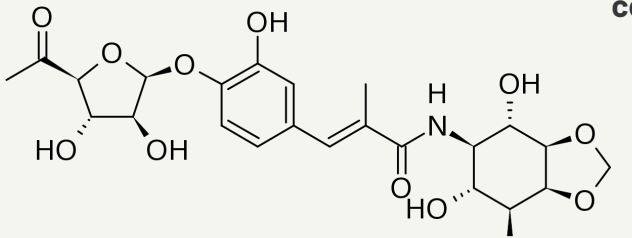
EARLY STAGES





Taking doxycycline

Taking hygromycin A

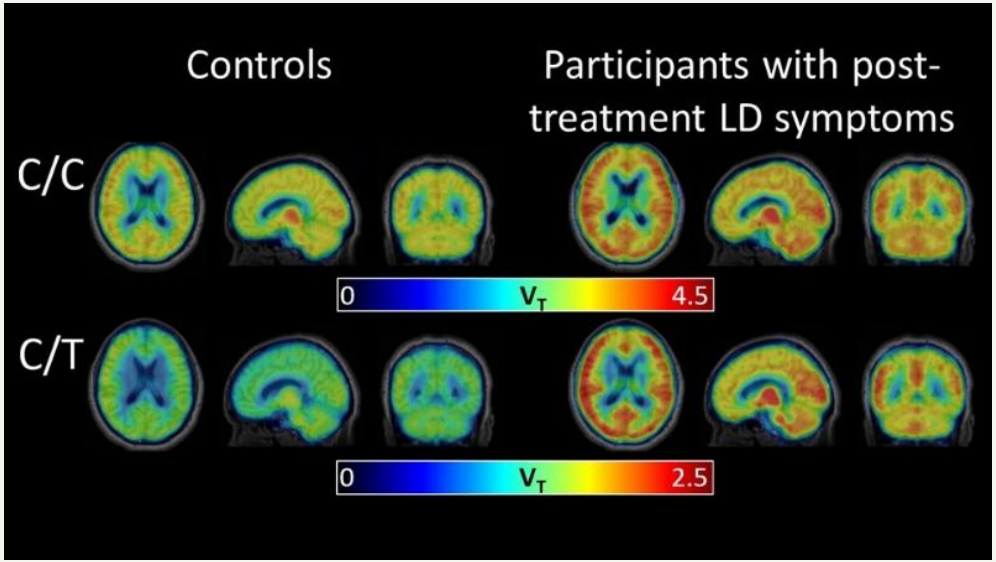


Bacteria may be completely removed

Patient may be completely cured in 2-4 weeks

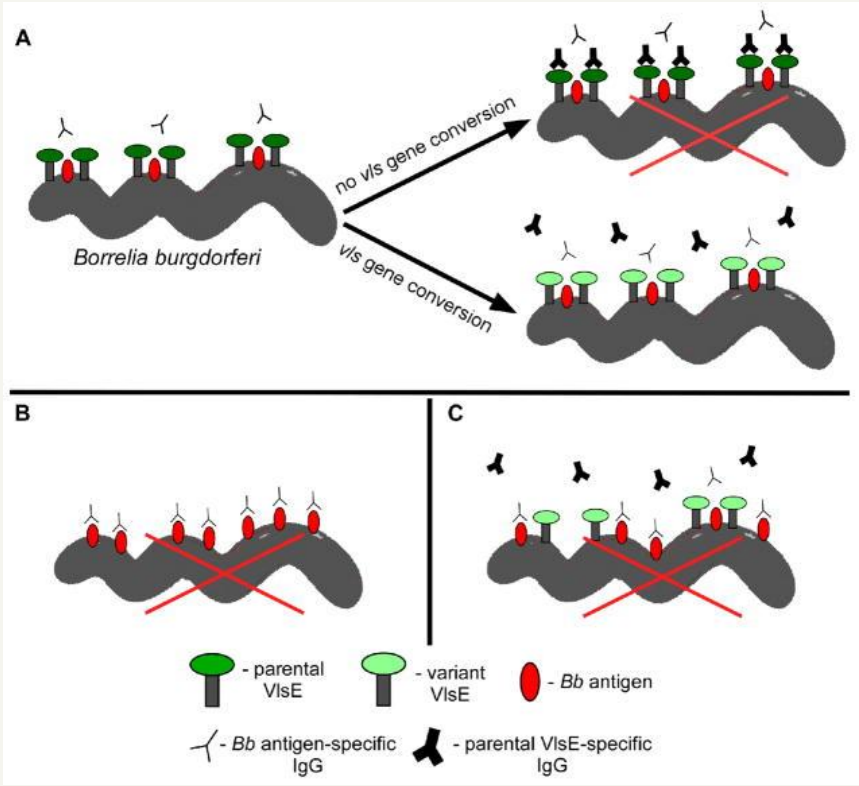
Post-Lyme disease syndrome (PLDS)

- 15% of patients treated will have disease symptoms that persist after they complete treatment, including:
  - joint or muscle aches
  - cognitive dysfunction
  - Fatigue
- Patients may feel the lingering effects of this condition for over 6 months after they finish initial treatment
- Certain studies showed no significant improvement compared to individuals on placebo
- prolonged or incorrect usage of antibiotics can lead to serious damage to various internal organs or even death



Antigenic Variation

- allow bacteria to evade the **antigen-specific immune responses** previously developed from infection
- infection with pathogen alternatives will not elicit responses from existing antibodies or immune cells
- a number of preventative measures can be taken to limit re-infection such as **ensuring full skin coverage in tick prone areas** and **to use repellant**
- most characteristic sign of re-infection: appearance of **Erythema migrans** with **presence of punctum**
- Symptoms reduce in intensity until **third infection**
- The lower levels of **IgG** and **memory B cell** generation can reflect the unsuccessful attempts of the host immune system at resolving subsequent infections



Late Treatments

- More long term conditions develop
- at a predisposed position of risk for relapse (distinctly different from reinfection)
    - usually occurs within a year of the initial infection
    - does not depend on the usual tick season (spring or summer)
    - no punctum is observed
- difference between reinfection and relapse can be characterized by:
    - Seasonality
    - presence of punctum
    - timeline of sickness

References

1. CDC. Transmission [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2022 Feb 18]. Available from: https://www.cdc.gov/lyme/transmission/index.html

2. The bulls-eye rash of Lyme disease: Investigating the cutaneous host-pathogen dynamics of erythema migrans [Internet]. ASM.org. 2018 [cited 2022 Feb 18]. Available from: https://asm.org/Articles/2018/April/going-skin-deep-investigating-the-cutaneous-host-p

3. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget [Internet]. 2018 [cited 2022 Feb 18];9(6):7204–18. Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC5805548/

4. What to know about erythema migrans [Internet]. WebMD. [cited 2022 Feb 18]. Available from: https://www.webmd.com/skin-problems-and-treatments/what-to-know-erythema-migrans

5. Aristizábal B, González Á. Innate immune system. El Rosario University Press; 2013.

6. Kaplan DH. Ontogeny and function of murine epidermal Langerhans cells. Nat Immunol [Internet]. 2017 [cited 2022 Feb 18];18(10):1068–75. Available from: https://pubmed.ncbi.nlm.nih.gov/28926543/

7. Bockenstedt LK, Wooten RM, Baumgarth N. Immune response to Borrelia: Lessons from Lyme disease spirochetes. Curr Issues Mol Biol [Internet]. 2021 [cited 2022 Feb 18];42:145–90. Available from: https://pubmed.ncbi.nlm.nih.gov/33289684/

8. Skogman BH, Hellberg S, Ekerfelt C, Jenmalm MC, Forsberg P, Ludvigsson J, et al. Adaptive and innate immune responsiveness to Borrelia burgdorferi sensu lato in exposed asymptomatic children and children with previous clinical Lyme borreliosis. Clin Dev Immunol [Internet]. 2012 [cited 2022 Feb 18];2012:294587. Available from: https://www.hindawi.com/journals/jir/2012/294587/

9. Tkáčová Z, Bhide K, Mochnáčová E, Petroušková P, Hruškovicová J, Kulkarni A, et al. Comprehensive mapping of the cell response to Borrelia bavariensis in the brain microvascular endothelial cells in vitro using RNA-seq. Front Microbiol [Internet]. 2021;12:760627. Available from: http://dx.doi.org/10.3389/fmicb.2021.760627

10. Nguyen GT, Green ER, Mecsas J. Neutrophils to the ROScue: Mechanisms of NADPH oxidase activation and bacterial resistance. Front Cell Infect Microbiol [Internet]. 2017;7. Available from: http://dx.doi.org/10.3389/fcimb.2017.00373

11. Xu Q, Seemanapalli SV, Reif KE, Brown CR, Liang FT. Increasing the recruitment of neutrophils to the site of infection dramatically attenuates Borrelia burgdorferi infectivity. J Immunol [Internet]. 2007 [cited 2022 Feb 18];178(8):5109–15. Available from: https://pubmed.ncbi.nlm.nih.gov/17404293/

12. Uribe-Querol E, Rosales C. Phagocytosis: Our current understanding of a universal biological process. Front Immunol [Internet]. 2020;11:1066. Available from: http://dx.doi.org/10.3389/fimmu.2020.01066

13. Medzhitov R, Janeway C Jr. The Toll receptor family and microbial recognition. Trends Microbiol [Internet]. 2000 [cited 2022 Feb 18];8(10):452–6. Available from: https://pubmed.ncbi.nlm.nih.gov/11044679/

14. Oosting M, Buffen K, van der Meer JWM, Netea MG, Joosten LAB. Innate immunity networks during infection with Borrelia burgdorferi. Crit Rev Microbiol [Internet]. 2016 [cited 2022 Feb 18];42(2):233–44. Available from: https://pubmed.ncbi.nlm.nih.gov/24963691/

15. Cervantes JL, Hawley KL, Benjamin SJ, Weinerman B, Luu SM, Salazar JC. Phagosomal TLR signaling upon Borrelia burgdorferi infection. Front Cell Infect Microbiol [Internet]. 2014 [cited 2022 Feb 18];4:55. Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC4033037/

16. Petnicki-Ocwieja T, Kern A. Mechanisms of Borrelia burgdorferi internalization and intracellular innate immune signaling. Front Cell Infect Microbiol [Internet]. 2014;4:175. Available from: http://dx.doi.org/10.3389/fcimb.2014.00175

17. Giambartolomei GH, Dennis VA, Lasater BL, Philipp MT. Induction of pro- and anti-inflammatory cytokines by Borrelia burgdorferi lipoproteins in monocytes is mediated by CD14. Infect Immun [Internet]. 1999 [cited 2022 Feb 18];67(1):140–7. Available from: https://pubmed.ncbi.nlm.nih.gov/9864208/

18. Shin JJ, Strle K, Glickstein LJ, Luster AD, Steere AC. Borrelia burgdorferi stimulation of chemokine secretion by cells of monocyte lineage in patients with Lyme arthritis. Arthritis Res Ther [Internet]. 2010;12(5):R168. Available from: http://dx.doi.org/10.1186/ar3128

19. Parra-Medina R, Quintero-Ronderos P, Rodríguez ÉG. The complement system. El Rosario University Press; 2013.

20. Singh SK, Girschick HJ. Molecular survival strategies of the Lyme disease spirochete Borrelia burgdorferi. Lancet Infect Dis [Internet]. 2004 [cited 2022 Feb 18];4(9):575–83. Available from: https://pubmed.ncbi.nlm.nih.gov/15336225/

21. Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Principles of innate and adaptive immunity. London, England: Garland Science; 2001.

22. Coburn J, Garcia B, Hu LT, Jewett MW, Kraiczy P, Norris SJ, et al. Lyme disease pathogenesis. Curr Issues Mol Biol [Internet]. 2021 [cited 2022 Feb 18];42:473–518. Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8046170/

23. Gair CMA, Jane MCA. 23.2. Adaptive immune response. In: Concepts of Biology-1st Canadian Edition Molnar Class. 2015.

24. Adaptive immunity – humoral and cellular immunity [Internet]. Healio.com. [cited 2022 Feb 18]. Available from: https://www.healio.com/hematology-oncology/learn-immuno-oncology/the-immune-system/adaptive-immunity-humoral-and-cellular-immunity

25. Vaz A, Glickstein L, Field JA, McHugh G, Sikand VK, Damle N, et al. Cellular and humoral immune responses to Borrelia burgdorferi antigens in patients with culture-positive early Lyme disease. Infect Immun [Internet]. 2001 [cited 2022 Feb 18];69(12):7437–44. Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC98832/

26. Anderson C, Brissette CA. The brilliance of Borrelia: Mechanisms of host immune evasion by Lyme disease-causing spirochetes. Pathogens [Internet]. 2021 [cited 2022 Feb 18];10(3):281. Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8001052/

27. Tracy KE, Baumgarth N. Borrelia burgdorferi manipulates innate and adaptive immunity to establish persistence in rodent reservoir hosts. Front Immunol [Internet]. 2017 [cited 2022 Feb 18];8:116. Available from: https://pubmed.ncbi.nlm.nih.gov/28265270/

28. Ramsey ME, Hyde JA, Medina-Perez DN, Lin T, Gao L, Lundt ME, et al. A high-throughput genetic screen identifies previously uncharacterized Borrelia burgdorferi genes important for resistance against reactive oxygen and nitrogen species. PLoS Pathog [Internet]. 2017;13(2):e1006225. Available from: http://dx.doi.org/10.1371/journal.ppat.1006225

29. Hastey CJ, Elsner RA, Barthold SW, Baumgarth N. Delays and diversions mark the development of B cell responses to Borrelia burgdorferi infection. J Immunol [Internet]. 2012 [cited 2022 Feb 18];188(11):5612–22. Available from: https://pubmed.ncbi.nlm.nih.gov/22547698/

30. Elsner RA, Hastey CJ, Baumgarth N. CD4+ T cells promote antibody production but not sustained affinity maturation during Borrelia burgdorferi infection. Infect Immun [Internet]. 2015 [cited 2022 Feb 18];83(1):48–56. Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC4288900/

31. Nicholson LB. The immune system. Essays Biochem [Internet]. 2016 [cited 2022 Feb 18];60(3):275–301. Available from: https://portlandpress.com/essaysbiochem/article/60/3/275/78223/The-immune-system

32. Dixon BREA, Radin JN, Piazuelo MB, Contreras DC, Algood HMS. IL-17a and IL-22 induce expression of antimicrobials in gastrointestinal epithelial cells and may contribute to epithelial cell defense against Helicobacter pylori. PLoS One [Internet]. 2016 [cited 2022 Feb 18];11(2):e0148514. Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC4750979/

Thank you!