REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

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 promotor 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 *et al.*, 2021)**. The activation of the complement system could be performed through the Lectin pathway, the classic pathway, and the alternative pathway **(Dunkelberger *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

SNP rs number	Region in MBL2 gene
rs5030737	codon 52 (exon 1)
rs1800450	codon 54 (exon 1)
rs1800451	codon 57 (exon 1)
rs11003125 (L/H)	promoter region
rs7096206 (Y/X)	promoter region
rs7095891 (P/Q)	promoter region

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 promotor 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 in their meta-analysis 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:

Boldt, A. B., Goeldner, I., & de Messias-Reason, I. J. (2012). Relevance of the lectin pathway of complement in rheumatic diseases. Advances in clinical chemistry, 56, 105–153.

Epp Boschmann, S., Goeldner, I., Tuon, F. F., Schiel, W., Aoyama, F., & de Messias-Reason, I. J. (2016). Mannose-binding lectin polymorphisms and rheumatoid arthritis: A short review and meta-analysis. Molecular immunology, 69, 77–85.

Goeldner, I., Skare, T. L., Utiyama, S. R., Nisihara, R. M., Tong, H. v., Messias-Reason, I. J., & Velavan, T. P. (2014). Mannose binding lectin and susceptibility to rheumatoid arthritis in Brazilian patients and their relatives. PloS one, 9(4), e95519.

Calabresi, E., Petrelli, F., Bonifacio, A. F., Puxeddu, I., & Alunno, A. (2018). One year in review 2018: pathogenesis of rheumatoid arthritis. Clinical and experimental rheumatology, 36(2), 175–184.

Dunkelberger, J. R., & Song, W. C. (2010). Complement and its role in innate and adaptive immune responses. Cell research, 20(1), 34–50.

Defendi, F., Thielens, N. M., Clavarino, G., Cesbron, J. Y., & Dumestre-Pérard, C. (2020). The Immunopathology of Complement Proteins and Innate Immunity in Autoimmune Disease. Clinical reviews in allergy & immunology, 58(2), 229–251.

Kalia, N., Singh, J., & Kaur, M. (2021). The ambiguous role of mannose-binding lectin (MBL) in human immunity. Open medicine (Warsaw, Poland), 16(1), 299–310.

Lee, Y. H., Witte, T., Momot, T., Schmidt, R. E., Kaufman, K. M., Harley, J. B., *et al* (2005). The mannose-binding lectin gene polymorphisms and systemic lupus erythematosus: two case-control studies and a meta-analysis. Arthritis and rheumatism, 52(12), 3966–3974.

Lee, Y. H., Lee, H. S., Choi, S. J., Ji, J. D., & Song, G. G. (2012). The association between the mannose-binding lectin codon 54 polymorphism and systemic lupus erythematosus: a meta-analysis update. Molecular biology reports, 39(5), 5569–5574.

Lee, Y. H., Witte, T., Momot, T., Schmidt, R. E., Kaufman, K. M., Harley, J. B., *et al*. (2005). The mannose-binding lectin gene polymorphisms and systemic lupus erythematosus: two case-control studies and a meta-analysis. Arthritis and rheumatism, 52(12), 3966–3974.

Martiny, F. L., Veit, T. D., Brenol, C. V., Brenol, J. C., Xavier, R. M., Bogo, M. R., *et al*. (2012). Mannose-binding lectin gene polymorphisms in Brazilian patients with rheumatoid arthritis. The Journal of rheumatology, 39(1), 6–9.

Mahto, H., Pati, A., Sahu, S. K., Sharma, H. P., Padhi, A., & Panda, A. K. (2020). Association of MBL-2 gene polymorphisms with systemic lupus erythematosus: an updated meta-analysis and trial sequential analysis. Lupus, 29(10), 1227–1237.

Sawada, T., Fujimori, D., & Yamamoto, Y. (2019). Systemic lupus erythematosus and immunodeficiency. Immunological medicine, 42(1), 1–9.

Warwick, C. A., Keyes, A. L., Woodruff, T. M., & Usachev, Y. M. (2021). The complement cascade in the regulation of neuroinflammation, nociceptive sensitization, and pain. The Journal of biological chemistry, 297(3), 101085. Advance online publication.

Xie, Q., Wang, S. C., Bian, G., Zhan, F. L., Xie, J. K., & Li, J. (2012). Association of MIF-173G/C and MBL2 codon 54 gene polymorphisms with rheumatoid arthritis: a meta-analysis. Human immunology, 73(9), 966–971.

Xu, J., Chen, G., Yan, Z., Qiu, M., Tong, W., Zhang, X., *et al*. (2021). Effect of mannose-binding lectin gene polymorphisms on the risk of rheumatoid arthritis: Evidence from a meta-analysis. International journal of rheumatic diseases, 24(3), 300–313.

Xu, W. D., Peng, H., Zhou, M., Zhang, M., Li, B. Z., Pan, H. F., *et al*. (2013). Association of RANTES and MBL gene polymorphisms with systemic lupus erythematosus: a meta-analysis. Molecular biology reports, 40(2), 941–948.

Zhang, C., Zhu, J., Li, S. L., Wang, H., & Zhu, Q. X. (2015). The association of mannose-binding lectin genetic polymorphisms with the risk of rheumatoid arthritis: a meta-analysis. Journal of receptor and signal transduction research, 35(4), 357–362.

Zhou, J., Hu, M., Li, J., Liu, Y., Luo, J., Zhang, L., *et al* (2019). Mannan-Binding Lectin Regulates Inflammatory Cytokine Production, Proliferation, and Cytotoxicity of Human Peripheral Natural Killer Cells. Mediators of inflammation, 2019, 6738286.