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Lyme arthritis: linking infection, inflammation and autoimmunity

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Abstract

Infectious agents can trigger autoimmune responses in a number of chronic inflammatory diseases. Lyme arthritis, which is caused by the tick-transmitted spirochaete *Borrelia burgdorferi*, is effectively treated in most patients with antibiotic therapy; however, in a subset of patients, arthritis can persist and worsen after the spirochaete has been killed (known as post-infectious Lyme arthritis). This Review details the current understanding of the pathogenetic events in Lyme arthritis, from initial infection in the skin, through infection of the joints, to post-infectious chronic inflammatory arthritis. The central feature of post-infectious Lyme arthritis is an excessive, dysregulated pro-inflammatory immune response during the infection phase that persists into the post-infectious period. This response is characterized by high amounts of IFNγ and inadequate amounts of the anti-inflammatory cytokine IL-10. The consequences of this dysregulated pro-inflammatory response in the synovium include impaired tissue repair, vascular damage, autoimmune and cytotoxic processes, and fibroblast proliferation and fibrosis. These synovial characteristics are similar to those in other chronic inflammatory arthritides, including rheumatoid arthritis. Thus, post-infectious Lyme arthritis provides a model for other chronic autoimmune or autoinflammatory arthritides in which complex immune responses can be triggered and shaped by an infectious agent in concert with host genetic factors.

Microbial infections have long been hypothesized to have a role in triggering autoimmunity in chronic inflammatory diseases[1]. However, the clinical onset of autoimmune disorders often develops over years or decades, making it difficult to establish a causal link between exposure to an infectious trigger and subsequent disease. Uniquely in Lyme arthritis, a late

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Competing interests

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manifestation of Lyme disease, the triggering event, *Borrelia burgdorferi* infection, is known with certainty.

Lyme disease (also known as Lyme borreliosis) occurs in temperate regions of North America, Europe and Asia (FIG. 1), and causes ~300,000 cases annually in the USA[2]. Lyme disease is caused by the tick-transmitted spirochaete *B. burgdorferi* sensu lato (*B. burgdorferi* in the general sense), which consists of 20 different species[2]. However, the human infection is caused primarily by three species, *B. burgdorferi* sensu stricto (*B. burgdorferi* in the strict sense, hereafter called *B. burgdorferi*) in the USA, and *Borrelia afzelii* and *Borrelia garinii* in Europe and Asia. Less common species that can infect humans include *Borrelia mayonii* in upper midwestern USA, *Borrelia bavariensis* (which is closely related to *B. garinii*) in Europe and Asia, and *B. burgdorferi* in Europe. Each species or subtype is associated with distinct clinical features; for example, the common subtypes of *B. burgdorferi* that are found in north-eastern USA are particularly arthritogenic, whereas *B. garinii* and *B. afzelii* rarely cause Lyme arthritis[2].

Infection with *B. burgdorferi* usually begins with an expanding erythema migrans skin lesion, which develops at the site of the tick bite[2] (FIG. 2a). Within weeks, spirochaetal strains from north-eastern USA can disseminate to a number of sites[3], a process that is often accompanied by flu-like symptoms and can be shortly followed by organ-specific involvement, particularly neurological or cardiac abnormalities[4]. Months later, many patients develop Lyme arthritis, which is characterized by intermittent or persistent joint swelling and pain, primarily in large joints (especially the knees) for a period of several years[5,6]. In some patients, early infection is asymptomatic and Lyme arthritis is the presenting manifestation of Lyme disease.

Most patients with Lyme arthritis respond to appropriate oral and, if needed, intravenous antibiotic therapy, and the arthritis resolves (termed antibiotic-responsive Lyme arthritis)[7,8]. However, in a small percentage of patients, joint swelling lessens but synovitis persists or worsens after spirochaetal killing with antibiotic therapy[7,9]. These patients develop massive synovial hyperplasia[10], often accompanied by autoimmune T and B cell responses that can last for several years[11–16], called post-infectious (or post-antibiotic or antibiotic-refractory) Lyme arthritis. After appropriate oral and intravenous antibiotic therapy, such patients are treated with DMARDs[17], the standard of care for chronic autoimmune or autoinflammatory types of arthritis. As only one knee is usually affected in post-infectious Lyme arthritis, synovectomy is also an option[18]. The synovial lesion in post-infectious Lyme arthritis is similar to that seen in other forms of chronic inflammatory arthritis (FIG. 2b), including rheumatoid arthritis (RA)[9,10,19].

In addition to relevant human studies, several in-bred, congenic and knockout strains of mice have provided critical insights into Lyme arthritis pathogenesis (TABLE 1). *B. burgdorferi*-infected C3H/HeN (C3H) mice develop severe arthritis of the tibiotarsal joint with thickening of the tibiotarsal tendon sheath, which peaks several weeks following infection and then spontaneously resolves[20]. By contrast, *B. burgdorferi*-infected C57BL/6 (B6) mice have only mild arthritis and quickly repair damaged tissue, leading to a reduction in all parameters of joint disease[21]. Comparison of how these two strains respond to *B.*

burgdorferi infection has led to the identification of genetic and immune factors that are important for arthritis development[22]. However, important differences exist between mice and humans. Mice primarily rely on innate immune responses to control *B. burgdorferi* infection, whereas humans employ both innate and adaptive immune responses throughout infection. In humans, arthritis usually only develops after months of infection within the context of expanded innate and adaptive responses, which can become excessive and maladaptive. Immune responses to *B. burgdorferi* in mice and humans are discussed in more detail elsewhere[23].

In this Review, we integrate human and mouse studies to detail the pathogenetic features of Lyme arthritis, from initial infection of the skin, to infection of joints, to post-infectious arthritis. We emphasize how, in genetically susceptible individuals, infection with certain *B. burgdorferi* strains can trigger an excessive, dysregulated immune response that results in post-infectious inflammatory synovitis similar to that seen in other forms of chronic autoimmune or inflammatory arthritis, including RA.

Skin infection and dissemination

After the injection of *Borrelia* spp. into the skin by an *Ixodes* tick, spirochaetes multiply in erythema migrans lesions[24] (FIG. 3a). The immune response in the skin includes T cells, macrophages, dendritic cells and a small number of B cells[25,26], and the main cytokines expressed are the pro-inflammatory cytokines IFNγ and IL-6, and the anti-inflammatory cytokine IL-10 (REFS[25,27]). In the USA, *B. burgdorferi* often disseminates in the blood during the first few weeks of infection in a process that requires the binding of *Borrelia* surface adhesins to host integrins on the vascular endothelium[28–30] (FIG. 3b). As shown in mice, the spread of *B. burgdorferi* through the vasculature or lymphatics is dependent on the interactions of spirochaetal surface molecules and endothelial cell membrane proteins. Bacterial–endothelial cell interactions result in the loosening of tight junctions and migration of spirochaetes into the synovial extracellular matrix via small vascular lesions[31,32] (FIG. 3c). In response, natural killer T (NKT) cells, tissue-resident macrophages, polymorphonuclear cells and stromal cells have an important role in maintaining endothelial cell barrier function, limiting spirochaetal invasion into extravascular tissues and suppressing tissue damage and arthritis development[33]. NKT cells secrete IFNγ in response to immunogenic *B. burgdorferi* glycolipids[34,35] that are presented by CD1-expressing antigen-presenting cells[36,37]. Macrophages, polymorphonuclear cells, fibroblasts and endothelial cells respond to spirochaetal invasion by producing large amounts of innate immune response and tissue repair proteins. Notably, variations in these responses greatly affect arthritis severity and outcome.

According to one subtyping system[38], out of 23 *B. burgdorferi* outer-surface protein C (OspC) subtypes, types A, B, I and K are the most likely to disseminate in humans[39]. In patients with disseminated early infection, many interferon-associated genes are upregulated in peripheral blood mononuclear cells[27,40]. Serum samples often show high concentrations of the macrophage-recruiting chemokine CCL2 and of the innate immune mediators IL-6 and TNF, although the anti-inflammatory cytokine IL-10 is also prominent[41]. Patients with disseminated infection also have high serum concentrations of T helper 1

(T_H1) cell-associated immune mediators, including IFNγ and the IFNγ-inducible T cell chemokines CXCL9 and CXCL10 (REFS[41,42]). Many patients' sera contain numerous T_H17 cell-associated mediators, particularly IL-23 (REF.[43]). Infection with the OspC type A (RST1) strain is particularly inflammatory, leading to more severe symptoms in patients with erythema migrans[41,42]. Similarly, strain-specific OspC also has an important role in spirochaetal joint invasion and colonization in mice[44].

Lyme disease spirochaetes are only transiently present in the blood[45] and rapidly migrate to extravascular tissues via transendothelial migration[46]. With their unique planar wave motion, these bacteria are highly adapted to move through dense connective tissue, which requires the binding of plasminogen or its activators to the surface of the organism[47]. The spirochaetal adhesins decorin binding protein A (DbpA) and DbpB bind to host decorin[48], a proteoglycan that is bound to collagen, and spirochaetes can also bind directly to, invade and colonize native type I collagen lattices[32]. The binding of DbpA and DbpB to host decorin probably explains the alignment of spirochaetes with collagen fibrils in connective tissue in joints, heart or nerves[49]. Genetic variability in *Borrelia* outer-surface adhesins at least partially explains differences in tissue tropism between strains[41,50,51]. For example, in a mouse study, *B. burgdorferi* OspC subtypes that bound dermatan sulfate were associated with joint invasion[44], which the authors suggest could explain the exceptional arthritogenicity of certain spirochaetal strains found in north-eastern USA.

The antibody response to *B. burgdorferi* develops slowly, and during the first few weeks of infection an IgM response is seen in only a minority of patients[52]. Total IgM concentrations can also be increased during early infection, suggestive of polyclonal activation of B cells[53]. As *B. burgdorferi* disseminates and infects host tissues, an increasingly higher percentage of patients develop IgM and IgG responses to the spirochaete[52,54]. To evade the host antibody response, spirochaetes seek protected niches and change the expression profile of their outer-surface proteins[55]. In particular, the lipoprotein VlsE undergoes extensive antigenic variation[56]. In addition, *B. burgdorferi* evade innate immune responses by binding host complement regulator proteins to their surface, which inactivate complement and induce innate immune tolerance[57].

Dysregulation of innate immune responses during early disseminated infection might promote subsequent arthritis development. In C3H mice, type I interferons (IFNα and IFNβ) have a particularly important role during the first week of infection and set the stage for the subsequent development of arthritis[58]. Importantly, the type I interferon response (typically associated with anti-viral immunity) is maladaptive and has no effect on host defence[59]. This type I interferon response is accompanied by downregulation of numerous genes involved in tissue repair and wound healing, such as extracellular matrix proteins and transforming growth factor-β-inducible genes[60]. By contrast, B6 mice, which develop only mild Lyme arthritis, lack the robust interferon signature seen in arthritogenic C3H mice and exhibit marked upregulation of tissue repair and wound healing genes in joints at 1 week post-infection[60].

As in C3H mice, early type I interferon responses are likely to be arthritogenic in humans with Lyme arthritis. Human peripheral blood mononuclear cells stimulated with the highly

inflammatory OspC type A (RST1) strain of *B. burgdorferi* secrete type I interferons as well as type II interferon (IFNγ)[42]. In addition, type I and II interferons are predominant in erythema migrans skin lesions[27]. Moreover, type I interferons are known to be important in the development of a number of rheumatic and autoimmune diseases[61]. Given that patients with erythema migrans who are treated with antibiotics do not develop subsequent arthritis, it is difficult to directly test the importance of early type I interferon responses in the subsequent development of arthritis in humans. However, a role for type I interferons can be inferred from responses in C3H mice. On the basis of studies in this mouse model, we hypothesize that during early disease, dysregulated type I interferon responses to *B. burgdorferi* in the skin or joint set the stage for severe Lyme arthritis and autoimmunity later in the disease.

Lyme arthritis during active infection

Months after the initial infection, along with an expansion of the immune response to *B. burgdorferi*, untreated patients often develop marked joint swelling, frequently in one or both knees. *B. burgdorferi* has rarely been cultured from the synovial fluid of patients with Lyme arthritis, but prior to antibiotic treatment, *B. burgdorferi* DNA (but not mRNA) can be found in the synovial fluid of ~70% of these patients[24,62]. This finding suggests that live spirochaetes might survive only in protected tissue niches within joints and are killed if they escape into synovial fluid. During joint infection, immune responses are focused on spirochaetal killing, primarily through acute inflammatory responses to pathogen-associated molecular patterns (PAMPs), antibody production and the infiltration of polymorphonuclear cells into synovial fluid[9], which might be the principal barrier preventing spirochaetal escape. In addition, large amounts of NF-κB-induced acute pro-inflammatory cytokines and chemokines are found in synovial tissue and synovial fluid from patients with Lyme arthritis[41,42,63], typical of innate immune responses to bacterial infections.

Robust anti-*B. burgdorferi* antibody responses develop towards a large array of spirochaetal proteins[52,64]. Patients with Lyme arthritis can have antibody reactivity to as many as 89 spirochaetal proteins[65], primarily outer-surface proteins, many of which are lipidated and might serve as immune adjuvants[66]. Two spirochaetal glycolipids, acylated cholesteryl galactoside (*Bb*GL1) and monogalactosyl diacylglycerol (*Bb*GL2), are also highly immunogenic[34]. Moreover, patients with Lyme arthritis can have antibody responses to spirochaetal antigens that are ordinarily expressed only in the tick, such as OspA, OspD and *Borrelia* iron and copper-binding protein A (BicA), a phenomenon found almost exclusively in the highly inflammatory milieu of joints in North American patients with Lyme arthritis[67]. Similarly, *B. burgdorferi* can be induced to express tick-specific proteins in mice in a highly inflammatory environment[68].

Marked T_H1 cell responses to *B. burgdorferi* antigens also occur in patients with Lyme arthritis, particularly among synovial fluid mononuclear cells, which produce large amounts of IFNγ[69–71]. The role of these cells might be primarily to help B cells to produce neutralizing antibodies against the spirochaete. Anti-borrelial antibodies are predominantly T cell-dependent IgG1 and IgG3 isotypes, which are capable of inducing opsonization and activating complement[72]. Most synovial fluid mononuclear cells also express memory

markers[71], which helps to explain why *B. burgdorferi* T cell and B cell responses typically persist for many years after the resolution of Lyme arthritis, and why reinfection occurs only rarely, if at all, after Lyme arthritis.

Animal model studies have provided insights into important innate immune effectors in Lyme arthritis (TABLE 1). Mice deficient in certain innate immune response pathways, particularly those involved in recognition of *B. burgdorferi* surface lipoproteins, including Toll-like receptor 2 (TLR2) and myeloid differentiation primary response protein MyD88, have impaired host defence and develop severe Lyme arthritis[73–76]. In addition, C3H mice have a hypomorphic allele (*Bbaa2* locus on Chromosome 5) encoding the lysosomal enzyme β-glucuronidase, which allows the accumulation of arthritogenic glycosaminoglycans in infected joints[77,78]. Similarly, the *Bbaa1* locus on Chromosome 4 in C3H mice, which contains the type I interferon locus, is involved in dysregulated type I interferon responses and severe Lyme arthritis[79–81].

Untreated patients with Lyme arthritis often have intermittent flares of arthritis or persistent arthritis over a period of several years[5]. One theory is that spirochaetes might survive in relatively avascular sites, such as the tendons in and around joints, and then escape from these sites occasionally to repopulate the synovial tissue[82,83]. Consistent with this hypothesis, joint swelling might be more severe and prolonged in recurrent flares, and the very high antibody responses that occur in patients with Lyme arthritis are consistent with repeated waves of antigenic exposure to spirochaetes[5]. As affected joints are no longer swollen after treatment in antibiotic-responsive patients, post-infection immune responses cannot be assessed in these patients' joints. However, we predict that antibacterial responses are downregulated after spirochaetal killing and wound repair genes are upregulated, leading to tissue repair, a return to joint homeostasis and arthritis resolution (FIG. 4), similar to the strong tissue repair signature that occurs in the joints of infected B6 mice[60].

Post-infectious Lyme arthritis

Rather than resolution of arthritis after antibiotic therapy, a small percentage of patients with Lyme arthritis have persistent synovitis that can worsen in the post-antibiotic period[7]. In these patients, the synovial lesion — the target of the immune response — shows massive synovial fibroblast proliferation and fibrosis, infiltration of mononuclear cells, large amounts of antigen presentation, marked vascular proliferation and, in some patients, obliterative microvascular lesions and massive fibrin deposition suggestive of microscopic bleeding[84,85] (FIG. 5). These histological findings are similar to those that occur in other autoimmune or autoinflammatory forms of arthritis, including RA, albeit with a greater emphasis on microvascular damage in post-infectious Lyme arthritis[10,12,84–86]. Damage to the microvasculature, including obliterative microvascular lesions, seems to be a common feature of Lyme disease and can be found in other affected tissues, including the heart[49,87,88], skeletal muscle[49,89] and dura mater[90]. The inflammatory process in the joints can be accompanied by tendon sheath thickening (tenosynovitis) and tendon calcification (tendonitis) and, occasionally, by mild-to-moderate cartilage damage[91]. Although synovial fluid contains a very high percentage of neutrophils during active infection, in the post-infectious stage it contains relatively fewer neutrophils and proportionally more monocytes,

macrophages and lymphocytes, suggestive of an expanded inflammatory response in the post-infectious phase[9]. In contrast with RA, post-infectious Lyme arthritis eventually resolves in all patients — often with the aid of DMARD therapy — usually within 1–2 years, but within a maximum of 4–5 years[7,17]. Presumably, without the immune stimuli provided by live spirochaetes, the immune response eventually regains homeostasis and the arthritis resolves.

These changes in the cellular infiltrate in synovial fluid result from an inadequately restrained, excessive pro-inflammatory immune response that begins during infection and continues into the post-infectious period[92]. Infection with the highly inflammatory OspC Type A (RST1) strain of *B. burgdorferi* more commonly results in this outcome[42,51]. In studies of *B. burgdorferi* isolates from erythema migrans skin lesions, OspC type A strains were found in the USA in 21 of 58 isolates (36%) from New England states[93], 46 of 291 isolates (16%) from New York state[39] and only 2 of 65 isolates (3%) from Wisconsin, an upper midwestern state[94], compared with 0 of 29 isolates from Slovenia[95]. These results might explain why post-infectious Lyme arthritis is most often found in New England. Nevertheless, a 2019 French study described patients with post-infectious Lyme arthritis that were similar to those found in the USA[96], suggesting that highly inflammatory strains of *B. burgdorferi* might occur in certain regions in Europe.

Although the strain of *B. burgdorferi* is an important factor in stimulating excessive immune responses during infection, culture and PCR results have been uniformly negative in synovial tissue obtained from patients with Lyme arthritis months to years after antibiotic therapy[24], hence the use of the term post-infectious Lyme arthritis[10]. Moreover, after oral and intravenous antibiotic therapy, re-emergence of infection has not been noted while patients are being treated with DMARDs[7]. However, spirochaetal remnants can persist during the post-infectious period[82]. A 2019 study found that *B. burgdorferi* peptidoglycan, a predominant cell wall component, is detectible in post-infectious Lyme arthritis synovial fluid up to several years after antibiotic treatment[97]. *B. burgdorferi* peptidoglycan is shed during cell replication and is uniquely difficult to clear[97]. Thus, uncleared peptidoglycan might be an important factor in promoting innate immune responses in the post-infectious period in genetically predisposed individuals.

Host factors associated with excessive immune responses.

Transcriptomic analysis of synovia from patients with post-infectious Lyme arthritis shows prominent gene signatures associated with innate immune responses, antigen presentation and cell-mediated immune activation[10]. As in erythema migrans skin lesions, a large number of interferon-response genes are highly or moderately enriched in synovial tissue from all patients with post-infectious Lyme arthritis[10]. Importantly, this high interferon signature correlates inversely with tissue repair response gene signatures[10], indicating that high concentrations of interferons impair wound healing. Supporting the transcriptomic data, large percentages of T cells and natural killer (NK) cells isolated from synovial tissue or synovial fluid test positive for IFNγ by intracellular cytokine staining[10,70,71]. Thus, in patients with post-infectious Lyme arthritis, high numbers of IFNγ-producing lymphocytes present in synovial tissue might prevent appropriate repair of tissue damaged

by *B. burgdorferi* infection, blocking the return to tissue homeostasis even after the bacteria themselves are cleared[9].

Both host and spirochaetal genetic factors can contribute to this exceptionally high IFNγ response. In individuals with a *TLR1* single nucleotide polymorphism (1805GG) that affects the recognition of PAMPs by innate immune cells, infection with OspC type A (RST1) strains of *B. burgdorferi* leads to exceptionally high levels of IFNγ and signal transducer and activator of transcription 1 (STAT1)-dependent cytokines in joints[41]. In an initial study, this *TLR1* polymorphism was present in 24 of 47 European Americans (51%), but in only 2 of 24 African Americans (8%) and 0 of 390 Vietnamese individuals[98].

Among patients with Lyme arthritis in New England, the 18055GG polymorphism was present in 35 of 76 patients with antibiotic-responsive arthritis (47%) compared with 62 of 101 patients with post-infectious arthritis (62%)[41]. This polymorphism is within the portion of the gene that encodes the transmembrane region of TLR1 and might impair cell surface localization and downstream NF-κB signalling in response to the TLR1 and TLR2 ligand Pam3CSK4 (REF.[99]). Paradoxically, patients with Lyme arthritis who have this polymorphism have exceptionally high amounts of IFNγ, as well as STAT1-regulated and NF-κB-regulated pro-inflammatory immune mediators in their joints, but unremarkable amounts of IL-10 (REF.[41]). This polymorphism is hypothesized to be associated with excessive inflammatory responses to *B. burgdorferi* because it results in a deficiency in Janus kinase–STAT, NF-κB and mitogen-activated protein kinase feedback loop inhibitors, such as the regulatory microRNA miR-146a[100] and the anti-inflammatory cytokine IL-10 (REF.[101]).

Antigen presentation of certain *B. burgdorferi* peptides by specific HLA-DR molecules might also lead to high IFNγ concentrations. In one study, 7 of 14 HLA-DRB molecules — HLA-DRB1*04:01 in particular — bound to a peptide from *B. burgdorferi* OspA (OspA163–175), whereas the other seven HLA-DRB molecules (including HLA-DRB1*11:01) did not[102]. Among patients with post-infectious Lyme arthritis, 56 of 71 (79%) had at least one HLA-DRB molecule that bound *B. burgdorferi* OspA163–175, compared with 23 of 50 patients with antibiotic-responsive Lyme arthritis (46%)[102]. As mentioned previously, immune responses to OspA are found primarily in the highly inflammatory joint milieu of patients with Lyme arthritis in North America[67]. In transgenic mice, those expressing the human HLA-DR4 allele had higher IFNγ responses and lower titres of anti-*Borrelia* antibodies than mice expressing the human HLA-DR11 allele, which had higher anti-*Borrelia* antibody titres but lower IFNγ responses[103]. Thus, presentation of OspA163–175 by certain HLA-DR molecules is associated with high IFNγ concentrations and with post-infectious Lyme arthritis.

Two NF-κB-regulated microRNAs, miR-146a and miR-155, which have been associated with a number of inflammatory joint diseases[104], including RA, are also prominent in Lyme arthritis[9,104]. Experiments in mice have shown that these two microRNAs fine-tune the amplitude of inflammatory responses to *B. burgdorferi* to balance host defence and tissue damage in Lyme arthritis[100,105]. miRNA-146a functions as a feedback inhibitor of NF-κB signalling, and mice lacking miR-146a develop more severe Lyme arthritis than wild-type

mice, despite having fewer bacteria in their joints[100]. By contrast, miR-155 enhances acute inflammation by potentiating NF-κB and STAT1 signal transduction[105]. In humans with post-infectious Lyme arthritis, miR-155 is particularly enriched in synovial fluid and correlates positively with arthritis duration, but is below or near the limit of detection in patients with antibiotic-responsive Lyme arthritis[9]. Concentrations of both miR-146a and miR-155 remain persistently elevated in synovial tissue and fluid from patients with post-infectious Lyme arthritis, providing further evidence of chronic NF-κB activation in the inflamed synovium[9].

Several other types of immune regulation imbalance can result in high concentrations of IFNγ. In patients with post-infectious Lyme arthritis, a high percentage of $CD4^+CD25^+$ T cells, which are ordinarily regulatory T (T_{reg}) cells, become effector cells that secrete large amounts of IFNγ, thereby skewing the T_H1 cell–T_{reg} cell balance[71,106]. By contrast, in patients with antibiotic-responsive Lyme arthritis, T_{reg} cells secrete large amounts of anti-inflammatory IL-10 and negligible amounts of IFNγ[71]. IL-10 produced by T_{reg} cells and other immune cells is critical to limiting NF-κB and STAT1 signalling, which is necessary for the development of innate and adaptive immune responses to *B. burgdorferi*. In mice, T_{reg} cells are an important source of IL-10, and T_{reg} cell-depleted mice develop more severe Lyme arthritis than immunocompetent mice[107]. Similarly, HLA-DR4 transgenic mice that lack the co-stimulatory molecule CD28, which greatly reduces the number of T_{reg} cells, also develop persistent arthritis after spirochaetes have been killed[108].

The critical role of the balance between IFNγ and IL-10 in post-infectious Lyme arthritis is underscored by studies in IL-10 knockout (*Il10*$^{-/-}$) mice. Similar to patients with post-infectious Lyme arthritis, these mice have greatly increased innate and adaptive immune responses to infection with *B. burgdorferi*, resulting in severe arthritis despite having low to undetectable amounts of bacteria in inflamed joint tissues[105,109,110]. Longitudinal transcriptomic analysis of joints from infected B6 *Il10*$^{-/-}$ mice show marked upregulation in the transcription of IFNγ-stimulated genes and the pro-inflammatory microRNA miR-155, with a corresponding downregulation of mRNA transcripts and microRNAs involved in tissue repair and response to wounding, similar to human post-infectious Lyme arthritis[60,105]. This transcriptomic profile is probably the result of the impaired ability of IL-10 to regulate STAT1 activation in these mice[105]. The dysregulated IFNγ response in these mice is caused by TLR2-mediated bystander activation of both $CD4^+$ and $CD8^+$ T cells[110]. Importantly, spirochaetes are no longer detectable in synovial tissue at 16 weeks post-infection, and depletion of $CD4^+$ and $CD8^+$ T cells in B6 *Il10*$^{-/-}$ mice results in less severe Lyme arthritis[110], demonstrating that a dysregulated T_H1 cell response is arthritogenic. In the human disease, bystander activation of T cells could also cause a break in immune tolerance, providing a critical intermediate step on the path towards autoimmunity.

Consequences of excessive, dysregulated pro-inflammatory responses.

A model of the cellular architecture in the synovial lesion of post-infectious Lyme arthritis and the proposed roles of the main immune cells, peptidoglycan, autoantigens and IFNγ responses are summarized in FIG. 6. Immune dysregulation during microbial infection,

particularly pathogenic T_H17 cell responses, can trigger autoimmunity[1,111]. In a study in which HLA-DR-presented peptides were eluted from synovia of patients with post-infectious Lyme arthritis, four immunogenic peptides were identified that were derived from self-proteins[112], including endothelial cell growth factor[11], annexin A2 (REF.[13]), apolipoprotein B100 (REF.[14]) and matrix metalloproteinase 10 (REF.[15]). Similarly, HLA-DR molecules expressed on *B. burgdorferi*-stimulated dendritic cells obtained from healthy individuals presented peptides derived from all of these self-proteins, with the exception of matrix metalloproteinase 10 (REF.[113]). HLA-DR presentation of these self-proteins might reflect previous damage to endothelial cells and/or to the extracellular matrix by spirochaete invasion[12]. Moreover, autoantibodies to these self-proteins can sometimes be found in patients with early-stage *B. burgdorferi* infection, Lyme carditis, neuroborreliosis or antibiotic-responsive Lyme arthritis[11–16], albeit usually without T cell responses. Thus, initial autoimmune responses might be triggered by increased T_H17 cell responses during early infection, but T cell responses to autoantigens are not usually apparent at that time. By contrast, both T cell and B cell responses to these autoantigens are often found in patients with post-infectious Lyme arthritis, suggestive of further maturation of the immune response[11,13–15]. Amounts of T_H17 cell-associated cytokines, particularly IL-23, that correlate with anti-*B. burgdorferi* antibody titres in early disease, correlate strongly with autoantibody titres in post-infectious Lyme arthritis[43], suggesting a shift from protective anti-*Borrelia* responses to autoreactive immunity.

Although the pathogenic nature of Lyme autoantibodies has not yet been delineated, IgG4 Lyme disease autoantibody titres correlate with the magnitude of obliterative microvascular lesions and fibrosis in synovial tissue[72]. Curiously, a 2020 study using humanized mice indicated that loss of the inhibitory Fc receptor Fcγ-receptor IIb, which binds to IgG4 immune complexes, might contribute to infection-induced autoantibody responses in Lyme arthritis[114]. Although IgG4 responses are typically considered to be anti-inflammatory, clinical data imply a pathogenic role for these autoantibodies.

The timeline for the development of putative pathogenic autoantibodies in Lyme arthritis could have parallels with RA. In RA, anti-citrullinated protein antibodies (ACPAs) typically develop years before inflammatory arthritis manifests[115]. Prior to arthritis development, ACPAs can undergo epitope spreading, which, together with the appearance of innate immune mediators including IL-1, IL-6 and TNF, can lead to the development of clinical arthritis[116]. Moreover, in a study from the Netherlands, IgG4 ACPAs were noted in 104 of 373 patients with RA (28%), and anti-carbamylated protein antibodies were found in 209 of the 373 patients (56%)[117]. Similarly, in a study from France, 35 of 141 patients with RA (25%) had IgG4 antibodies that recognized citrullinated fibrinogen, a common target of ACPAs[118]. In a Chinese study, patients with IgG4 antibodies were more difficult to treat successfully with DMARDs[119], suggesting that serum IgG4 autoantibodies might define a specific clinical phenotype associated with more severe disease.

Cytotoxic immune responses had not previously been thought to be involved in synovial pathology, yet a 2019 transcriptomic analysis of synovial tissue from patients with post-infectious Lyme arthritis or RA showed marked upregulation of genes associated with cell-mediated cytotoxicity[10]. Cells associated with cytotoxic potential include $CD8^+$ T cells, NK

cells and, less commonly, γδ T cells[120]. However, each of these cell types can also secrete cytokines, which has been thought to be their primary function in chronic inflammatory arthritides. During spirochaete dissemination and in the infectious phase of Lyme arthritis, these cells probably function as part of a complex web of inflammatory responses that are important for spirochaetal killing. For example, innate-like cytotoxic lymphocytes, such as NK cells and NKT cells, could initially have a role in trapping spirochaetes in obliterative microvascular lesions[35,84,121]. However, the role of cells with cytotoxic potential and the cellular targets of such responses are yet to be clarified in post-infectious Lyme arthritis and in other chronic inflammatory arthritides.

Synovial fibroblasts, the most common cells in the synovial lesion, function as important immune effector cells in inflamed synovial tissue[70]. When stimulated with IFNγ and *B. burgdorferi* in vitro, primary synovial fibroblasts derived from patients with post-infectious Lyme arthritis secrete large amounts of NF-κB-regulated and STAT1-regulated cytokines, chemokines and pattern recognition receptors[70]. These cells also secrete T_H1 cell-promoting immune mediators and proteins involved in antigen presentation to T cells, including HLA-DR molecules and co-stimulatory molecules. These data[70] suggest that synovial fibroblasts function as non-professional antigen-presenting cells and might contribute to T cell reactivity to HLA-DR-presented Lyme autoantigens. Furthermore, when synovial fibroblasts obtained from patients with post-infectious Lyme arthritis were grown in culture, the gene signature of IFNγ-stimulated cells in vitro was quite similar to that found in vivo in the synovia from such patients[10], confirming a central role for IFNγ and synovial fibroblasts in post-infectious Lyme arthritis. Thus, immune dysregulation in post-infectious Lyme arthritis leads to pro-inflammatory and tumour-like proliferative responses by synovial fibroblasts, rather than the wound healing and appropriate tissue repair responses that are probably orchestrated by these cells in antibiotic-responsive Lyme arthritis following antibiotic therapy. In RA, genetic, epigenetic and phenotypic changes in synovial fibroblasts are likely to contribute to inflammatory synovitis and the development of autoimmunity[122–124]. Taken together, these studies indicate a central role for synovial fibroblasts in the pathogenesis of a number of forms of chronic inflammatory arthritis, including Lyme arthritis and RA[125].

Linking infection and autoimmunity

The main message from post-infectious Lyme arthritis for other forms of chronic autoimmune or autoinflammatory arthritis is that this complex immune response can begin with an antimicrobial immune response, and is shaped by complex interactions between pathogen and host. Such an immune response could be triggered by an invading pathogen, as is the case in Lyme arthritis, or by commensals in the host microbiome. In RA, evidence is emerging that bacteria-induced inflammation at mucosal sites in the periodontium, lung or bowel might trigger or enhance autoimmunity and joint disease in predisposed individuals[126]. For example, the periodontal pathogen *Porphyromonas gingivalis* is associated with RA[127,128], as is the gut commensal *Prevotella copri*[129,130]. In ankylosing spondylitis and Crohn's disease-associated spondyloarthritis, strains of *Escherichia coli* or *Prevotella* spp. that adhere to the bowel mucosa have been implicated in the pathogenesis of joint disease[131,132]. Similarly, in psoriatic arthritis, skin flora might have a role in pathogenesis[133,134]. As with other arthritides, changes in host microflora could

also affect the pathogenesis of Lyme arthritis. *B. burgdorferi* modulate the host microbiomes of their tick vectors to facilitate colonization[135] and this process could also occur during tick-to-mammal transmission, disrupting the normal skin flora and altering the local immune environment.

Interestingly, patients have been reported to develop systemic autoimmune diseases, including RA and spondyloarthritis, within months of having Lyme disease[136]. Although these occurrences could be coincidental, we speculate that latent autoimmunity might be induced non-specifically by the adjuvant effects of infection, or alternatively, that autoimmune-promoting conditions that develop during Lyme disease might trigger other systemic autoimmune diseases. The Lyme arthritis story underscores the importance of research into the potential role of specific infectious agents in various forms of chronic inflammatory arthritis, research that is hoped to provide breakthroughs in approaches to diagnosis and treatment.

Conclusions

After *B. burgdorferi* infection of the skin, early dissemination of spirochaetes to joints accompanied by dysregulation of innate immune responses (particularly type I interferon responses), might promote subsequent arthritis development. Months later, clinical arthritis develops within the context of an expanded adaptive immune response to the spirochaete. Rather than the arthritis resolving following antibiotic therapy, a small percentage of patients have persistent synovitis that can worsen in the post-antibiotic period. In these patients, the central pathogenetic feature is an excessive, dysregulated pro-inflammatory immune response characterized by exceptionally high amounts of IFNγ coupled with inadequate amounts of the anti-inflammatory cytokine IL-10. The consequences of this dysregulated response in synovia include chronic vascular damage and impaired tissue repair, autoimmune T cell and B cell responses, and tumour-like fibroblast proliferation and fibrosis. These histological characteristics are similar to those seen in other chronic inflammatory arthritides, including RA. Thus, post-infectious Lyme arthritis might serve as a model to aid our understanding of other forms of arthritis in which an infectious agent triggers or shapes the complex interactions between pathogen and host immune responses, leading to joint inflammation. However, important gaps remain in understanding the link between infection and autoimmunity in Lyme arthritis. Future research should focus on determining the initial steps in the break in immune tolerance during infection, on elucidating the role of *B. burgdorferi* peptidoglycan or other spirochaetal remnants in the pathogenesis of Lyme arthritis, on studying antibody specificities and function, and on identifying how autoimmune responses seem to evolve over time to become increasingly T cell dependent and more pathogenic.

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Key points

- A combination of spirochaetal and host genetic factors shape the outcome of Lyme arthritis, which ranges from mild, antibiotic-responsive joint inflammation to persistent, antibiotic-refractory autoinflammatory or autoimmune synovitis.
- Certain highly inflammatory strains of *Borrelia burgdorferi* most commonly found in north-eastern USA are present at an increased frequency among patients who subsequently develop post-infectious Lyme arthritis.
- The histology of post-infectious Lyme arthritis synovia is similar to that in other chronic inflammatory arthritides, such as rheumatoid arthritis, but there is greater microvascular damage in Lyme arthritis.
- *B. burgdorferi* is no longer present in synovia after treatment with antibiotics, but *B. burgdorferi* peptidoglycan might persist and could be an important promoter of innate immune responses.
- Dysregulated, excessive IFNγ responses and inadequate amounts of the anti-inflammatory cytokine IL-10 are a central feature of post-infectious Lyme arthritis, and contribute to persistent inflammation and the development of autoimmunity.
- Synovial fibroblasts, the most common cell in the synovial lesion, become immune effector cells capable of altering the innate and adaptive immune microenvironment in Lyme arthritis.

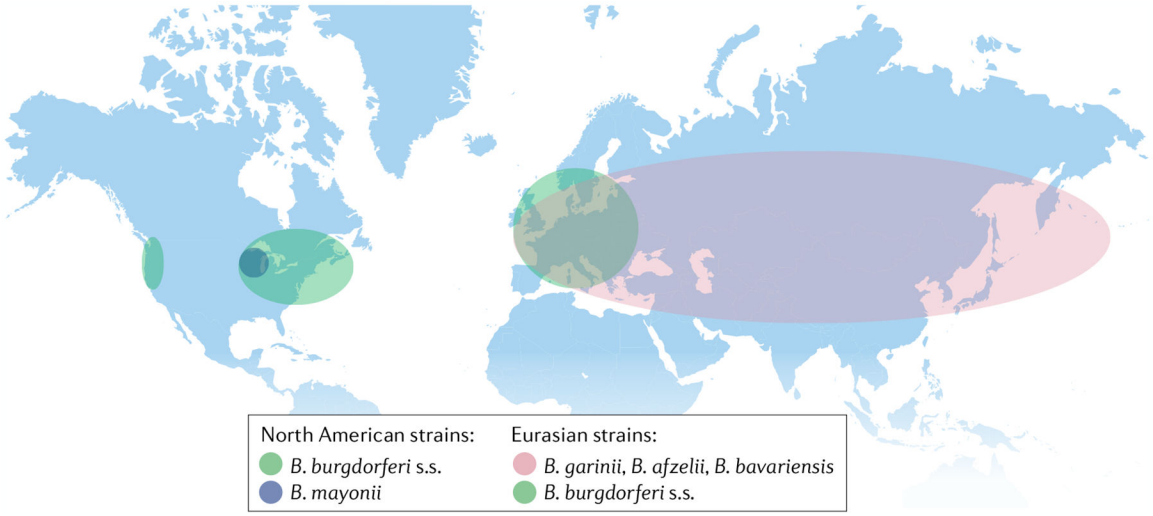

Fig. 1 |. Geographic distribution of *Borrelia burgdorferi* species relevant to human disease.
Borrelia burgdorferi sensu stricto (*B. burgdorferi* s.s.) is the major species in North America and is primarily found in the USA in the north-eastern and mid-Atlantic states, the upper Midwest, in northern California and, to a lesser degree, in Oregon and Washington. *B. burgdorferi* s.s. also extends into Canada at each of the bordering USA locations. *Borrelia mayonii* is much less common than *B. burgdorferi* s.s. and is restricted to the upper midwestern states in the USA. European strains include *Borrelia garinii* and *Borrelia afzelii* and, to a lesser extent, *B. burgdorferi* s.s. and *Borrelia bavariensis*, which is closely related to *B. garinii*. In Asia, *B. garinii* is the predominant species, but *B. bavariensis* and *B. afzelii* are also found there.

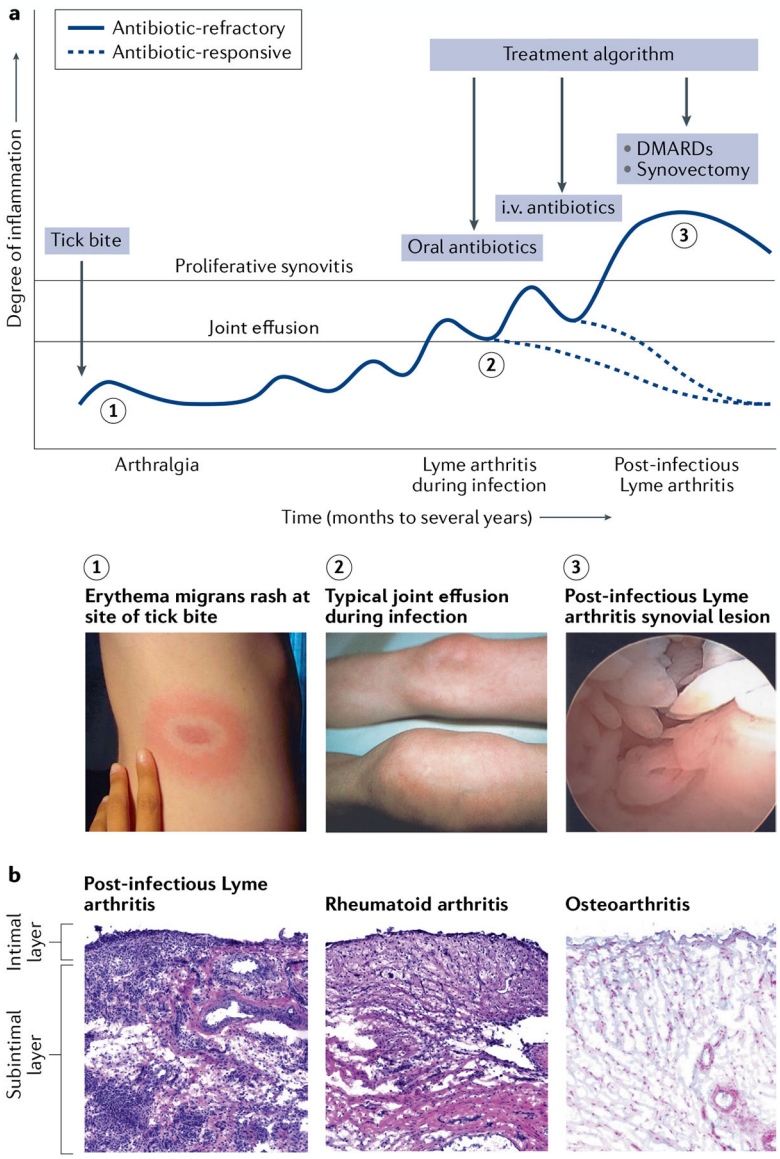

Fig. 2 |. Lyme arthritis stages and characteristics.

a | In untreated patients, Lyme disease occurs in stages, with different manifestations present at each stage. A slowly expanding erythema migrans rash commonly appears 3 to 32 days after a bite by a *Borrelia burgdorferi*-infected *Ixodes* tick (1), which can be accompanied by flu-like symptoms such as fever, headache, myalgias, arthralgias, malaise and fatigue. In the north-eastern states of the USA, Lyme arthritis typically causes large joint effusions, particularly affecting the knees (2), which develop a median of 6 months after the initial skin lesion. Arthritis usually resolves after 1–3 months of oral and, if necessary, intravenous (i.v.) antibiotic therapy (antibiotic-responsive Lyme arthritis). In a small subset of patients, arthritis persists or worsens despite 2–3 months of antibiotic therapy and apparent spirochaetal killing (post-infectious Lyme arthritis). These patients typically develop a highly proliferative synovial lesion (3) that does not respond to further courses of antibiotic therapy (antibiotic-refractory Lyme arthritis). Treatments such as

DMARDs or arthroscopic synovectomy help to resolve their arthritis. **b** | The synovial lesion in post-infectious Lyme arthritis is similar to the lesion in rheumatoid arthritis and other inflammatory arthritides. By contrast, osteoarthritis synovium typically has minimal cellular infiltrate, the intimal layer is not inflamed or thickened, and the subintimal layer is composed of healthy, intact microvasculature and highly organized collagen fibres. In this figure, the synovial lesions from Lyme arthritis and rheumatoid arthritis are stained with haematoxylin and eosin (H&E), and osteoarthritis synovium is stained with H&E and Alcian blue to show acidic glycosaminoglycans on the outer surface of collagen fibre bundles and along the synovial lining. Image of the knee in part **a** reprinted with permission from REF.[137], Elsevier.

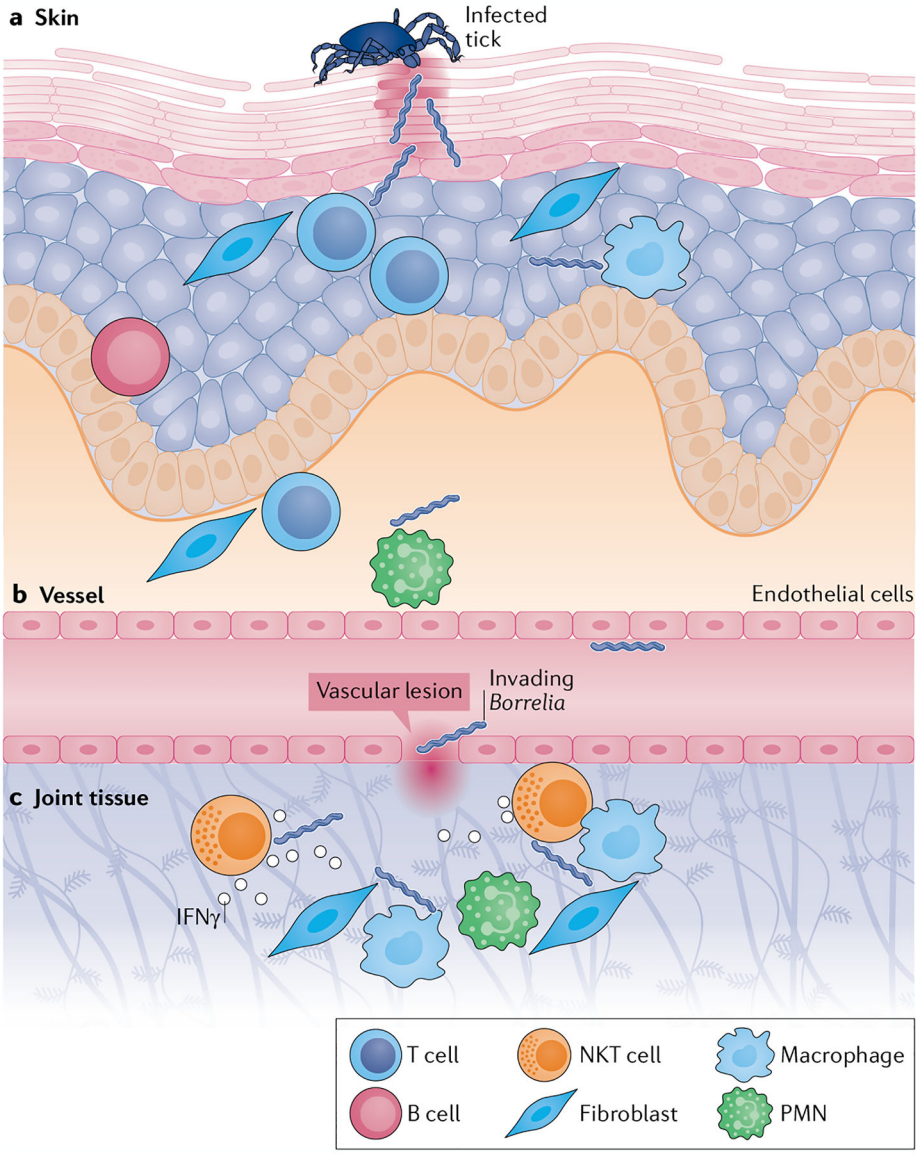

Fig. 3 |. Spirochaete invasion into joint tissue.

a | Spirochaetes invade the skin during the bloodmeal of an infected *Ixodes* tick. Upon entry, tissue-resident T cells, B cells, resident antigen-presenting cells (such as macrophages and dendritic cells), some polymorphonuclear cells (PMNs) and stromal cells (such as fibroblasts, keratinocytes, epithelial cells and endothelial cells) are responsible for early-acute immune responses to infection. **b** | A small number of spirochaetes escape the site of invasion and enter the vasculature, where *Borrelia* surface lipoproteins interact with vascular endothelial cells to induce the loosening of tight junctions. **c** | Spirochaetes enter the extracellular matrix of joint tissue through vascular lesions. Once in the joint tissue, they induce acute inflammatory responses by resident cells such as endothelial cells and synovial fibroblasts, which produce adhesion molecules, matrix metalloproteinases and innate immunity cytokines and chemokines. Natural killer T (NKT) cells produce IFNγ in response to CD1-presented immunogenic *Borrelia* glycolipids, thereby enhancing vascular

barrier function and limiting spirochaetal invasion and chronic inflammation. The cytotoxic function of NKT cells might also directly contribute to spirochaetal killing. The nature and magnitude of these early immune responses in the skin and joint help to set the stage for subsequent arthritis development.

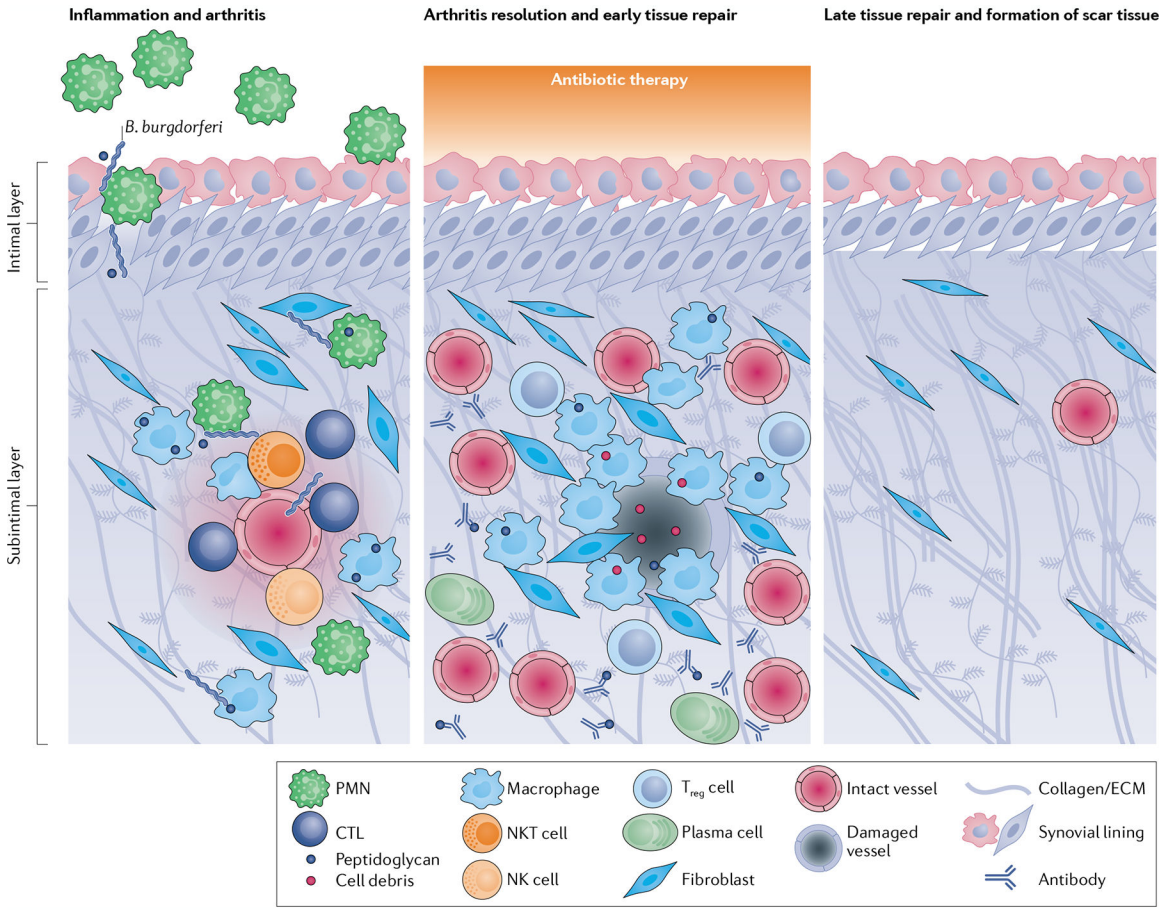

Fig. 4 |. Stages of arthritis and proposed tissue repair in antibiotic-responsive lyme arthritis. Immune responses to *Borrelia burgdorferi* and *B. burgdorferi* peptidoglycan by endothelial cells, fibroblasts, lymphocytes (such as natural killer (NK cells), natural killer T (NKT) cells and cytotoxic T lymphocytes (CTLs)) and myeloid cells (such as macrophages and polymorphonuclear cells (PMNs)) in the synovium trigger localized inflammation, tissue damage and arthritis. Antibiotic therapy is given during acute joint infection and inflammation, facilitating arthritis resolution and the initiation of early tissue repair responses. These responses are dominated by pro-angiogenic factors and the activation of tissue-repairing macrophages and fibroblasts, which remove bacterial debris and damaged cells from the damaged microvasculature, extracellular matrix (ECM) and fibrotic tissue. Other immune cells such as regulatory T (T_{reg}) cells and plasma cells might also be present during arthritis resolution. Over several months, synovial fibroblasts differentiate into myofibroblasts and lay down collagen and form scar tissue, leading to full recovery.

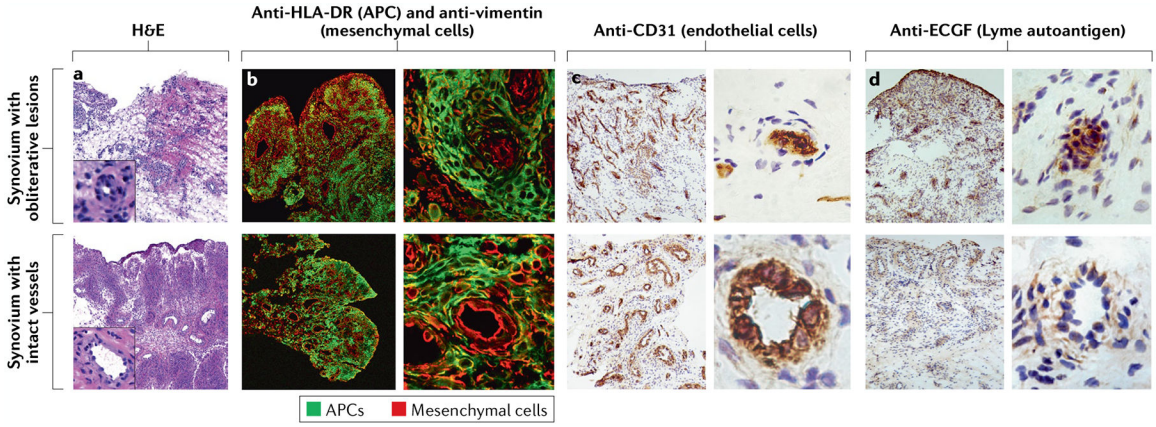

Fig. 5 |. Microvascular involvement in the synovial lesion of post-infectious lyme arthritis.

a | Haematoxylin and eosin (H&E)-stained sections of synovial tissue from representative patients with post-infectious Lyme arthritis with varying degrees of inflammation, fibrosis and vascular damage (insets show enlarged images of vessels). **b** | Synovial tissue sections stained with fluorescently labelled anti-HLA-DR (green) and anti-vimentin (red) antibodies, showing localization of antigen-presenting cells (APCs) and mesenchymal cells (such as fibroblasts and endothelial cells), respectively. **c** | Around half of patients with post-infectious Lyme arthritis have evidence of vascular damage, including obliterative microvascular lesions, as shown by staining with the endothelial cell marker CD31. **d** | Obliterative microvascular lesions are also enriched with the Lyme disease autoantigen endothelial cell growth factor (ECGF). In panels **b–d**, the panels on the left show the general architecture of the synovial tissue at low magnification, and the panels on the right show single blood vessels from the same sections at high magnification. Parts **c** and **d** adapted with permission from REF.[12], Wiley. © 2014 by the American College of Rheumatology.

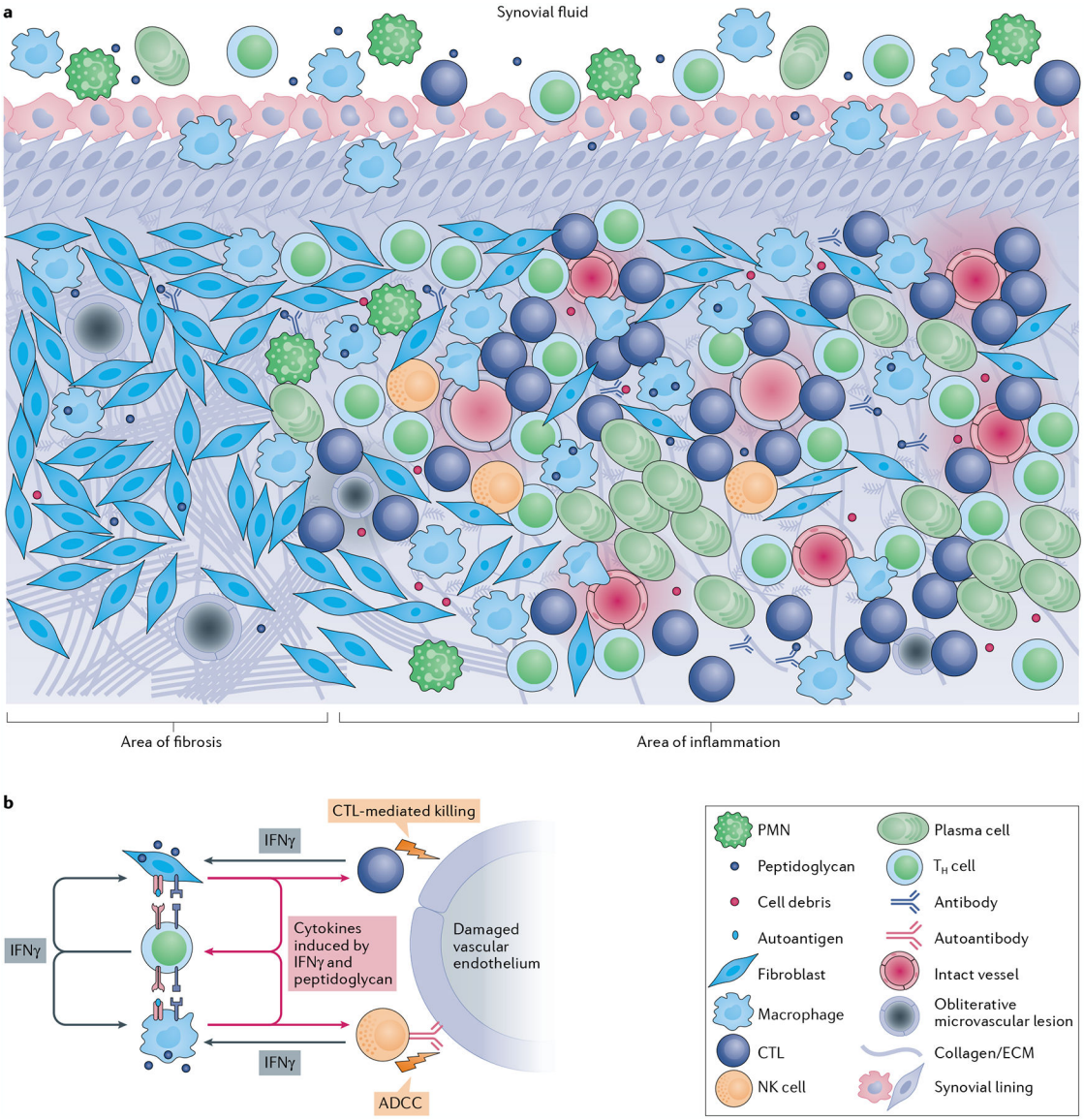

Fig. 6 |. Cellular architecture of the post-infectious lyme arthritis synovial lesion.

a | The post-infectious Lyme arthritis synovial lesion is characterized by widespread fibrosis and areas of marked inflammation. Fibrotic areas contain large numbers of synovial fibroblasts, obliterative microvascular lesions, disordered collagen and other extracellular matrix (ECM) proteins. Areas of inflammation are found primarily in highly vascularized synovial intimal and subintimal layers that can contain obliterative microvascular lesions and/or intact vessels. Immune cells, such as macrophages, $CD4^+$ T helper (T_H) cells, cytotoxic T lymphocytes (CTLs; mostly $CD8^+$ T cells with a few γδ T cells), natural killer (NK) cells, and large numbers of antibody-producing plasma cells, are found primarily in vascularized areas, but can be found throughout the tissue. Vascularized areas also contain many HLA-DR-expressing synovial fibroblasts; however, they tend to have less fibrotic tissue. Bacterial peptidoglycan is present in synovial fluid and might additionally be present in inflamed tissue, along with degraded cellular and ECM debris.

Only a few polymorphonuclear cells (PMNs) are present in post-infectious Lyme arthritis synovial tissue, but more are present in synovial fluid. **b** | In this panel, a hypothesis is developed regarding the roles of important cells and immune mediators in autoimmune-mediated damage to the endothelium in inflamed synovia. Large amounts of IFNγ produced by T_H cells, CTLs and NK cells induce potent responses by HLA-DR-expressing synovial fibroblasts and macrophages, which upregulate proteins associated with antigen presentation, T cell activation and inflammation. *Borrelia burgdorferi* peptidoglycan and cell debris might amplify these responses. Synovial fibroblasts and macrophages present MHC class II-restricted peptides derived from Lyme autoantigens, which are abundant in synovial tissue, to autoreactive T_H cells, perpetuating IFNγ responses in the tissue. Endothelial cells, which were damaged during infection with *B. burgdorferi*, can be targeted for killing by CTLs, either through direct CTL-mediated killing or through autoantibody-dependent cell-mediated cytotoxicity (ADCC), or both. Further damage to the microvasculature releases more autoantigens and debris, leading to a feedback loop of chronic inflammation and tissue damage.

Table 1 |

Characteristics of mouse models of lyme arthritis

Mouse model	Immune defect	Effect on arthritis	Effect on host defence	Relevance to human disease	Refs
C57BL/6 (B6)	NA	Mild, self-resolving Lyme arthritis	NA	Probably mimics patients who develop only mild Lyme arthritis	20
C3H/HeN (C3H)	NA	Severe, acute, self-resolving Lyme arthritis	NA	Most similar to severe Lyme arthritis during active infection	20
Il10$^{-/-}$ (B6)	Dysregulated NF-κB and T_H1 cell responses; impaired regulatory T cells	More severe (increased innate and adaptive inflammation)	Very few *Borrelia burgdorferi* in joints compared with B6 or C3H mice	Mimics dysregulated T_H1 cell responses seen in patients who develop post-infectious Lyme arthritis[9,10,43,70,71]	101,109,110
Tlr1$^{-/-}$ or *Tlr2*$^{-/-}$ (B6 or C3H)	Impaired response to *Borrelia* lipoproteins (such as OspA and OspC)	More severe (probably owing to impaired host defence)	~100-foid more *B. burgdorferi* in joints compared with wild-type mice; OspA vaccine non-protective	Low TLR1 in vaccine low responders[75]; TLR1 hypomorph associated with severe Lyme arthritis[41]	74,75
Mir146a$^{-/-}$ (B6)	Hyperactive NF-κB signalling	More severe (increased acute inflammation)	Slightly fewer *B. burgdorferi* in joints compared with wild-type mice	Probably reflects the central importance of NF-κB regulation in host defence and arthritis during infection[9]	100
Ifnar$^{-/-}$ (C3H)	Defect in type I interferon signalling	Less severe (type I interferon is arthritogenic)	No effect	Unclear, might be important in early infection of skin	59
C3H *Gusb* allele (B6)	B6 mice with C3H *Gusb* allele are unable to clear ECM debris	More severe (accumulated glycosaminoglycans in joints)	No effect	Unclear, might be important in clearing *B. burgdorferi* peptidoglycan and host ECM debris	77

ECM, extracellular matrix; NA, not applicable; Osp, outer-surface protein; T_H1 cell, T helper 1 cell; TLR1, Toll-like receptor 1.

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