Mannose binding lectin defects and autoimmune diseases

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Abstract

Complement system has a very important role in our defense against different pathogens and harmful immune complexes. The lectin pathway of complement system is activated by mannose binding lectin leading to complement cascade ending with the removal of these invading pathogens and the injuring immune complexes. Defects in mannose binding lectin were found to be associated with MBL2 gene polymorphisms such as exon 1 polymorphisms and promoter region polymorphisms. These defects were linked to serious autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. The aim of our review is to provide an overview of mannose binding lectin role in complement system and to outline the information about mannose binding lectin defects with systemic lupus erythematosus and rheumatoid arthritis in addition to the possible related explanations. Mannose binding lectin variants were believed to have an association with these autoimmune disorders by many studies with the presence of conflicted studies as well.

Keywords: Complement, mannose binding lectin, polymorphisms, autoimmune.

1. Introduction

One of the most important components of our immune system is the complement system that plays a vital role in defending our body against different pathogens and harmful immune complexes. Complement system has more than forty proteins which initiate and complete the complement cascade ending with the opsonization and the phagocytosis in addition to the activation of different immune cells (Warwick \textit{et al.}, 2021). The activation of the complement system could be performed through the Lectin pathway, the classic pathway, and the alternative pathway (Dunkelberger \textit{et al.}, 2010). Mannose binding lectin (MBL) is a pattern recognition molecule that
is responsible for activating the Lectin pathway in addition to modulating the response of our immune system (Zhou et al., 2019). The mannose-binding lectin has the ability to activate the lectin pathway by recognizing the invading pathogen and binding to its surface resulting in activating MBL-associated serine proteases (MASPs) that results in cleaving C2 and C4 molecules and forming C3 convertase molecule. C3 convertase initiate the cascade that ends with forming the membrane attack complex that attack the pathogen. In addition, different opsonic fragments are generated with their important role in phagocytosis process (Defendi et al., 2020). The defects in Mannose binding lectin were shown to be related to serious autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis (Kalia et al., 2021). These defects were shown to be related to polymorphisms in MBL2 gene such as exon 1 polymorphisms; rs5030737 in codon 52, rs1800450 in codon 54 and rs1800451 in codon 57 in addition to polymorphisms of the promoter region such as rs11003125, rs7096206 and rs7095891 polymorphisms Table 1 (Kalia et al., 2021). The existence of any polymorphism of the three polymorphisms in exon one is collectively called O variant (Martiny et al., 2012).

2. Mannose binding lectin defects and systemic lupus erythematosus

Systemic lupus erythematosus is an autoimmune disease in which immune complexes and autoantibodies are produced. Therefore, many organs are damaged (Lee et al., 2005). Systemic lupus erythematosus is a complex disease with many environmental and genetic factors. Polymorphisms in complement system genes especially in MBL2 were suspected to be related to systemic lupus erythematosus susceptibility (Sawada et al., 2019). Different studies were performed to investigate this relationship and many meta-analysis studies were performed to analyze the results of these studies. The 2020 meta-analysis conducted by Mahto and colleagues showed that MBL-2 polymorphism in codon 52 and the combined A/O variant associated significantly with systemic lupus erythematosus susceptibility, on the other hand the MBL-2 polymorphism in promoter region (-221Y > X) was found to have a protect effect against systemic lupus erythematosus (Mahto et al., 2020). Moreover, Xu and colleagues found also in their meta-analysis that A/O variant might have an association with systemic lupus erythematosus as the analysis that included all the studies found a significant association with systemic lupus erythematosus, while after stratifying by European ethnicity no significant result was found (Xu et al., 2013). Furthermore, Lee and colleagues found in their meta-analysis that codon 54 variant had an association with developing systemic lupus erythematosus in Europeans, Africans and Asians (Lee et al., 2012). In addition, Lee and colleagues found in their meta-analysis that mannose binding lectin polymorphisms could be considered as factors for increasing risk of systemic lupus erythematosus, although in their two case-control studies, no significant association were found (Lee et al., 2005).

The role of MBL polymorphism in systemic lupus erythematosus could be explained by the resulting impairment in the clearance of immune complexes and apoptotic bodies that lead to the increase in the production of autoantibodies, otherwise, the increasing exposure to infection associated with MBL defects could trigger that serious disease in some susceptible individuals (Sawada et al., 2019).

3. Mannose binding lectin defects and rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease with persistent inflammation in joints and a production of autoantibodies that could lead to cartilage damage and bone destruction. This disease is believed to result from both genetic and environmental factors leading to harmful activation of immune system and the presence of autoantigens leading finally to synovitis, the inflammation of joints and the serious complications (Calabresi et al., 2018). About 60% of susceptibility to rheumatoid arthritis is believed to be controlled by genetic factors (Xu et al., 2021).

Mannose binding lectin was believed to have a relationship with rheumatoid arthritis pathogenesis. On one hand, Mannose binding lectin was believed to be responsible for identifying immune complexes, thus, high levels of Mannose binding lectin were believed to exacerbate rheumatoid arthritis and increase the deterioration of this disease (Goeldner et al., 2014). On the other hand, Mannose binding lectin variants and its low levels were linked to the predisposition to rheumatoid arthritis and this was referred to the resulting
Table 1. Important SNPs in MBL2 gene

<table>
<thead>
<tr>
<th>SNP rs number</th>
<th>Region in MBL2 gene</th>
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</thead>
<tbody>
<tr>
<td>rs5030737</td>
<td>codon 52 (exon 1)</td>
</tr>
<tr>
<td>rs1800450</td>
<td>codon 54 (exon 1)</td>
</tr>
<tr>
<td>rs1800451</td>
<td>codon 57 (exon 1)</td>
</tr>
<tr>
<td>rs11003125 (L/H)</td>
<td>promoter region</td>
</tr>
<tr>
<td>rs7096206 (Y/X)</td>
<td>promoter region</td>
</tr>
<tr>
<td>rs7095891 (P/Q)</td>
<td>promoter region</td>
</tr>
</tbody>
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impairment of mannose binding lectin role in phagocytosis enhancement and cytokines modulation (Boldt et al., 2012). Therefore, big efforts were performed to investigate this possible relationship accompanied by the publishing of several meta-analysis studies as well. A meta-analysis study conducted in 2021 by Xu and colleagues found that the variants in exon 1 may have a significant association with rheumatoid arthritis in Indian and Brazilian people, meanwhile, in East Asians, they were the promoter region variants that showed an association with rheumatoid arthritis (Xu et al., 2021). Furthermore, a meta-analysis study conducted by Zhang and colleagues found that the variant in codon 54 may have a predisposition to rheumatoid arthritis and in particular the erosive rheumatoid arthritis. The East Asians showed more liability to this defect which may highlight the role of ethnicity in this liability (Zhang et al., 2015). On the other side, other meta-analysis studies showed absence of association between MBL2 SNPs and rheumatoid arthritis, Epp Boschmann and colleagues found that variants in exon 1 in addition to the variant in the position of −220 in the promoter region did not show a significant association with rheumatoid arthritis risk in Asian, European and Brazilian populations (Epp Boschmann et al., 2016). Moreover, Xie and colleagues found an absence of association with rs1800450 SNP in exon 1 in all studies in their meta-analysis study, but, they found an association with dominant model in Asian people after the stratification according to ethnicity (Xie et al., 2012).

4. Conclusion
Mannose-binding lectin is responsible for the activation of the lectin pathway of the complement system ending with clearing the different pathogens and the injuring immune complexes. Mannose-binding lectin defects resulting from gene polymorphisms are believed to have an association with systemic lupus erythematosus and rheumatoid arthritis. Many studies found a significant association between mannose-binding lectin polymorphisms and these serious autoimmune diseases with the existence of studies with conflicted results as well.

5. References:


