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Borrelia burgdorferi: Cell Biology and Clinical Manifestations in Latent Chronic Lyme

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Abstract

Chronic Lyme disease is predicated by an infection with *Borrelia burgdorferi* via tick vector. *B. burgdorferi* has been extensively researched with regard to its genome and cell biology. There are many unique characteristics to the bacteria itself; however, serological diagnostics and diagnosis based on symptoms can be complicated and potentially misleading. Other promising diagnostics were also evaluated in this review. Treatment of the chronic Lyme disease can be complicated and at times ineffective. The purpose of this review is to examine *B. burgdorferi* from a biological and clinical perspective.

Keywords

Lyme Disease, *Borrelia Burgdorferi*, Genome, Cellular Process, Epidemiology, CD57, C4a, Diagnostics, Treatment

1. Introduction

The most common vector borne disease in America is Lyme disease. The disease was first categorized by European physicians as Garin-Bujadoux-Bannwarth syndrome [1] and in the US as Lyme arthritis [2]. The bacteria *Borrelia burgdorferi* (Bb) has the capacity to live in both Ixodes ticks in addition to mammalian hosts. This spirochete is unusual with respect to its genetic makeup in addition to its ability to scavenge for nutrients that are commonly synthesized by most microorganisms. Bb has the capacity to evade and attenuate the immune system which under certain circumstances, like acute early infections, can be difficult to detect Bb for diagnostic purposes. The current diagnostic criteria is problematic and often leads to type I and type II errors in addition to doctor ambiguity with regard to recognizing the symptoms associated with Lyme disease since the symptoms of

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Lyme disease mimic other common diseases. Chronic Lyme disease symptoms overlap with diseases like chronic fatigue, fibromyalgia rheumatoid arthritis and Parkinson's disease. The migration of the disease by Ixode ticks also plays a role in diagnostic criteria since locations more commonly associated with Lyme disease are more likely to be diagnosed by doctors. In other words, areas not normally associated with Lyme disease are less likely to undergo diagnostic measures to detect Bb. Difficulty in syndromic definitions can lead to failure to respond with proper antimicrobial therapy where disease progression is often associated with misdiagnosis or treatment failure.

2. Genome

There are currently 12,543 genes identified for numerous strains of Bb with various virulences. Wei-Gang Qiu and Che L. Martin [3] reviewed and analyzed 28 known strains of Bb even though there are many strains that have yet to be discovered. Bb's genome as a whole is one of the most complicated genome of any bacteria [4]-[7]. The genome consists of an approximately 950 kb in addition to several circular and linear plasmids that consists of 9 to 62 kb in length. The genome is not GC rich with about 28% of the genome consisting of G + C base pairing. Linear plasmids consist of covalently sealed telomere region [8] that requires resolvase ResT for replication [6] [9]. The vast majority of the house-keeping genes are found in the genome but there are other house-keeping genes found in various plasmids. Lipoproteins are mostly encoded in the plasmids and represent 7.8% of all open reading frames. These lipoproteins, in the enzootic cycle, are differentially expressed in plasmids [10]-[12].

Coevolution of Bb with mammalian and tick host is likely the reason why Bb lacks the ability to synthesize nucleotides, amino acids, and fatty acids [7] [13]. Bb has the capacity to import these essential precursors to functional macromolecules by importing them with possibly more than 52 transporter and/or binding proteins to sequester carbohydrates, peptides, and amino acids [14].

vls (variable major protein-like sequence) is used as a mechanism to alter the epitopes of lipoproteins in a manner that evades the mammalian host immune system [15]. There are approximately 15 cassettes upstream to the vlsE gene loci where the cassettes and the vlsE region are flanked with 17 bp of highly repetitive nucleotides. The DNA at the vlsE locus is shuffled by nonreciprocal homologous recombination [16] creating altered amino acid sequence which protects Bb from being detected by the host's adaptive immunity respectively.

3. Cellular Processes

Analysis of the genome of Bb revealed limitations of its ability to undergo de novo biosynthetic synthesis which suggests Bb dependence to the host for metabolic processes [17]. The mechanisms for acquiring nutrients from the host must be dynamic since the Bb is a parasite for two vastly different hosts; ticks and mammals. For example, host defense often involves the sequestration of key nutrients for cellular processes; an example being iron. However, Bb has evolved in a way that allows the bacteria to survive without Iron and instead uses manganese and zinc.

Bb does not have the capacity for the synthesis of purines which suggest a process that involves the uptake of guanine for the synthesis of DNA [18]-[20]. Hypoxanthine is also imported into Bb before it is modified to be incorporated into DNA as dGMP or RNA as GMP. Bb is also thought to import nucleotide monophosphates (NMP) as well as deoxynucleated monophosphate to be used for the synthesis of RNA and DNA. This notion is supported by an identified nucleotidase as a means to dephosphorylate NMP and dNMP in addition to a nucleoside transport system [7] [21]. Bb also scavenges amino acids via oligopeptide permease A (oppA) [7]. The expression of oppA-II, oppA-III, and oppA-V in murine infections suggest the possibility that these genes are induced in humans [22].

Bb has limited ability to synthesize various organic molecules and therefore is found in niche areas particularly in the enzootic lifecycle [7]. Glucose, mannose, GlcNAc, maltose, glycerol, and chitbiose are utilized by Bb *in vitro* [23]. Chitobiose utilization suggests that Bb can use ticks as a carbon source [23] [24]. Glycerol is another carbon source that is used by *B. burgdorferi* as studied in vitro by attenuating glpD and by deletion of the glp operon [25] [26].

There are no genes that encode the synthesis of fatty acids in Bb and it is hypothesized that it acquires fatty acids through scavenging the host. The cellular membrane of Bb is composed of phosphatidylglycerol (PG), phosphatidylcholine (PC), sterol galactoside, and monofalatosyl diacylglycerol (MGalDAG). There is a signifi-

cantly high proportion of polyunsaturated fatty acids in Bb than in other bacteria and it is hypothesized that this is the case since it is highly likely that Bb scavenges for fatty acids [20] [27] [28]. There is also functional evidence in vitro using *E. coli* as a model to study the synthesis of MGalDAG by monogalctosyl-1,2-diacylglycerol synthase [29], PC by phosphatidylcholine synthase, and PG by phosphatidylglycerolphosphate synthase [30].

DNA repair mechanisms for Bb are significantly limited compared to other bacterial species [31] even though UvrA was identified as intra-chain and inter-chain DNA damage repair. UvrB, UVrC and UvrD are other components associated with DNA excision repair pathways [32] and are involved in the protection of DNA from both DNA damage from UV radiation and nitrosative damage.

Motility and chemotactic function is distributed by 6% of their genes found in the linear chromosome [33]. Motility for Bb involves two motor-hook-filament structures [34] with a ribbon within the periplasmic space [35]. These structures allow Bb to travel through liquid environments like blood, cerebral spinal fluid, and lymph in addition to being able to tunnel within extracellular matrix as wells as connective tissue. Bb twin flagella are found in the front and back of the cell where the bacteria uses a clockwise and counter clockwise motion in order to control its motility.

4. Evading Immune System

Bb must evade the immune system in both early and late stages of infection. Early immune evasion involves avoiding the innate response which includes defending itself against oxidative defense, Toll-like receptors, NOD-like receptors, and complement system [36]. Avoiding adaptive immune responses involves antigenic recombination in addition to down-regulating immunodominant antigens to deceive the later stages of adaptive immunity [37].

Resistance to oxidative stress is associated with not uptaking iron where the limited intracellular iron provides an environment that intrinsically avoids oxidative damage from the host immune system [38]. Bb also does not have enzymes associated with the tricarboxylic acid cycle and respiration, a common target for ROS [7] [39]. dps, /napA, sodA, and cdr are associated with BosR gene regulation and contribute to the ROS resistance [40]-[44]. dps proteins have the capacity to sequester iron which is associated with the prevention of ROS-resistant nucleoids [45]. sodA codes for superoxide dismutase containing a manganese cofactor which detoxifies ROS species [7] [46]-[49]. Since Bb does not code for catalase or peroxidase enzymes, it is likely that the accumulated ROS are detoxified by CoA disulfide reductase or cdr to regenerate the oxidized state of CoA [7] [40].

Variation in antigenic surface proteins is a process used by many pathogenic bacteria to evade the immune system by changing epitopes so they are not targeted by the adaptive immune system [50]-[54]. The structure of these surface proteins involves the variable region to be presented on the outside of the cellular membrane while the highly antigenic constant region is buried in the cellular membrane [55]-[57]. The variation of the surface epitopes occurred in various tissues by the vlsE recombination events. The function of vlsE recombination is unknown but thought to be a decoy antigen specifically made for the evasion of the host immune system.

Bb's survival in serum is critical in a given host and must evade the host immune system by host complement inhibitors especially since C3 has the capacity to bind to most strains of Bb [58] [59]. This is done in part by complement regulator acquiring surface proteins (CRASPs) to complimentarily bind to factor H, factor H-like proteins 1 (FHL-1) or related proteins to factor H which is associated with the cleavage and inactivation of C3b [59]-[64]. There are several recognized CRASP genes which bind to factor H with differing affinities. Such redundancy is thought to allow *B. burgdorferi*'s ability to evade the host immune system in various vertebrates [65] [66].

Chemoreceptor arrays at the poles of Bb allow Bb to follow chemoattractant trails that lead to host cell compartments [67] [68]. Bb will then use adhesins to bind to glycosaminoglycans, fibronectin, and decorin [69]-[71]. Such niche seeking behavior allows Bb to evade the immune system by essentially seeking an environment that contains nutrients for Bb to survive while simultaneously hiding from the immune system. The host immune system is able to clear Bb, even in immune compromised individuals, if Bb loses its ability to recognize chemoattractants [72].

While chronic bacterial infections are virtually always associated with biofilms, acute infections are typically free floating and disseminate throughout the body accordingly. Those that have chronic infections of Bb are likely to have Bb within a biofilm community. Biofilms are a community of a complex of polymicrobia within

an exopolymeric gel. These microenvironments are also regulated by quorum sensing which detects and then responds to cell density by releasing diffusible signals that induce changes in gene expression among other nearby species of cells [73]. When Bb recognizes cell density described in a quarum, it will begin to release anti-inducing molecules including pheromone known as autoinductor (AI)-2 via LuxS enzyme synthesis [74]. In addition to Bb ability to protect itself from the immune system within biofilm, the biofilm also protects the bacteria from antibiotics.

5. Epidemiology

Geographic range change is one process in which diseases can emerge or re-emerge [75]. The emergence and change in range of *Ixodes scapularis* is documented by location in order to understand the spread of tick borne infectious disease like Lyme disease. Current northward expansion in the United States in recent decades and increase of incidence in the north eastern region of the United States of tick borne infections like Lyme disease has captured the attention of epidemiologist [76]-[79]. Monitoring the spread of and genetic diversity of ticks and tick borne pathogens is significant from an ecological, pathological, and diagnostic detectability of the ticks and their association with Lyme disease [80].

The two major features of the spread of Lyme disease involves an epidemiological and ecological understanding of the life cycle of tick borne infections in new regions and the mechanism of tick borne dispersion in the endemic regions between hosts and new ecological suitable locations. Both are associated with the density of ticks and the density of tick hosts where tick density is a major factor for the threshold of the tick borne pathogen transmission cycle and higher tick density is associated with spread of Lyme disease [81] [82].

Patterns of diversity among ticks are associated with the population expansion. The mortality rate of ticks in an environment associated with extreme temperature, drowning, desiccation and potentially predation are significant factors in the geographic spreading of Lyme disease [83]-[85]. Strains that are more adaptable might be favored in northeastern states in the US as compared to the Midwest US [82] since *I. scapularis* in larval and nymphal has a higher seasonal coincidence in the Midwest [86].

Lyme disease is also common in northern Europe in particular. Approximately 13.7% of all ticks in Europe are infected in Bb even though the prevalence of the disease is 18.6% in adult ticks as compared to 10.1% in nymphs [87]. The prevalence in Austria, Czech Republic, Germany, Switzerland, Slovenia, and Slovakia has is greater than 20% in adult ticks and greater than 11% in nymphs [87]. The spread of Bb is most common in spring and autumn in microenvironments where there is 85% humidity and deciduous or mixed woodland microenvironments [88] [89], suburban environments [90], and roadsides [91].

6. Chronic Lyme Disease

Often an infection of Bb will cause sub-acute symptoms, many times weeks to a few months after a tick bite before subsiding with or without antibiotic treatment [92]-[95]. The clinical manifestations may include neuroborreliosis, Lyme arthritis, Lyme carditis, skin manifestation, and flu like symptoms. The onset of neuroborreliosis can include mild meningism including headaches, lancinating radicular pain, and cranial neuritis. While chronic neuroborreliosis typically involves cognitive impairment, various kinds of paresis, extrapyramidal symptoms, bladder problems, psychosis, sensory disturbances, and spastic gate [96]. Stroke like symptoms are common and are caused by vasculitis [97] in addition to mononeuritis maultiplex or rediculitis [98]-[101]. In America, the most common symptoms of early onset include headache and meningitis while encephalopathy and neuropathy occur rarely [102].

It is important to note that early and chronic neuroborreliosis is typically indistinct. Lyme arthritis, often manifested in the knees, is characterized by inflammation of joints. Lyme arthritis can persist after the infection has been eliminated since the ailment is likely caused by an immunological mechanism. Lyme carditis ecompasses conduction defects, myocarditis and/or pericarditis [103]. Late forms of Lyme cardiac symptoms, in particular cardiomyopathy is rarely reported in Europe [104] [105] and not in America. Skin manifestations include erythema migrans and borrelia lymphocytoma and in later stages acrodermatitis chronica atrophicans (ACA), which may or may not be associated with focal neuropathy [106], is rarely seen in the United States [107].

Chronic infections of Bb have the capacity for creating an environment that leads to oncogenesis, particularly with non-Hodgkin lymphoma. The suspected mechanism of Bb leading to oncogenesis involves chronic antigen-dependent immunostimulation which is associated with constant and sustained lymphoid proliferation of

B-cells [108] [109]. Primary cutaneous B-cell lymphoma (PCBCL) has been found around skin lesions associated with area where the tick has bitten the skin in addition to patients that have serology of previous infection [110]-[112]. Horizontal gene transfer is likely the cause of Bb DNA to be found in nodal lymphoma like mantle cell lymphoma (MCL) in a patient with a history of being infected by Bb [113]. Having a history of being infected with Bb increases the likelihood of developing of acquiring MCL by 300% [114].

Transplacental transmission of Bb has been documented in various animal models with risk associated with adverse fetal outcomes [115]. In animal models, an infection at the beginning of the pregnancy might be correlated with an increase abortion rates in mice [116]. There are a few documented cases of women with Lyme disease having complications with their pregnancy. A premature birth and subsequently short life span of baby whose mother was diagnosed with Lyme disease during the pregnancy revealed severe cardiovascular defects and Bb like spirochetes found in the splean, kidney tubules, and bone marrow in the premature fetus [117]. Another case involving a mother with Lyme disease potentially leading to complications with child development involved a mother that gave birth to a child with spirochetes found in the brain [118]. Although there is significant evidence in animal models as well as some anecdotal cases in humans, studies have not confirmed causal relationships between Bb infections and adverse outcomes during pregnancy [119]. In addition, there is some evidence that acute infections of Lyme disease are more detrimental to the child than a mother who has chronic Lyme disease [119].

7. Lyme Disease and Its Effect on CD57

The most common tickborne disease in the United States is Lyme disease [120] [121]. Lyme disease is considered acute within a period of a month after exposure while chronic Lyme disease can occur months or years after exposure [122]. Chronic exposure to Lyme disease takes a toll on the immunesystem; in particular CD57 [123]. CD57 is typically 60 - 360 cells/μl and although the CD57 count rebounds back to the normal range, Striker and Winger have shown that 51% of patients with Lyme disease have significantly lower levels of CD57 prior to antibiotic treatment [123]. CD57 levels might also be used to determine the effectiveness of the treating Lyme disease. Acutely infected patients with Lyme disease did not have a remarkably low level of CD57. Levels of CD4 and CD8 were also found to be normal in these patients. In comparison to CD4 and CD8, CD57 is poorly characterized [124] [125] but CD57 is known to have natural killer capability like CD56 but remains distinct form CD56 NK cells [126] [127]. Low levels of CD57 were predominantly shown in patients with neurological symptoms as opposed to patients with musculoskeletal disease. It is important to note that there are conflicting reports of CD57 levels in neurological and rheumatological diseases in general [128]-[132].

8. C4a Levels in Patients with Lyme Disease

Higher than normal levels of C4a in patients with Lyme disease are apparent in patients with acute [133] and chronic Lyme disease [134]. Patients that respond better to antibiotic treatment had significantly lower levels of C4a than patients who responded poorly. An increase in C4a in patients with musculoskeletal symptoms while neurologic symptoms associated with Lyme disease did not have an elevated level of C4a. Although C4a is an anaphylatoxin, C4a is not known to cause significant neurological inflammation in the CNS [135] [136] It is important to note that patients with chronic fatigue, a condition that could be mistakenly diagnosed instead of Lyme disease, C4a is also increased [137]. Although C4a levels have the potential to detect Lyme disease at an early stage, increased levels by itself is inadequate for a diagnosis of Lyme disease.

9. Diagnostics

The methods for diagnostics are often not sensitive enough or are administered too early to detect antibodies associated with an infection by Bb. Detection of serum IgG antibodies is the most prevalent in detecting Bb in 90% - 100% of patients with chronic Lyme disease. ELISA testing using recombinant antigens or single antigens for Bb to detect the presence of Bb is the most common form of diagnostic measures [138]-[141]. Western blot is used for further verification of Bb by ELISA however, detection using Western blot for and a negative results using ELISA are considered as antibody negative [142]-[144]. Serological test using IgM often have false positives and should not be used as a diagnostic criterion [145]. It is also possible that antibodies can exist even after Bb has been eliminated from the body, which can lead to false positives [146]. Methodology of diag-

nosis with PCR, by screening cerebral spinal fluid [143], chronic skin lesions [147] [148], synovial fluid [149] [150], blood [151], and urine [152], vary in sensitivity and specificity. PCR can also lead to false positives through improper laboratory techniques [153].

One of the challenges surrounding a proper diagnosis with Lyme disease is the symptoms of Lyme disease are very similar to other conditions. Often times the same symptoms are diagnosed differently depending on whether the patient is within an endemic region of Lyme disease. Two commonly confused diagnoses involve either fibromyalgia or chronic fatigue when a patient may actually be experiencing symptoms associated with chronic Lyme disease (**Table 1**). Symptoms related to neuroborreliosis can also resemble Parkinson's disease in some patients. It is important that the signs and symptoms vary from patient to patient, particularly in advanced stages of Lyme disease. Some of these symptoms can persist even after serological evidence suggests that Bb has been eliminated. It is also important to note again that even a positive serological diagnostics may be due to residual antibodies circulating after Bb has been eliminated.

10. Treatment of Lyme Disease

Treatments of Lyme disease depend on the progression of bacterial infection and its manifestation. The treatments also vary depending on the region where the patient resides. There are several treatment guidelines that can be used to treat chronic Lyme disease. ILADS recommends several months of IV prior to oral treatment of antibiotics [154] while IDSA [155] and EUCALB [156] recommend treatment for 2 - 4 weeks. IDSA and EUCALB recommend oral administration of doxycycline or IV administration of penicillin, ceftriaxone, or cefotaxime respectively. Guidelines associated with the treatment of neuroborreliosis with peripheral neuropathy and acrodermatitis chronica atrophicans (ACA) by EFNS in Europe [157] recommends 3 weeks of either oral doxycycline or ceftriaxone by IV administration. EFNS also recommends 3 weeks of IV ceftriaxone for patients with chronic neuroborreliosis if there are manifestations from the central nervous system. The evaluation of the effectiveness of antibiotic treatment should occur 3 - 6 months after complete administration of the antibiotics. Retreatment for refractory arthritis may involve an additional 2 - 4 weeks of treatment.

11. Discussion

There are many challenges in the diagnosis and treatment of Lyme disease. These challenges arise particularly when a patient develops chronic Lyme disease in a region that is typically not considered in the endemic region. The diagnostic criteria can also be problematic leading to type I and type II errors depending on which kind of diagnostic method is used. It is possible for a patient to diagnostically be considered as a host for Bb even after successful treatment since the antibodies associated with Bb might still be in circulation. There is also an opportunity for many of the symptoms, especially neurological symptoms, to persist after Bb has been eradicated from the host. Arthritis symptoms may also persist after the infection has been cleared.

Table 1. The following diagram is to better explain why certain conditions can be confused with symptoms associated with chronic Lyme disease. The symptoms found in chronic fatigue, fibromyalgia, rheumatoid arthritis, and Parkinson's disease are not exhausted in this table since the goal is to document the overlap of symptoms. Of the diseases listed in this table, the symptoms of fibromyalgia are more closely related to chronic Lyme disease. Issues in diagnosing Lyme disease over fibromyalgia is complicated by poor serologic diagnostic criteria associated with detecting Bb.

	Chronic Lyme Disease	Chronic Fatigue	Fibromyalgia	Rheumatoid Arthritis	Parkinson's Disease
Fatigue	X	X	X	X	X
Loss of Concentration/Short Term Memory Loss	X	X	X		X
Joint Pain	X	X	X	X	
Poor Sleep	X	X	X	X	X
Mood Problems/Depression, Anxiety, etc.	X	X	X	X	X
Muscle Skeletal Pain	X	X	X	X	X
Neurological Presentation	X	X	X		X
Muscle Stiffness	X		X		X

Better diagnostic methods are sorely needed to enhance the diagnosis of Bb infections. This is particularly true with early detection of Bb to specifically reduce the disease progression before many of the major symptoms have emerged. Although recognizing a tick bite may inform the doctor for early treatment of Lyme disease, there are many patients who do not recall being bitten by a tick that does not have the luxury of identifying the early stages of infection.

The potential for coinfections with *Babasi microti*, *Bartonella henselae*, *Ehrlichia rickettsiales*, *Coltivirus*, *Mycoplasma*, *Powassan encephalitis* virus, *Coxiella burnetii*, *Rickettsia slovaca*, *Rickettsia helvetica*, and *Francisella tularensis* can complicate an infection with Bb. These bacteria and viruses can be found in the Ixode ticks and although they are phylogenetically distant from each other, they transmit themselves from tick to vertebrates via tick bite like Bb. Further screening to determine if an infection is actually a coinfection should be examined by clinicians to make sure the treatment protocol is sound for the patient.

Novel forms of antibiotics have recently been lagging with regard to drug discovery. There is potential for new treatments that have a higher success rate to be discovered. Treatment of Bb neurological symptoms during and after infection is also sorely needed to enhance the quality of life of patients. Since Bb scavenge for nutrients that it cannot produce on its own, there is potential for novel drugs that mimic many of these nutrients in a manner that could prevent disease progression.

More research is necessary with regard to the promotion of cancer from infected patients with Bb. A better understanding of the mechanism is important and recognizing or predicting patients with a higher likelihood of developing cancer may play a role in treatment alongside the antibiotic treatment that is currently used.

The complex nature of Bb's genome and the potential for horizontal gene transfer could lead to new strains of Bb. Such new strains may present antigens that may not be detected by current methods of diagnosis. Research of Bb that is not readily identified by the current diagnostic criteria should be more closely examined to determine if this is the case.

References

[1] Garin, C. and Bujadoux, A. (1922) Paralysie par les tiques. *J Med Lyon*, **71**, 765-767.

[2] Steere, A.C., Malawista, S.E., Hardin, J.A., Ruddy, S., Askenase, W. and Andiman, W.A. (1977) Erythema Chronicum Migrans and Lyme Arthritis. The Enlarging Clinical Spectrum. *Annals of Internal Medicine*, **86**, 685-698. http://dx.doi.org/10.7326/0003-4819-86-6-685

[3] Qiu, W. and Martin, C. (2014) Evolutionary Genomics of *Borrelia burgdorferi* Sensu Lato: Findings, Hypotheses, and the Rise of Hybrids. *Infection, Genetics* and *Evolution*, **27**, 576-593. http://dx.doi.org/10.1016/j.meegid.2014.03.025

[4] Casjens, S., Palmer, N., van Vugt, R., Huang, W.M., Stevenson, B., *et al*. (2000) A Bacterial Genome in Flux: The Twelve Linear and Nine Circular Extrachromosomal DNAs in an Infectious Isolate of the Lyme Disease Spirochete *Borrelia burgdorferi*. *Molecular Microbiology*, **35**, 490-516. http://dx.doi.org/10.1046/j.1365-2958.2000.01698.x

[5] Casjens, S.R., Mongodin, E.F., Qiu, W.-G., Luft, B.J., Schutzer, S.E., *et al*. (2012) Genome Stability of Lyme Disease Spirochetes: Comparative Genomics of *Borrelia burgdorferi* Plasmids. *PLoS ONE*, **7**. http://dx.doi.org/10.1371/journal.pone.0033280

[6] Chaconas, G. and Kobryn, K. (2010) Structure, Function, and Evolution of Linear Replicons in Borrelia. *Annual Review of Microbiology*, **64**, 185-202. http://dx.doi.org/10.1146/annurev.micro.112408.134037

[7] Fraser, C.M., Casjens, S., Huang, W.M., Sutton, G.G., Clayton, R., *et al*. (1997) Genomic Sequence of a Lyme Disease Spirochete, *Borrelia burgdorferi*. *Nature*, **390**, 580-586. http://dx.doi.org/10.1038/37551

[8] Barbour, A.G. and Garon, C.F. (1987) Linear Plasmids of the Bacterium *Borrelia burgdorferi* Have Covalently Closed Ends. *Science*, **237**, 409-411. http://dx.doi.org/10.1126/science.3603026

[9] Kobryn, K. and Chaconas, G. (2002) ResT, a Telomere Resolvase Encoded by the Lyme Disease Spirochete. *Molecular Cells*, **9**, 195-201. http://dx.doi.org/10.1016/S1097-2765(01)00433-6

[10] Radolf, J.D., Caimano, M.J., Stevenson, B. and Hu, L.T. (2012) Of Ticks, Mice and Men: Understanding the Dualhost Lifestyle of Lyme Disease Spirochaetes. *Nature Reviews Microbiology*, **10**, 87-99.

[11] Samuels, D.S. (2011) Gene Regulation in *Borrelia burgdorferi*. *Annual Review of Microbiology*, **65**, 479-499. http://dx.doi.org/10.1146/annurev.micro.112408.134040

[12] Singh, S.K. and Girschick, H.J. (2004) Molecular Survival Strategies of the Lyme Disease Spirochete *Borrelia burgdorferi*. *The Lancet Infectious Diseases*, **4**, 575-583. http://dx.doi.org/10.1016/S1473-3099(04)01132-6

[13] Gherardini, F., Boylan, J., Lawrence, K. and Skare, J. (2010) Metabolism and Physiology of Borrelia. Borrelia: Molecular Biology, Host Interaction and Pathogenesis. Caister Academic Press, Norfolk, 103-138.

[14] Saier Jr., M.H. and Paulsen, I.T. (2000) Whole Genome Analyses of Transporters in Spirochetes: *Borrelia burgdorferi* and *Treponema pallidum*. *Journal of Molecular Microbiology and Biotechnology*, **2**, 393-399.

[15] Zhang, J.-R., Hardham, J.M., Barbour, A.G. and Norris, S.J. (1997) Antigenic Variation in Lyme Disease Borreliae by Promiscuous Recombination of VMP-Like Sequence Cassettes. *Cell*, **89**, 275-285. http://dx.doi.org/10.1016/S0092-8674(00)80206-8

[16] Zhang, J.-R. and Norris, S.J. (1998) Genetic Variation of the *Borrelia burgdorferi* Gene vlsE Involves Cassette-Specific, Segmental Gene Conversion. *Infection and Immunity*, **66**, 3698-3704.

[17] Barbour, A.G. (1984) Isolation and Cultivation of Lyme Disease Spirochetes. *Yale Journal of Biology and Medicine*, **57**, 521-525.

[18] Corbin, B.D., Seeley, E.H., Raab, A., Feldmann, J., Miller, M.R., Torres, V.J., *et al.* (2008) Metal Chelation and Inhibition of Bacterial Growth in Tissue Abscesses. *Science*, **319**, 962-965. http://dx.doi.org/10.1126/science.1152449

[19] Papp-Wallace, K.M. and Maguire, M.E. (2006) Manganese Transport and the Role of Manganese in Virulence. *Annual Review of Microbiology*, **60**, 187-209. http://dx.doi.org/10.1146/annurev.micro.60.080805.142149

[20] Wandersman, C. and Delepelaire, P. (2004) Bacterial Iron Sources: From Siderophores to Hemophores. *Annual Review of Microbiology*, **58**, 611-647. http://dx.doi.org/10.1146/annurev.micro.58.030603.123811

[21] Overbeek, R., Larsen, N., Walunas, T., D'Souza, M., Pusch, G., Selkov Jr., E., *et al.* (2003) The ERGO Genome Analysis and Discovery System. *Nucleic Acids Research*, **31**, 164-171. http://dx.doi.org/10.1093/nar/gkg148

[22] Wang, X.G., Lin, B., Kidder, J.M., Telford, S. and Hu, L.T. (2002) Effects of Environmental Changes on Expression of the Oligopeptide Permease (*opp*) Genes of *Borrelia burgdorferi*. *Journal of Bacteriology*, **184**, 6198-6206. http://dx.doi.org/10.1128/JB.184.22.6198-6206.2002

[23] von Lackum, K. and Stevenson, B. (2005) Carbohydrate Utilization by the *Lyme borreliosis* Spirochete, *Borrelia burgdorferi*. *FEMS Microbiology Letters*, **243**, 173-179. http://dx.doi.org/10.1016/j.femsle.2004.12.002

[24] Tilly, K., Elias, A.F., Errett, J., Fischer, E., Iyer, R., Schwartz, I., *et al.* (2001) Genetics and Regulation of Chitobiose Utilization in *Borrelia burgdorferi*. *Journal of Bacteriology*, **183**, 5544-5553. http://dx.doi.org/10.1128/JB.183.19.5544-5553.2001

[25] He, M., Ouyang, Z., Troxell, B., Xu, H., Moh, A., Piesman, J., *et al.* (2011) Cyclic di-GMP Is Essential for the Survival of the Lyme Disease Spirochete in Ticks. *PLoS Pathogens*, **7**, e1002133. http://dx.doi.org/10.1371/journal.ppat.1002133

[26] Pappas, C.J., Iyer, R., Petzke, M.M., Caimano, M.J., Radolf, J.D. and Schwartz, I. (2011) *Borrelia burgdorferi* Requires Glycerol for Maximum Fitness during the Tick Phase of the Enzootic Cycle. *PLoS Pathogens*, 7, e1002102. http://dx.doi.org/10.1371/journal.ppat.1002102

[27] Barbour, A.G. and Hayes, S.F. (1986) Biology of Borrelia Species. *Microbiological Reviews*, **50**, 381-400.

[28] Boylan, J.A., Lawrence, K.A., Downey, J.S. and Gherardini, F.C. (2008) *Borrelia burgdorferi* Membranes Are the Primary Targets of Reactive Oxygen Species. *Molecular Microbiology*, **68**, 786-799. http://dx.doi.org/10.1111/j.1365-2958.2008.06204.x

[29] Ostberg, Y., Berg, S., Comstedt, P., Wieslander, A. and Bergstrom, S. (2007) Functional Analysis of a Lipid Galactosyltransferase Synthesizing the Major Envelope Lipid in the Lyme Disease Spirochete *Borrelia burgdorferi*. *FEMS Microbiology Letters*, **272**, 22-29. http://dx.doi.org/10.1111/j.1574-6968.2007.00728.x

[30] Wang, X.G., Scagliotti, J.P. and Hu, L.T. (2004) Phospholipid Synthesis in *Borrelia burgdorferi*: BB0249 and BB0721 Encode Functional Phosphatidylcholine Synthase and Phosphatidylglycerolphosphate Synthase Proteins. *Microbiology*, **150**, 391-397. http://dx.doi.org/10.1099/mic.0.26752-0

[31] Sambir, M., Ivanova, L.B., Bryksin, A.V., Godfrey, H.P. and Cabello, F.C. (2011) Functional Analysis of *Borrelia burgdorferi* uvrA in DNA Damage Protection. *FEMS Microbiology Letters*, **317**, 172-180. http://dx.doi.org/10.1111/j.1574-6968.2011.02226.x

[32] Hardy, P.O. and Chaconas, G. (2013) The Nucleotide Excision Repair System of *Borrelia burgdorferi* Is the Sole Pathway Involved in Repair of DNA Damage by UV Light. *Journal of Bacteriology*, **195**, 2220-2231. http://dx.doi.org/10.1128/JB.00043-13

[33] Johnson, L. and Stricker, R. (2010) The Infectious Diseases Society of America Lyme Guidelines: A Cautionary Tale about the Development of Clinical Practice Guidelines. *Philosophy, Ethics, and Humanities in Medicine*, **5**, 9. http://dx.doi.org/10.1186/1747-5341-5-9

[34] Sal, M.S., Li, C., Motalab, M.A., Shibata, S., Aizawa, S. and Charon, N.W. (2008) *Borrelia burgdorferi* Uniquely Regulates Its Motility Genes and Has an Intricate Flagellar Hook-Basal Body Structure. *Journal of Bacteriology*, **190**, 1912-1921. http://dx.doi.org/10.1128/JB.01421-07

[35] Charon, N.W., Goldstein, S.F., Marko, M., *et al.* (2009) The Flat Ribbon Configuration of the Periplasmic Flagella of

Borrelia burgdorferi and Its Relationship to Motility and Morphology. *Journal of Bacteriology*, **191**, 600-607. http://dx.doi.org/10.1128/JB.01288-08

[36] Berende, A., Oosting, M., Kullberg, B.J., Netea, M.G. and Joosten, L.A. (2010) Activation of Innate Host Defense Mechanisms by Borrelia. *European Cytokine Network*, **21**, 7-18.

[37] Weis, J.J. and Bockenstedt, L.K. (2010) Host Response. In: Samuels, D.S. and Radolf, J., Eds., *Borrelia—Molecular biology, Host Interaction and Pathogenesis*, Caister Academic Press, Norfolk, 413-441.

[38] Posey, J.E. and Gherardini, F.C. (2000) Lack of a Role for Iron in the Lyme Disease Pathogen. *Science*, **288**, 1651-1653. http://dx.doi.org/10.1126/science.288.5471.1651

[39] Iuchi, S. and Weiner, L. (1996) Cellular and Molecular Physiology of *Escherichia coli* in the Adaptation to Aerobic Environments. *Journal of Biochemistry*, **120**, 1055-1063. http://dx.doi.org/10.1093/oxfordjournals.jbchem.a021519

[40] Boylan, J.A., Hummel, C.S., Benoit, S., Garcia-Lara, J., Treglown-Downey, J., Crane, E.J., *et al.* (2006) *Borrelia burgdorferi* bb0728 Encodes a Coenzyme A Disulphide Reductase Whose Function Suggests a Role in Intracellular Redox and the Oxidative Stress Response. *Molecular Microbiology*, **59**, 475-486. http://dx.doi.org/10.1111/j.1365-2958.2005.04963.x

[41] Boylan, J.A., Posey, J.E. and Gherardini, F.C. (2003) Borrelia Oxidative Stress Response Regulator, BosR: A Distinctive Zn-Dependent Transcriptional Activator. *Proceedings of the National Academy of Sciences of the United States of America*, **100**, 11684-91168. http://dx.doi.org/10.1073/pnas.2032956100

[42] Hyde, J.A., Seshu, J. and Skare, J.T. (2006) Transcriptional Profiling of *Borrelia burgdorferi* Containing a Unique bosR Allele Identifies a Putative Oxidative Stress Regulon. *Microbiology*, **152**, 2599-2609. http://dx.doi.org/10.1099/mic.0.28996-0

[43] Ouyang, Z., Deka, R.K. and Norgard, M.V. (2011) BosR (BB0647) Controls the RpoN-RpoS Regulatory Pathway and Virulence Expression in *Borrelia burgdorferi* by a Novel DNA-Binding Mechanism. *PLoS Pathogens*, **7**, e1001272. http://dx.doi.org/10.1371/journal.ppat.1001272

[44] Seshu, J., Boylan, J.A., Hyde, J.A., Swingle, K.L., Gherardini, F.C. and Skare, J.T. (2004) A Conservative Amino Acid Change Alters the Function of BosR, the Redox Regulator of *Borrelia burgdorferi*. *Molecular Microbiology*, **54**, 1352-1363. http://dx.doi.org/10.1111/j.1365-2958.2004.04352.x

[45] Zhao, G., Ceci, P., Ilari, A., Giangiacomo, L., Laue, T.M., Chiancone, E., *et al.* (2002) Iron and Hydrogen Peroxide Detoxification Properties of DNA-Binding Protein from Starved Cells. A Ferritin-Like DNA-Binding Protein of *Escherichia coli*. *The Journal of Biological Chemistry*, **277**, 27689-27696. http://dx.doi.org/10.1074/jbc.M202094200

[46] Aguirre, J.D., Clark, H.M., McIlvin, M., Vazquez, C., Palmere, S.L., Grab, D.J., *et al.* (2013) A Manganese-Rich Environment Supports Superoxide Dismutase Activity in a Lyme Disease Pathogen, *Borrelia burgdorferi*. *The Journal of Biological Chemistry*, **288**, 8468-8478. http://dx.doi.org/10.1074/jbc.M112.433540

[47] Esteve-Gassent, M.D., Elliott, N.L. and Seshu, J. (2009) *sodA* Is Essential for Virulence of *Borrelia burgdorferi* in the Murine Model of Lyme Disease. *Molecular Microbiology*, **71**, 594-612. http://dx.doi.org/10.1111/j.1365-2958.2008.06549.x

[48] Troxell, B., Xu, H. and Yang, X.F. (2012) *Borrelia burgdorferi*, Pathogen That Lacks Iron, Encodes Manganese-Dependent Superoxide Dismutase Essential for Resistance to Streptonigrin. *The Journal of Biological Chemistry*, **287**, 19284-19293. http://dx.doi.org/10.1074/jbc.M112.344903

[49] Whitehouse, C.A., Williams, L.R. and Austin, F.E. (1997) Identification of Superoxide Dismutase Activity in *Borrelia burgdorferi*. *Infection and Immunity*, **65**, 4865-4868.

[50] Barbour, A.G. (1990) Antigenic Variation of a Relapsing Fever Borrelia Species. *Annual Review of Microbiology*, **44**, 155-171. http://dx.doi.org/10.1146/annurev.mi.44.100190.001103

[51] Barbour, A.G. and Restrepo, B.I. (2000) Antigenic Variation in Vector-Borne Pathogens. *Emerging Infectious Diseases*, **6**, 449-457. http://dx.doi.org/10.3201/eid0605.000502

[52] Deitsch, K.W., Moxon, E.R. and Wellems, T.E. (1997) Shared Themes of Antigenic Variation and Virulence in Bacterial, Protozoal, and Fungal Infections. *Microbiology and Molecular Biology Reviews*, **61**, 281-293.

[53] Palmer, G.H. and Brayton, K.A. (2007) Gene Conversion Is a Convergent Strategy for Pathogen Antigenic Variation. *Trends in Parasitology*, **23**, 408-413. http://dx.doi.org/10.1016/j.pt.2007.07.008

[54] Vink, C., Rudenko, G. and Seifert, H.S. (2011) Microbial Antigenic Variation Mediated by Homologous DNA Recombination. *FEMS Microbiology Reviews*, **5**, 917-948.

[55] Eicken, C., Sharma, V., Klabunde, T., Lawrenz, M.B., Hardham, J.M., Norris, S.J., *et al.* (2002) Crystal Structure of Lyme Disease Variable Surface Antigen VlsE of *Borrelia burgdorferi*. *The Journal of Biological Chemistry*, **277**, 21691-2166. http://dx.doi.org/10.1074/jbc.M201547200

[56] Liang, F.T., Alvarez, A.L., Gu, Y., Nowling, J.M., Ramamoorthy, R. and Philipp, M.T. (1999) An Immunodominant

Conserved Region within the Variable Domain of VlsE, the Variable Surface Antigen of *Borrelia burgdorferi*. *The Journal of Immunology*, **163**, 5566-5573.

[57] Liang, F.T., Nowling, J.M. and Philipp, M.T. (2000) Cryptic and Exposed Invariable Regions of VlsE, the Variable Surface Antigen of *Borrelia burgdorferi* sl. *Journal of Bacteriology*, **182**, 3597-3601. http://dx.doi.org/10.1128/JB.182.12.3597-3601.2000

[58] Kraiczy, P., Peters, S., Seitz, C., Wurzner, R., Oschmann, P. and Brade, V. (1998) Growth Inhibitory and Bactericidal Efficacy of Sera from *Lyme borreliosis* Patients on *Borrelia burgdorferi* Strains. *Wiener Klinische Wochenschrift*, **110**, 886-893.

[59] Kraiczy, P., Skerka, C., Kirschfink, M., Brade, V. and Zipfel, P.F. (2001) Immune Evasion of *Borrelia burgdorferi* by Acquisition of Human Complement Regulators FHL-1/Reconectin and Factor H. *European Journal of Immunology*, **31**, 1674-1684. http://dx.doi.org/10.1002/1521-4141(200106)31:6<1674::AID-IMMU1674>3.0.CO;2-2

[60] Gordon, D.L., Kaufman, R.M., Blackmore, T.K., Kwong, J. and Lublin, D.M. (1995) Identification of Complement Regulatory Domains in Human Factor H. *The Journal of Immunology*, **155**, 348-356.

[61] Kraiczy, P., Skerka, C., Brade, V. and Zipfel, P.F. (2001) Further Characterization of Complement Regulator-Acquiring Surface Proteins of *Borrelia burgdorferi*. *Infection and Immunity*, **69**, 7800-7809. http://dx.doi.org/10.1128/IAI.69.12.7800-7809.2001

[62] Kuhn, S., Skerka, C. and Zipfel, P.F. (1995) Mapping of the Complement Regulatory Domains in the Human Factor H-Like Protein 1 and in Factor H1. *The Journal of Immunology*, **155**, 5663-5670.

[63] Kuhn, S. and Zipfel, P.F. (1996) Mapping of the Domains Required for Decay Acceleration Activity of the Human Factor H-Like Protein 1 and Factor H. *European Journal of Immunology*, **26**, 2383-2387. http://dx.doi.org/10.1002/eji.1830261017

[64] Lindahl, G., Sjobring, U. and Johnsson, E. (2000) Human Complement Regulators: A Major Target for Pathogenic Microorganisms. *Current Opinion in Immunology*, **12**, 44-51. http://dx.doi.org/10.1016/S0952-7915(99)00049-7

[65] Kurtenbach, K., De Michelis, S., Etti, S., Schafer, S.M., Sewell, H.S., Brade, V., *et al.* (2002) Host Association of *Borrelia burgdorferi* Sensu Lato—The Key Role of Host Complement. *Trends in Microbiology*, **10**, 74-79. http://dx.doi.org/10.1016/S0966-842X(01)02298-3

[66] Stevenson, B., El-Hage, N., Hines, M.A., Miller, J.C. and Babb, K. (2002) Differential Binding of Host Complement Inhibitor Factor H by *Borrelia burgdorferi* Erp Surface Proteins: A Possible Mechanism Underlying the Expansive Host Range of Lyme Disease Spirochetes. *Infection and Immunity*, **70**, 491-497. http://dx.doi.org/10.1128/IAI.70.2.491-497.2002

[67] Xu, H., Raddi, G., Liu, J., Charon, N.W. and Li, C. (2011) Chemoreceptors and Flagellar Motors Are Subterminally Located in Close Proximity at the Two Cell Poles in Spirochetes. *Journal of Bacteriology*, **193**, 2652-2656. http://dx.doi.org/10.1128/JB.01530-10

[68] Zhang, K., Liu, J., Tu, Y., Xu, H., Charon, N.W. and Li, C. (2012) Two CheW Coupling Proteins Are Essential in a Chemosensory Pathway of *Borrelia burgdorferi*. *Molecular Microbiology*, **85**, 782-794. http://dx.doi.org/10.1111/j.1365-2958.2012.08139.x

[69] Parveen, N. and Leong, J.M. (1998) Identification of a Candidate Glycosaminoglycan-Binding Adhesin of the Lyme Disease Spirochete *Borrelia burgdorferi*. *Molecular Microbiology*, **35**, 1220-1234. http://dx.doi.org/10.1046/j.1365-2958.2000.01792.x

[70] Guo, B.P., Brown, E.L., Dorward, D.W., Rosenberg, L.C. and Höök, M. (1998) Decorin-Binding Adhesins from *Borrelia burgdorferi*. *Molecular Microbiology*, **30**, 711-723. http://dx.doi.org/10.1046/j.1365-2958.1998.01103.x

[71] Probert, W.S. and Johnson, B.J. (1998) Identification of a 47 kDa Fibrinonectin-Binding Protein Expressed by *Borrelia burgdorferi* Isolate B31. *Molecular Microbiology*, **30**, 1003-1015. http://dx.doi.org/10.1046/j.1365-2958.1998.01127.x

[72] Sze, C.S., Zhang, K., Kariu, T., Pal, U. and Li, C. (2012) *Borrelai burgdorferi* Needs Chemotaxis to Establish Infection in Mammals and to Accomplish Its Enzootic Cycle. *Infection and Immunity*, **80**, 2485-2492. http://dx.doi.org/10.1128/IAI.00145-12

[73] Rutherford, S.T. and Bassler, B.L. (2012) Bacterial Quorum Sensing: Its Role in Virulence and Possibilities for Its Control. *Cold Spring Harb Perspect Med.*, **2**, Article ID: a012427.

[74] Surette, M.G., Miller, M.B. and Bassler, B.L. (1999) Quorum Sensing in *Escherichia coli*, *Salmonella typhimurium*, and *Vibrio harveyi*: A New Family of Genes Responsible for Autoinducer Production. *Proceedings of the National Academy of Sciences of the United States of America*, **96**, 1639-1644. http://dx.doi.org/10.1073/pnas.96.4.1639

[75] Kilpatrick, A.M. and Randolph, S.E. (2012) Drivers, Dynamics, and Control of Emerging Vector-Borne Zoonotic Diseases. *The Lancet*, **380**, 1946-1955. http://dx.doi.org/10.1016/S0140-6736(12)61151-9

[76] Lindgren, E., Tälleklint, L. and Polfeldt, T. (2000) Impact of Climatic Change on the Northern Latitude Limit and

Population Density of the Disease-Transmitting European Tick *Ixodes ricinus*. *Environmental Health Perspectives*, **108**, 119-123. http://dx.doi.org/10.1289/ehp.00108119

[77] Ogden, N.H., Lindsay, R.L., Sockett, P.N., Morshed, M. and Artsob, H. (2009) Emergence of Lyme Disease in Canada. *Canadian Medical Association Journal*, **180**, 1221-1224. http://dx.doi.org/10.1503/cmaj.080148

[78] Léger, E., Vourc'h, G., Vial, L., Chevillon, C. and McCoy, K.D. (2013) Changing Distributions of Ticks: Causes and Consequences. *Experimental and Applied Acarology*, **59**, 219-244. http://dx.doi.org/10.1007/s10493-012-9615-0

[79] Medlock, J.M., Hansford, K.M., Bormane, A., Derdakova, M., Estrada-Pena, A., George, J.C., *et al.* (2013) Driving Forces for Changes in Geographical Distribution of *Ixodes ricinus* Ticks in Europe. *Parasites & Vectors*, **6**, 1. http://dx.doi.org/10.1186/1756-3305-6-1

[80] Ogden, N.H., Margos, G., Aanensen, D.M., Drebot, M.A., Feil, E.J., Hanincová, K., *et al.* (2011) Investigation of Genotypes of *Borrelia burgdorferi* in *Ixodes scapularis* Ticks Collected in Surveillance in Canada. *Applied and Environmental Microbiology*, **77**, 3244-3254. http://dx.doi.org/10.1128/AEM.02636-10

[81] Norman, R., Bowers, R.G., Begon, M. and Hudson, P.J. (1999) Persistence of Tick-Borne Virus in the Presence of Multiple Host Species: Tick Reservoirs and Parasite Mediated Competition. *Journal of Theoretical Biology*, **200**, 111-118. http://dx.doi.org/10.1006/jtbi.1999.0982

[82] Ogden, N.H., Bigras-Poulin, M., O'Callaghan, C.J., Barker, I.K., Lindsay, L.R., Maarouf, A., *et al.* (2007) Tick Seasonality, Host Infection Dynamics and Fitness of *Ixodes scapularis*-Borne Pathogens. *Parasitology*, **134**, 209-227. http://dx.doi.org/10.1017/S0031182006001417

[83] Lindsay, L.R., Barker, I.K., Surgeoner, G.A., McEwen, S.A., Gillespie, T.J. and Addison, E.M. (1998) Survival and Development of the Different Life Stages of *Ixodes scapularis* (Acari: Ixodidae) Held within Four Habitats on Long Point, Ontario, Canada. *Journal of Medical Entomology*, **35**, 189-199.

[84] Lindsay, L.R., Barker, I.K., Surgeoner, G.A., McEwen, S.A., Gillespie, T.J. and Robinson, J.T. (1995) Survival and Development of *Ixodes scapularis* (Acari: Ixodidae) under Various Climatic Conditions in Ontario, Canada. *Journal of Medical Entomology*, **32**, 143-152.

[85] Ogden, N.H., Barker, I.K., Beauchamp, G., Brazeau, S., Charron, D., Maarouf, A., *et al.* (2006) Investigation of Ground Level and Remote-Sensed Data for Habitat Classification and Prediction of Survival of *Ixodes scapularis* Ticks in Habitats of Southeastern Canada. *Journal of Medical Entomology*, **43**, 403-414. http://dx.doi.org/10.1603/0022-2585(2006)043[0403:IOGLAR]2.0.CO;2

[86] Gatewood, A.G., Liebman, K.A., Vourc'h, G., Bunikis, J., Hamer, S.A., Cortinas, R., *et al.* (2009) Climate and Tick Seasonality Are Predictors of *Borrelia burgdorferi* Genotype Distribution. *Applied and Environmental Microbiology*, **75**, 2476-2483. http://dx.doi.org/10.1128/AEM.02633-08

[87] Rauter, C. and Hartung, T. (2005) Prevalence of *Borrelia burgdorferi* Sensu Lato Genospecies in *Ixodes ricinus* Ticks in Europe: A Metaanalysis. *Applied and Environmental Microbiology*, **71**, 7203-7216. http://dx.doi.org/10.1128/AEM.71.11.7203-7216.2005

[88] Estrada-Peña, A., Venzal, J.M. and Sanchez Acedo, C. (2006) The Tick *Ixodes ricinus*: Distribution and Climate Preferences in the Western Palaearctic. *Medical and Veterinary Entomology*, **20**, 189-197. http://dx.doi.org/10.1111/j.1365-2915.2006.00622.x

[89] Jaenson, T.G., Eisen, L., Comstedt, P., Mejlon, H.A., Lindgren, E., Bergström, S., *et al.* (2009) Risk Indicators for the Tick *Ixodes ricinus* and *Borrelia burgdorferi* Sensu Lato in Sweden. *Medical and Veterinary Entomology*, **23**, 226-237. http://dx.doi.org/10.1111/j.1365-2915.2009.00813.x

[90] Pejchalová, K., Zákovská, A., Mejzlíková, M., Halouzka, J. and Dendis, M. (2007) Isolation, Cultivation and Identification of *Borrelia burgdorferi* Genospecies from *Ixodes ricinus* Ticks from the City of Brno, Czech Republic. *Annals of Agricultural and Environmental Medicine*, **14**, 75-79.

[91] Haemig, P.D., Waldenstrom, J. and Olsen, B. (2008) Roadside Ecology and Epidemiology of Tick-Borne Diseases. *Scandinavian Journal of Infectious Diseases*, **40**, 853-858.

[92] Ljostad, U., Skogvoll, E., Eikeland, R., *et al.* (2008) Oral Doxycycline versus Intravenous Ceftriaxone for European Lyme Neuroborreliosis: A Multicentre, Non-Inferiority, Doubleblind, Randomised Trial. *The Lancet Neurology*, **7**, 690-695. http://dx.doi.org/10.1016/S1474-4422(08)70119-4

[93] Kruger, H., Kohlhepp, W. and Konig, S. (1990) Follow-Up of Antibiotically Treated and Untreated Neuroborreliosis. *Acta Neurologica Scandinavica*, **82**, 59-67. http://dx.doi.org/10.1111/j.1600-0404.1990.tb01588.x

[94] Kruger, H., Reuss, K., Pulz, M., *et al.* (1989) Meningoradiculitis and Encephalomyelitis due to *Borrelia burgdorferi*: A Follow-Up Study of 72 Patients over 27 Years. *Journal of Neurology*, **236**, 322-328. http://dx.doi.org/10.1007/BF00314373

[95] Ljostad, U. and Henriksen, T.H. (2008) Management of Neuroborreliosis in European Adult Patients. *Acta Neurologica Scandinavica*, **188**, 22-28. http://dx.doi.org/10.1111/j.1600-0404.2008.01027.x

[96] Hansen, K. and Lebech, A.M. (1992) The Clinical and Epidemiological Profile of Lyme Neuroborreliosis in Denmark 1985-1990. A Prospective Study of 187 Patients with *Borrelia burgdorferi* Specific Intrathecal Antibody Production. *Brain*, **115**, 399-423. http://dx.doi.org/10.1093/brain/115.2.399

[97] Topakian, R., Stieglbauer, K., Nussbaumer, K. and Aichner, F.T. (2008) Cerebral Vasculitis and stRoke in Lyme Neuroborreliosis. Two Case Reports and Review of Current Knowledge. *Cerebrovascular Diseases*, **26**, 455-461. http://dx.doi.org/10.1159/000155982

[98] Oschmann, P., Dorndorf, W., Hornig, C., Schafer, C., Wellensiek, H.J. and Pflughaupt, K.W. (1998) Stages and Syndromes of Neuroborreliosis. *Journal of Neurology*, **245**, 262-272. http://dx.doi.org/10.1007/s004150050216

[99] Pfister, H.W. and Rupprecht, T.A. (2006) Clinical Aspects of Neuroborreliosis and Post-Lyme Disease Syndrome in Adult Patients. *International Journal of Medical Microbiology*, **296**, 11-16. http://dx.doi.org/10.1016/j.ijmm.2005.12.003

[100] Gorson, K.C., Kolb, D.A., Marks, D.S., Hayes, M.T. and Baquis, G.D. (2011) Acute Brachial Diplegia Due to Lyme Disease. *Neurologist*, **17**, 24-27. http://dx.doi.org/10.1097/NRL.0b013e31820038cd

[101] Elamin, M., Alderazi, Y., Mullins, G., Farrell, M.A., O'Connell, S. and Counihan, T.J. (2009) Perineuritis in Acute Lyme Neuroborreliosis. *Muscle & Nerve*, **39**, 851-854. http://dx.doi.org/10.1002/mus.21289

[102] Logigian, E.L., Kaplan, R.F. and Steere, A.C. (1990) Chronic Neurologic Manifestations of Lyme Disease. *The New England Journal of Medicine*, **323**, 1438-1444. http://dx.doi.org/10.1056/NEJM199011223232102

[103] Lelovas, P., Dontas, I., Bassiakou, E. and Xanthos, T. (2008) Cardiac Implications of Lyme Disease, Diagnosis and Therapeutic Approach. *International Journal of Cardiology*, **129**, 15-21. http://dx.doi.org/10.1016/j.ijcard.2008.01.044

[104] Vegsundvag, J., Nordeide, J., Reikvam, A. and Jenum, P. (1993) Late Cardiac Manifestation of Infection with *Borrelia burgdorferi* (Lyme Disease). *BMJ*, **307**, 173. http://dx.doi.org/10.1136/bmj.307.6897.173

[105] Stanek, G., Klein, J., Bittner, R. and Glogar, D. (1991) *Borrelia burgdorferi* as an Etiologic Agent in Chronic Heart Failure? *Scandinavian Journal of Infectious Diseases. Supplementum*, **77**, 85-87.

[106] Kindstrand, E., Nilsson, B.Y., Hovmark, A., Pirskanen, R. and Asbrink, E. (2002) Peripheral Neuropathy in Acrodermatitis Chronica Atrophicans—Effect of Treatment. *Acta Neurologica Scandinavica*, **106**, 253-257. http://dx.doi.org/10.1034/j.1600-0404.2002.01336.x

[107] Dicaudo, D.J., Su, W.P., Marshall, W.F., Malawista, S.E., Barthold, S. and Persing, D.H. (1994) Acrodermatitis Chronica Atrophicans in the United States: Clinical and Histopathologic Features of Six Cases. *Cutis*, **54**, 81-84.

[108] Jaffe, E.S., Harris, N.L., Stein, H. and Vardiman, J. (2001) World Health Organization Classification of Tumours. In: Jaffe, E.S., Harris, N.L., Stein, H. and Vardiman, J., Eds., *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*, IARC Press, Lyon, 10-302.

[109] Suarez, F., Lortholary, O., Hermine, O., *et al*. (2006) Infection-Associated Lymphomas Derived from Marginal Zone B Cells: A Model of Antigen-Driven Lymphoproliferation. *Blood*, **107**, 3034-3044. http://dx.doi.org/10.1182/blood-2005-09-3679

[110] Goos, M. (1971) Acrodermatitis Chronica Atrophicans and Malignant Lymphoma. *Acta Dermato-Venereologica* (*Stockholm*), **51**, 457-459.

[111] Garbe, C., Stein, H., Dienemann, D. and Orfanos, C.E. (1991) *Borrelia burgdorferi* Associated Cutaneous B Cell Lymphoma: Clinical and Immunologic Characterization of Four Cases. *Journal of the American Academy of Dermatology*, **24**, 584-590. http://dx.doi.org/10.1016/0190-9622(91)70088-J

[112] Rijlaarsdam, J.U., Van der Putte, S.C.J., Berti, E., *et al*. (1993) Cutaneous Immunocytomas: A Clinicopathological Study of 26 Cases. *Histopathology*, **23**, 117-125. http://dx.doi.org/10.1111/j.1365-2559.1993.tb00469.x

[113] Munksgaard, L., Obitz, E.R., Goodlad, J.R., *et al.* (2004) Demonstration of *B. burgdorferi*-DNA in Two Cases of Nodal Lymphoma. *Leukemia & Lymphoma*, **45**, 1721-1723. http://dx.doi.org/10.1080/10428190410001683723

[114] Schöllkopf, C., Melbye, M., Munksgaard, L., Smedby, K.E., Rostgaard, K., Glimelius, B., Chang, E.T., Roos, G., Hansen, M., Adami, H. and Hjalgrim, H. (2008) Borrelia Infection and Risk of Non-Hodgkin Lymphoma. *Blood*, **111**, 5524-5529. http://dx.doi.org/10.1182/blood-2007-08-109611

[115] Shapiro, E.D. and Gerber, M.A. (2006) Chapter 5. Lyme Disease. In: Baker, C.J., Klein, J. and Remington, J., Eds., *Infectious Diseases of the Fetus and Newborn Infant*, Elsevier, Philadelphia, 485-497. http://dx.doi.org/10.1016/B0-72-160537-0/50017-7

[116] Silver, R.M., Yang, L., Daynes, R.A., Branch, D.W., *et al.* (1995) Fetal Out Comein Murine Lyme Disease. *Infection and Immunity*, **63**, 66-72.

[117] Schlesinger, P.A., Duray, P.H., Burke, B.A., Steere, A.C. and Stillman, M.T. (1985) Maternal-Fetal Transmission of Lyme Disease Spirochete, *Borrelia burgdorferi*. *Annals of Internal Medicine*, **103**, 67-68. http://dx.doi.org/10.7326/0003-4819-103-1-67

[118] Weber, K., Bratzke, H.J., Neubert, U., Wilske, B. and Duray, P.H. (1988) *Borrelia burgdorferi* in a Newborn Despite Oral Penicillin for *Lyme borreliosis* during Pregnancy. *The Pediatric Infectious Disease Journal*, **7**, 286-289. http://dx.doi.org/10.1097/00006454-198804000-00010

[119] Mylonas, I. (2011) Borreliosis during Pregnancy: A Risk for the Unborn Child. *Vector-Borne and Zoonotic Diseases*, **11**, 891-898. http://dx.doi.org/10.1089/vbz.2010.0102

[120] Evans, J. (1999) Lyme Disease. *Current Opinion in Rheumatology*, **11**, 281-288. http://dx.doi.org/10.1097/00002281-199907000-00010

[121] Nadelman, R.B. and Wormser, G.P. (1998) *Lyme borreliosis. The Lancet*, **352**, 557-565. http://dx.doi.org/10.1016/S0140-6736(98)01146-5

[122] Pfister, H.W., Wilske, B. and Weber, K. (1994) *Lyme borreliosis*: Basic Science and Clinical Aspects. *The Lancet*, **343**, 1013-1016. http://dx.doi.org/10.1016/S0140-6736(94)90130-9

[123] Striker, R.B. and Winger, E.E. (2001) Decreased CD57 Lymphocyte Subset in Patients with Chronic Lyme Disease. *Immunology Letters*, **76**, 43-48. http://dx.doi.org/10.1016/S0165-2478(00)00316-3

[124] Sansoni, P., Cossarizza, A., Brianti, V., Fagnoni, F., Snelli, G., Monti, D., Marcato, A., Passeri, G., Ortolani, C. and Forti, E. (1993) Lymphocyte Subsets and Natural Killer Cell Activity in Healthy Old People and Centenarians. *Blood*, **82**, 2767-2773.

[125] Dinges, D.F., Douglas, S.D., Zaugg, L., Campbell, D.E., McMann, J.M., Whitehouse, W.G., Orne, E.C., Kapoor, S.C., Icaza, E. and Orne, M.T. (1994) Leukocytosis and Natural Killer Cell Function Parallel Neurobehavioral Fatigue Induced by 64 Hours of Sleep Deprivation. *Journal of Clinical Investigation*, **93**, 1930-1939. http://dx.doi.org/10.1172/JCI117184

[126] Wang, E.C. and Borysiewicz, L.K. (1995) The Role of CD8, CD57 Cells in Human Cytomegalovirus and Other Viral Infections. *Scandinavian Journal of Infectious Diseases*, **99**, 69-77.

[127] Yssel, H., Shanafelt, M.C., Soderberg, C., Schneider, P.V., Anzola, J. and Peltz, G. (1991) *Borrelia burgdorferi* Activates a T Helper Type 1-Like T Cell Subset in Lyme Arthritis. *The Journal of Experimental Medicine*, **174**, 593-601. http://dx.doi.org/10.1084/jem.174.3.593

[128] Kreuzfelder, E., Shen, G., Bittorf, M., Scheiermann, N., Thraenhart, O., Seidel, D. and Grosse-Wilde, H. (1992) Enumeration of T, B and Natural Killer Peripheral Blood Cells of Patients with Multiple Sclerosis and Controls. *European Neurology*, **32**, 190-194. http://dx.doi.org/10.1159/000116820

[129] Eoli, M., Ferrarini, M., Dufour, A., Heltaj, S., Bevilacqua, L., Comi, G., Cosi, V., Filippini, G., Martinelli, V. and Milanese, C. (1993) Presence of T-Cell Subset Abnormalities in Newly Diagnosed Cases of Multiple Sclerosis and Relationship with Short-Term Clinical Activity. *Journal of Neurology*, **240**, 79-82. http://dx.doi.org/10.1007/BF00858721

[130] Arai, K., Yamamura, S., Seki, S., Hanyu, T., Takahashi, H.E. and Abo, T. (1998) Increase of CD57 T Cells in Knee Joints and Adjacent Bone Marrow of Rheumatoid Arthritis Patients: Implication for an Anti-Inflammatory Role. *Clinical Experimental Immunology*, **111**, 345-352. http://dx.doi.org/10.1046/j.1365-2249.1998.00511.x

[131] Imberti, L., Sottini, A., Signorini, S., Gorla, R. and Primi, D. (1997) Oligoclonal CD4 CD57 T-Cell Expansions Contribute to the Imbalanced T-Cell Receptor Repertoire of Rheumatoid Arthritis Patients. *Blood*, **89**, 2822-2832.

[132] Gallo, P., Chiusole, M., Sanzari, M., Sivieri, S., Piccinno, M.G., Argentiero, V., Rizzotti, P. and Tavolato, B. (1994) Effect of High-Dose Steroid Therapy on T-Cell Populations. A Longitudinal Study in MS Patients. *Acta Neurologica Scandinavica*, **89**, 95-101. http://dx.doi.org/10.1111/j.1600-0404.1994.tb01642.x

[133] Shoemaker, R.C., Giclas, P.C., Crowder, C., House, D. and Glovsky, M.M. (2008) Complement Split Products C3a and C4a Are Early Markers of Acute Lyme Disease in Tick Bite Patients in the United States. *International Archives of Allergy and Immunology*, **146**, 255-261. http://dx.doi.org/10.1159/000116362

[134] Stricker, R.B., Savely, V.R., Montanya, N.C. and Giclas, P.C. (2008) Complement Split Products C3a and C4a in Chronic Lyme Disease. *Scandinavian Journal of Immunology*, **69**, 64-69. http://dx.doi.org/10.1111/j.1365-3083.2008.02191.x

[135] Mocco, J., Wilson, D.A., Komotar, R.J., *et al*. (2006) Alterations in Plasma Complement Levels after Human Ischemic Stroke. *Neurosurgery*, **59**, 28-33. http://dx.doi.org/10.1227/01.NEU.0000219221.14280.65

[136] Mack, W.J., Ducruet, A.F., Hickman, Z.L., *et al*. (2007) Early Plasma Complement C3a Levels Correlate with Functional Outcome after Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery*, **61**, 255-260. http://dx.doi.org/10.1227/01.NEU.0000255518.96837.8E

[137] Sorensen, B., Streib, J.E., Strand, M., *et al.* (2003) Complement Activation in a Model of Chronic Fatigue Syndrome. *Journal of Allergy and Clinical Immunology*, **112**, 397-403. http://dx.doi.org/10.1067/mai.2003.1615

[138] Panelius, J., Lahdenne, P., Saxen, H., *et al.* (2003) Diagnosis of Lyme Neuroborreliosis with Antibodies to Recombinant Proteins DbpA, BBK32, and OspC, and VlsE IR6 Peptide. *Journal of Neurology*, **250**, 1318-1327.

http://dx.doi.org/10.1007/s00415-003-0205-2

[139] Skarpaas, T., Liostad, U., Sobye, M. and Mygland, A. (2007) Sensitivity and Specificity of a Commercial C6 Peptide Enzyme Immuno Assay in Diagnosis of Acute Lyme Neuroborreliosis. *European Journal of Clinical Microbiology Infectious Diseases*, **26**, 675-677. http://dx.doi.org/10.1007/s10096-007-0336-y

[140] Tjernberg, I., Schon, T., Ernerudh, J., Wistedt, A.C., Forsberg, P. and Eliasson, I. (2008) C6-Peptide Serology as Diagnostic Tool in Neuroborreliosis. *APMIS*, **116**, 393-399. http://dx.doi.org/10.1111/j.1600-0463.2008.00842.x

[141] Vermeersch, P., Resseler, S., Nackers, E. and Lagrou, K. (2009) The C6 Lyme Antibody Test Has Low Sensitivity for Antibody Detection in Cerebrospinal Fluid. *Diagnostic Microbiology and Infectious Disease*, **64**, 347-349. http://dx.doi.org/10.1016/j.diagmicrobio.2009.03.013

[142] Wilske, B., Fingerle, V. and Schulte-Spechtel, U. (2007) Microbiological and Serological Diagnosis of *Lyme borreliosis*. *FEMS Immunology and Medical Microbiology*, **49**, 13-21. http://dx.doi.org/10.1111/j.1574-695X.2006.00139.x

[143] Brouqui, P., Bacellar, F., Baranton, G., *et al.* (2004) Guidelines for the Diagnosis of Tick-Borne Bacterial Diseases in Europe. *Clinical Microbiology and Infection*, **10**, 1108-1132. http://dx.doi.org/10.1111/j.1469-0691.2004.01019.x

[144] Johnson, B.J., Robbins, K.E., Bailey, R.E., *et al.* (1996) Serodiagnosis of Lyme Disease: Accuracy of a Two-Step Approach Using a Flagella-Based ELISA and Immunoblotting. *The Journal of Infectious Diseases*, **174**, 346-353. http://dx.doi.org/10.1093/infdis/174.2.346

[145] Ulvestad, E. and Kristoffersen, E.K. (2002) False Positive Serological Test in Suspected Borreliosis. *Tidsskrift For Den Norske Laegeforening*, **122**, 88-90.

[146] Mygland, A., Skarpaas, T. and Ljostad, U. (2006) Chronic Polyneuropathy and Lyme Disease. *European Journal of Neurology*, **13**, 1213-1215. http://dx.doi.org/10.1111/j.1468-1331.2006.01395.x

[147] Van Dam, A.P., Kuiper, H., Vos, K., *et al.* (1993) Different Genospecies of *Borrelia burgdorferi* Are Associated with Distinct Clinical Manifestations of *Lyme borreliosis*. *Clinical Infectious Diseases*, **17**, 708-717. http://dx.doi.org/10.1093/clinids/17.4.708

[148] Von Stedingk, L.V., Olsson, I., Hanson, H.S., Asbrink, E. and Hovmark, A. (1995) Polymerase Chain Reaction for Detection of *Borrelia burgdorferi* DNA in Skin Lesions of Early and Late *Lyme borreliosis*. *European Journal of Clinical Microbiology Infectious Diseases*, **14**, 1-5. http://dx.doi.org/10.1007/BF02112610

[149] Jaulhac, B., Heller, R., Limbach, F.X., *et al.* (2000) Direct Molecular Typing of *Borrelia burgdorferi* Sensu Lato Species in Synovial Samples from Patients with Lyme Arthritis. *Journal of Clinical Microbiology*, **38**, 1895-1900.

[150] Eiffert, H., Karsten, A., Thomssen, R. and Christen, H.J. (1998) Characterization of *Borrelia burgdorferi* Strains in Lyme Arthritis. *Scandinavian Journal of Infectious Diseases*, **30**, 265-268. http://dx.doi.org/10.1080/00365549850160918

[151] Cerar, T., Ogrinc, K., Cimperman, J., Lotric-Furlan, S., Strle, F. and Ruzic-Sabljic, E. (2008) Validation of Cultivation and PCR Methods for Diagnosis of Lyme Neuroborreliosis. *Journal of Clinical Microbiology*, **46**, 3375-3379. http://dx.doi.org/10.1128/JCM.00410-08

[152] Lebech, A.M. (2002) Polymerase Chain Reaction in Diagnosis of *Borrelia burgdorferi* Infections and Studies on Taxonomic Classification. *APMIS Supplement*, **105**, 1-40.

[153] Molloy, P.J., Persing, D.H. and Berardi, V.P. (2001) False-Positive Results of PCR Testing for Lyme Disease. *Clinical Infectious Diseases*, **33**, 412-413. http://dx.doi.org/10.1086/321911

[154] Cameron, D., Gaito, A., Harris, N., *et al.* (2004) Evidence-Based Guidelines for the Management of Lyme Disease. *Expert Review of Anti-infective Therapy*, **2**, S1-S13. http://dx.doi.org/10.1586/14789072.2.1.S1

[155] Wormser, G.P., Dattwyler, R.J., Shapiro, E.D., *et al.* (2006) The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, **43**, 1089-1134. http://dx.doi.org/10.1086/508667

[156] Stanek, G., O'Connell, S., Cimmino, M., *et al.* (1996) European Union Concerted Action on Risk Assessment in *Lyme borreliosis*: Clinical Case Definitions for *Lyme borreliosis*. *Wiener Klinische Wochenschrift*, **108**, 741-747.

[157] Mygland, A., Ljostad, U., Fingerle, V., Rupprecht, T., Schmutzhard, E. and Steiner, I. (2010) EFNS Guidelines on the Diagnosis and Management of European Lyme Neuroborreliosis. *European Journal of Neurology*, **17**, 8-16. http://dx.doi.org/10.1111/j.1468-1331.2009.02862.x

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