The role of CD57 in the Pathogenesis of Lyme Disease

Summary
CD57 is a cell-surface marker on Natural Killer (NK) cells whose expression has been associated with chronic symptoms in Lyme Disease. Patients presenting with persistent symptoms at a primary diagnosis of Lyme Disease often show lower than normal expression of CD57 on their NK cells. It has also been reported that reinitiation of treatment for Lyme Disease is accompanied by a rise in CD57 levels when symptoms improve. The MDL CD57 test by flow cytometry offers a straightforward method to monitor a patient’s CD57 levels. It may be helpful in the assessment of treatment options and progress when chronic Lyme Disease is suspected.

Lyme Disease
Lyme Disease is an emergent condition caused by infection with the spirochete Borrelia burgdorferi [1] and, more recently, other Borrelia species [2], following a bite by any one of a range of Ixodes ticks. Lyme Disease is reported to be the most commonly-diagnosed tickborne disease in the United States [3]. Acute Lyme Disease often presents with a typical and prominent “bullseye” rash and is responsive to antibiotic treatment. However, in some cases, and for reasons that are not fully defined, patients may go on to develop prolonged symptoms that include arthralgias, fatigue, and a range of neurologic and musculoskeletal symptoms; these may develop over months to even years after the initial infection [4]. Despite a greater awareness of this problem [5], solutions have not been forthcoming.

Flow Cytometry
Flow cytometry can categorize cells in the immune system into different lineages and functional status. For example, the various cell types (such as T-cells, B-cells, and monocytes) can be quantified and then further interrogated to determine whether they are activated or quiescent. This technique monitors the behaviors of certain lymphoid malignancies [6] and levels of the CD4+ (helper) T-cell population in HIV infection [7]. Accurate, reliable, and reproducible, Flow Cytometry can provide insight into changes in immune cell populations in individuals over time, as well as changes in disease or infection status.

Natural Killer Cells
NK cells are innate immune cells at the forefront of our initial protection from disease. Although often studied in relation to tumors [8] and viral infections [9], they play an important role in the immune response to intracellular bacterial or parasitic infection, too [10]. They also have a key role in protection from and patient response to the Lyme Disease pathogen Borrelia burgdorferi [11].

The Cell Surface Marker CD57
CD57 is a glycoprotein present on the surface of human NK cells [12] associated with a functionally discrete NK subset [13, 14]. CD57+ NK cells are highly cytotoxic, and their presence is viewed as beneficial in several conditions. Compared with their CD57- sisters, CD57+ NK cells proliferate poorly but retain higher Interferon-gamma secretion and aggressive killing capability [15]. The levels of CD57+ NK cells rise in a broad range of viral infections [16 - 19] and have favorable outcomes in a range of tumor types [20 - 23]. A lack of or reduction in the number of these cells may indicate a reduced capacity of the patient to elicit these important cells’ protective functions, allowing the persistence of chronic infections.

CD57+ NK Cells in Lyme Disease
In 2001, a published study suggested that CD57+ NK cells may indeed play a role in Lyme disease [24], particularly persistent (i.e., chronic) disease. They defined CD57+ NK cells as CD57+ cells that lacked the CD3 T-cell marker. The authors studied a group of 73 patients with chronic Lyme Disease. The patients were all diagnosed with Lyme Disease according to CDC criteria [25]. The chronic Lyme Disease patients had symptoms that persisted for between 3 months and 15 years, including musculoskeletal and neurologic symptoms. After the initiation of antibiotic therapy in this group, CD57 testing was performed. As a control group, ten patients with acute Lyme disease were tested for CD57. Within one month of a tick-bite, all met the criteria for acute disease, including the presence of the signature bullseye rash. CD57 testing was performed by flow cytometry.

Examination of the acute disease patients and a group of non-Lyme controls established a baseline range of 60 - 262 CD57+ NK cells per microliter of whole peripheral blood. Chronic Lyme Disease patients examined before antibiotic treatment showed much lower levels of these cells (range: 0 - 54 per microliter, n=31). Levels rose as treatment progressed (range: 15 - 149 per microliter, n=37). After the conclusion of treatment (range: 96 - 340 per microliter, n=5), they were indistinguishable from the acute disease patients. The authors reported that the significantly diminished CD57+ NK cells in chronic Lyme Disease patients were restored as treatment progressed and concluded. In patients where symptoms persisted despite treatment, CD57+ NK cell levels remained low. A case report showed that this could persist over as much as 10-years of relapsing-remitting chronic Lyme Disease [26].

CD57+ NK Cell Testing in Lyme Disease
CD57+ cells may present at low levels in several conditions, including other chronic infections (such as Chlamydial and Mycoplasmal Infections [27]) and chronic fatigue syndrome [28].
It is critically important that this test be used only in conjunction with a confirmed primary diagnosis of Lyme Disease or as a supplementary investigative test run in association with a test likely to reveal a primary Lyme Disease diagnosis, such as a test for IgM or IgG antibodies against *Borrelia burgdorferi* antigens, the cross-reactive C6 peptide, and in addition to the Lyme Disease Western Blot test.

Testing for cross-reactive responses, such as those to EBV, may be considered. If the infection is suspected to be recent, PCR tests for the presence of the *Borrelia burgdorferi* organism may also be considered.

Within that context, a patient suspected of having chronic Lyme Disease and presenting with lower-than-expected numbers of CD57+ NK cells may be responsive to antibiotic therapy, as per the work of Stricker and colleagues [24].

The MDL CD57+ NK Cell Testing

MDL has developed an assay by Flow Cytometry for the detection of CD57+ NK cells. Test 1803 Immune Deficiency Assay with CD57 by Flow Cytometry requires a minimum of 5mL of peripheral whole blood drawn into a lavender-top (EDTA) tube. The test is not available on serum or plasma. Specimens should be submitted to MDL for testing within 24 hours of collection.

In this assay, peripheral blood cells are first stained with the cell surface marker CD45 to identify lymphocytes and then subsequently stained with CD3, CD16, and CD56. NK cells are CD3–, CD16+ CD56+. These cells are then stained with CD57. The total number of CD57+ NK cells (i.e., CD3–, CD16+, CD56+, CD57+) per microliter of whole blood is calculated and reported.

Result Interpretation

CD57+ NK cell test results indicate the number of cells per microliter of whole blood sent for analysis which is compared to a reference range.

<table>
<thead>
<tr>
<th>Reference Range: 60 - 360 per CD57+ NK cells per microliter</th>
<th>Value</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>Low</td>
<td></td>
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<tr>
<td>60 – 360</td>
<td>Normal</td>
<td></td>
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<tr>
<td>&gt;360</td>
<td>High</td>
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Chronic Lyme Disease patients may present with a “Low” result, but are very unlikely to present with a “High” result.

Chronic Lyme Disease patients presenting with fewer than 60 cells per microliter will be indicated as “Low” on your MDL CD57+ NK cell results. Patients reporting higher than expected numbers of CD57+ NK cells may require referral to a hematologist.

Treating CD57+ NK Cell “Low” Chronic Lyme Disease Patients

Providers should follow and regularly review current CDC treatment guidelines. CD57+ NK cell testing is not a stand-alone primary diagnostic test for Lyme disease or any other disease or condition. The responsibility for its use in treatment decisions lies with the physician. CDC guidelines for treating Lyme Disease can be found at [https://www.cdc.gov/lyme/index.html](https://www.cdc.gov/lyme/index.html).

REFERENCES: