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Lyme Disease: Determining Differences from Immune System Responses

Lyme disease has become the most commonly spread tick-born disease in the United States, affecting approximately 300,000 people yearly.1 Because it can be acquired so easily it has become a serious public health concern. While the initial symptoms of Lyme disease are very treatable and not particularly severe, including at times a rash, fever, headache and fatigue, some cases can last for a prolonged period of time, even after treatment from antibiotics.2 It has become clear to the medical world that there is no such thing as a uniform case of Lyme disease. Why is Lyme different expressed so differently across the range of infected patients? Why do some patients have more severe symptoms? Why do some cases tend to last longer? Recent studies have presented new insights on the differences, which seem to center on the immune system and how it responds to the microbial mechanisms of Lyme disease.

First, the mechanisms behind the spread and infection of Lyme disease need to be understood. The North American strain of Lyme disease is transmitted by ticks (deer ticks in the Northeast and Midwest and western black-legged ticks in the Pacific coast region) that carry the spirochete *Borrelia burgdorferi*.3 If the tick goes unnoticed and is not removed, it generally bites its host, releasing the *Borrelia burgdorferi* into the host’s bloodstream. These bacteria find host cells in tissues around the body, triggering a multitude of symptoms. While most bacteria have obvious biological makeups that give themselves away to the host’s immune system, *Borrelia burgdorferi* have endoflagella in between a peptidoglycan helix and their outer membrane. This hides their flagella from the immune system, which is important because flagella can often be an identifier for harmful bacteria. It is also important to note that *Borrelia burgdorferi* do not possess cell walls, a characteristic which will be further discussed later.4 Because Lyme disease is difficult for the body to identify on its own, the disease tends to spread unstopped until symptoms appear. With some patients, a great deal of time can pass until a diagnosis is reached, which is one of the factors in the difficulty of subsequent treatment.

While there are cases of Lyme disease that are successfully treated quickly as well as chronic Lyme disease, both forms initially show the same outlying symptoms and no differences can be determined from outward appearances. The early symptoms of all Lyme disease cases are similar to those of someone afflicted with the common flu. Lyme disease patients experience fevers, overall tiredness, and severe headaches (possibly migraines). These rather common symptoms can be accompanied by hallucinations, but occurrence is infrequent. The most telling symptom of Lyme is the physically visible erythma mirgran, which occurs from as early as three days after a tick bite to as long as a month. This bull’s-eye rash is what makes Lyme identifiable from a physical standpoint.2

After diagnosis, which becomes easy after the classic bull’s eye rash appears, treatment is similar to that of many bacterial diseases. The standard forms of treatments are oral antibiotics such as doxycycline and amoxicillin.5 Antibiotics stop bacterial infections by limiting cell replication so that the immune system can combat the bacteria. Generally, antibiotics do this by inhibiting the production of cell walls, but since all *Borrelia* lack true cell walls, the antibiotics target the thin peptidoglycan layer within the bacteria’s periplasm.6 Amoxicillin has proven to be one of the most effective antibiotics against gram-negative bacteria, which is the key characteristic of all *Borrelia*.7 The initial treatment of antibiotics is generally enough to cure Lyme disease, but in some cases antibiotic therapy is required, which can last several weeks until symptoms recede.

Since these antibiotics can be so effective in treating the symptoms why do the symptoms linger far longer 10-20 percent of cases? Some theorize that the body’s immune system struggles to identify that all of the foreign spirochetes have been eliminated and continues to fight a non-existent infection. Some people still think that the answer is additional regimens of antibiotic therapy, but this has already been proven to be ineffective in most lingering cases. Without knowing the cause of post-treatment Lyme disease syndrome (PTLDS), or more commonly known chronic Lyme disease, treatment has become case-by-case to the point where a cure does not exist. Even though chronic Lyme disease is not uncommon it is not technically medically recognized in the United States. However, it is accepted by many figures in medicine to be a real syndrome. It is estimated that approximately 50,000 people new cases of chronic Lyme disease are identified each year, adding to the pre-existing cases.1 Clearly this condition needs to be addressed in order to help all those afflicted with chronic Lyme disease. This is where some of the current investigations have promise.

On this topic, researchers at Johns Hopkins University recently have taken a different approach to understanding Lyme disease. The research, led by Dr. Mark Soloski (Johns Hopkins, Ph.D), along with additional research by Stanford University, has been centralized around the differences in immune responses between various cases of Lyme disease. The immune system releases many molecules in response to inflammation and infection, particularly cytokines, chemokines and some lived-based proteins. These are the immune response molecules that the Hopkins doctors specifically analyzed.8

The importance of cytokines in the body’s immune response stems from their function as signal messengers. These cytokines are protein messengers that immune response cells release in order to trigger specific responses. Interleukins, a type of cytokine, are the messenger protein that signals for the creation of T cells.9 That is how much influence cytokines have in the body’s immune system. Without these messenger proteins, the immune system would fall apart.

Under the tree of cytokines are the more specific chemokines. These chemokines, or chemotactic cytokines, are a rather basic protein cytokine that relays a message that triggers chemotaxis in surrounding cells.10 Chemotaxis is the process of cell movement in response to specific nearby bodily chemicals. So in other words, these chemokines control cell movement to specific locations through their concentration levels. The reason that chemokines play an important role with a Lyme disease infection is that these proteins become plentiful surrounding inflamed regions of the body, such as with Lyme disease causes. The chemokines can help with the infection site through their ability to control cell movements, meaning they can control the repair and growth of regions.

While numerous chemokines are present at the site of inflammation, the liver releases protein mediators to the site as well.8 These mediators, or acute phase markers, are integral in immune system communication in response to inflammation events in the body. Positive acute phase proteins are innately part of the immune system and their concentration automatically changes in response to inflammation.11 They are summoned by inflamed cells that send out cytokines to signal the liver to produce these acute phase proteins. Acute phase proteins help combat the inflammation by simply destroying the invasive pathogens or trapping them in pre-existing blood clots. Both of these methods help curb the rate of infection.

The research teams at Johns Hopkins and Stanford have taken specific looks at all of these aforementioned proteins and have been trying to find relationships between concentration levels of each type of protein and the conditions of their subjects. In order to expedite the process, researchers chose specific chemokines to further examine rather than looking at the numerous amounts of chemokines present in the body. The chemokines that the teams focused on are CXCL9, CXCL10, and CCL19, because they mediate cytotoxic T cells X by binding to a receptor on the T cell and signaling it towards the site of infection.8 These T cells help expedite the fight against infection by eliminating foreign species, in this case, *Borrelia burgdorferi*.12 The research that has been done on concentrations of these chemokines relates to the concentration levels to the initial state of patients at diagnosis. In order to achieve this desired relationship in an organized manner, high levels of cytokines, chemokines, and acute-phase markers were deemed mediator-high. The opposite category, for low levels, was labeled mediator-low.8

The patients that were considered mediator-high after initial measurements essentially had more extreme immune responses in every microbial concentration level that was measured. They had extremely high levels of antibody production by the host, but most importantly had more severe preliminary symptoms. The correlation that Dr.Soloski’s team drew was that those who are designated mediator-high have more severe cases of simple Lyme disease. As expected, the mediator-low patients had non-severe cases of Lyme disease and the patients subsequently had less intense immune responses. In summary, the more proactive the body was towards combatting the disease the more likely that the infection was severe. Since this means that the immune system is doing what is supposed to do, what is the problem?

The initial response the body concocts is the proper one: the antibiotics have become so effective at limiting cell reproduction that there is often an overabundance of the mediator proteins left after the inflammation has receded. Dr. Soloski’s team postulates that this is why there is a strong correlation between people who have severe initial symptoms and those that suffer from chronic Lyme disease. These leftover response proteins serve the purpose of combatting disease, yet the body has a tendency to over-compensate at times. This situation is somewhat unique to the disease. For most diseases, when the body over-produces specific-function proteins it can recycle them back into amino acids,13 but in this case, they continue to be active cells in the host’s body. This can subsequently lead to the symptoms seen in chronic Lyme disease patients, such as fatigue, sleep disturbance, joint/muscle pain, arthritis, and cognitive deficiencies.2 The inflammation in joints can be directly attributed to the surplus of cytotoxic T cells in the bloodstream. While these T cells are helpful at eliminating foreign bodies, their presence causes increased inflammation.8

Although the immune response directly affects whether or not the individual will endure persistent symptoms, it also indirectly attributes to deficiencies elsewhere. For all bodily mechanisms, more production in one place means that there is less production in another place. It is the time-tested push-pull theory that describes many worldly phenomena. It is applicable in this instance because the extensive production of response proteins takes amino acids directly from a loosely finite pool in the body.14 Amino acids are provided through consumption so it is reasonable to set them as a constant amount in the body. It is plausible that a protein deficiency for a secondary mechanism in the host could arise, which could attribute to one of the previously mentioned symptoms.

With Dr. Soloski’s research being unveiled in the last month, the field on Lyme disease has been extensive furthered, but what is next? In summarizing his team’s experimentation, Dr. Soloski postulated, “Since the chemokines that were elevated are key to the movement of T cells, blocking them might prevent them from moving into tissues and prolonging inflammation. This is one of the long-term aims of our work.”8 What Soloski has done is to lay down a conceivable method for discovering a cure, or at least a better course of treatment than what is available. Since the arthritis in chronic Lyme disease patients is the most prominent symptom, blocking the chemokines from the T cell receptor site could alleviate most of the pain. The difficulty with this method seems like it would be to understand the appropriate timing of this proposed interference. The chemokines will always be instrumental in destroying existing foreign bodies, and lowering the concentration of the cytotoxic T cells could let the disease linger and allow *Borrelia burgdorferi* to replicate, spread, and cause more infection.

Whereas theoretically blocking the chemokines could benefit individuals with chronic Lyme disease, it could actually result in the opposite effect. A research team at Cambridge University, led by Dr. Shixin Qin, found that increasing the levels of an antibody (anti-CXCR3) for the chemokine binding cite CXCR3 led to more activated T cells in the blood stream rather than a lower quantity.15 While this research was not intended to educate for chronic Lyme disease, this discovery is pertinent because CXCR3 is the receptor for both CXCL9 and CXCL10. The take-away from Dr. Qin’s experimentation is that synthesizing an antibody to control the levels of CXCR MIG and CXCR3 IP-10 (other terms for CXCL9 and CXCL10 respectively) could, in fact, raise the amount of these proteins that bind the receptors, increasing inflammation instead of inhibiting it. It is clear that the mechanisms of chemokines play a key role in the cause of chronic Lyme disease, but at the same time not enough is known to use it as a segue for treatment.

Although the research did not definitively identify the sole protein that’s concentration determines whether or not a patient will have to endure lingering symptoms, it did help restate that these mediator levels can in fact influence this. Soloski believes that the most important mediator concentrations to analyze are the aforementioned chemokines (CXCL9, CXCL10, and CCL19). As he noted (page 7 above), his team currently believes that they can draw further correlations from similar experiments to determine a more specific relationship.

While treatments are scarce for those with persistent symptoms, one possible treatment that is being applied is hyperbaric oxygen therapy (HBO).16 HBO therapy has been used for other diseases, notably diabetes, and it works to alleviate pain by increasing oxygen levels in the blood stream, while also accelerating healing within the body. One problem with HBO therapy is that it takes between 30 to 60 individual sessions, which makes it a highly unrealistic option for many people with chronic Lyme disease even though it has worked in a few cases.17 Although it is impractical as a treatment for different reasons than synthesizing the anti-CXCR3’s, HBO therapy is not a feasible treatment for the masses at the moment. The full treatment cycle can cost up to $200,000,18 an enormous cost for such an easily contracted disease. Insurance rarely covers the expense of this treatment because it is still considered to be an experimental practice.

There are still the few doctors that advocate additional cycles of antibiotics as an effective treatment. This theory is becoming more and more obsolete as research such as Dr. Soloski’s becomes public. Since the problem no longer seems to be a persistent bacterial infection, antibiotics would have no benefits in helping with the symptoms. Drugs like amoxicillin can also induce side effects such as fatigue, dizziness, and even seizures.19 In previous studies of this form of treatment, some of the subjects have been hospitalized due to these side effects.20 In other words, a program of additional antibiotics would only be disadvantageous.

This synopsis of currently used treatments emphasizes the dearth of effective treatments available to patients with chronic Lyme disease. For one of the more commonly contracted diseases, more treatment options should be available, but this is not the case. Because there is no specific cure, research such as that of Dr. Soloski’s team is relevant and will remain relevant until a uniform cure can be found. It is not fair for people to have to live a lower quality of life for months or even years after being initially diagnosed with nothing to combat their symptoms. Prominent research universities likely will look further into this issue because the recent research has broken down the door to a possible cure. All that needs to be done is more experimentation.

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