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Pathogenesis of anti-melanoma differentiation-associated gene-5 *(MDA5)* dermatomyositis

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Dermatomyositis (DM) is an idiopathic inflammatory myopathy, with typical cutaneous manifestations and muscle lesions, usually involving multiple organs. Patients with anti-melanoma differentiation-associated gene-5 (*MDA5*) DM usually present with clinical amyopathic DM (CADM), which is characterized by a series of unique skin and systemic manifestations, including skin ulcer and interstitial lung disease (ILD). Among them, ILD is the most common complication of anti-MDA5 DM, and in some cases, it can develop into rapidly progressive ILD (RP-ILD).[1,2]

Although considerable progress has been made in understanding the pathogenesis of anti-MDA5 DM in recent years, much remains unclear. Therefore, we reviewed the relevant literature in recent years to explore the role of genetic, environmental, and immune factors in the pathogenesis of anti-MDA5 DM. The important pathogenesis of anti-MDA5 DM discovered in recent years is summarized in Supplementary Table 1, http://links.lww.com/CM9/A980.

In recent years, several genotyping studies have demonstrated that the major histocompatibility complex is the major genetic region associated with DM, and human leukocyte antigen (HLA) genes are important genetic risk factors for myositis and myositis-specific antibodies. Researchers have found that HLA-DRB1* 04:01 and HLA-DRB1*12:02 are involved in the production of anti-MDA5 antibody in patients with DM.[3] In addition, many type I interferon (IFN)-induced genes also play a critical role in anti-MDA5 DM, including IFN regulatory factor 7, signal transducer and activator of transcription 1, IFN-stimulated gene 15, and myxovirus resistance 1 genes.[4]

DM can be triggered by multiple environmental factors, including viruses, ultraviolet radiation, drugs, smoking, season, and residence. Viral infection may induce immune activation in patients with DM, but no specific virus has been successfully isolated from their muscle tissue. Recent studies have shown that sun exposure and nonsteroidal anti-inflammatory drugs are independent risk factors for the development of DM, while smoking has also been shown to be associated with the development of DM, ILD, and other complications. In addition, a recent study has shown that season and location of residence are closely related to the development of anti-MDA5-associated ILD. Specifically, anti-MDA5-associated ILD occurred mainly in individuals living near freshwater from October to March.[5]

Some scholars have found many similarities between patients with anti-MDA5 DM and patients with coronavirus disease 2019, suggesting that anti-MDA5 DM may be closely related to antiviral immune response.[6] Due to the important role of MDA5 in the defense against viruses, there is a widely accepted hypothesis [Figure 1]. The production of anti-MDA5 antibody is a sign of viral infection, which is associated with the development of CADM and RP-ILD. Specifically, the expression of MDA5 may be upregulated when a certain virus infects skin or lung epithelial cells. Subsequently, the antiviral immune response induces apoptosis of the infected cells, resulting in the release of many viruses and MDA5 complexes. This leads to loss of self-tolerance, tissue damage, and exposure to specific antigens, followed by the production of cryptic epitopes and a permanent autoimmune cycle.[7] Patients with anti-MDA5 DM showed higher levels of type I IFN in serum and affected skin, suggesting that type I IFN and viruses play an important role in the mechanism of anti-MDA5 DM.[4] However, this hypothesis remains unproven as the key unknown virus has not been discovered.

Type I IFN is the main component of innate immunity against viral infection. In recent years, many studies have proved that serum and affected skin of patients with anti-MDA5 DM show higher type I IFN levels than those of patients with anti-MDA5 antibody-negative DM. Among the increased type I IFN levels, IFN-α was most significantly upregulated, while IFN-β was not significantly upregulated. Type I IFN may participate in the pathogenesis of anti-MDA5 DM through various ways, including B-cell-activating factor (BAFF) pathway,[4] neutrophil extracellular trap (NET) pathway, and the release of type I IFN-associated proteins.[9]

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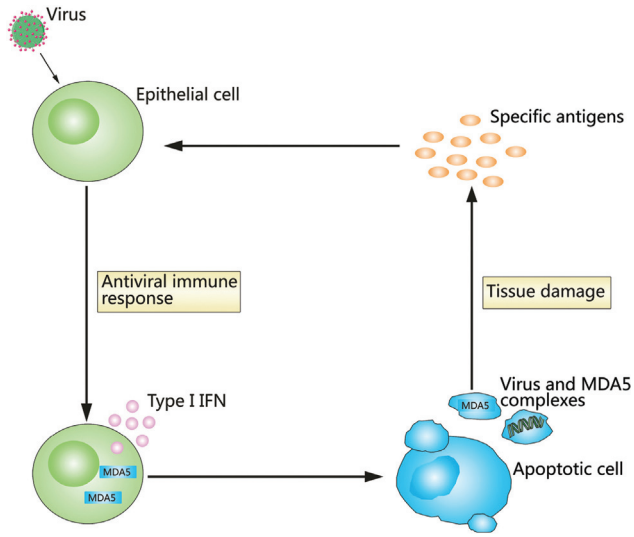

Figure 1: Hypothesis on the pathogenesis of anti-MDA5 DM. When a certain virus infects skin or lung epithelial cells, the body produces large amounts of MDA5 antibodies and type I IFN through an antiviral immune response. Subsequently, apoptosis of the infected cells results in the release of the virus and MDA5 complexes. This causes tissue damage and exposure to specific antigens, creating a permanent autoimmune cycle. DM: Dermatomyositis; IFN: Interferon; MDA5: Melanoma differentiation-associated gene-5.

BAFF is critical for the maturation and survival of B cells and plays an important role in the production of autoantibodies and in the activation and differentiation of T cells. In patients with DM, BAFF levels were significantly elevated and associated with creatine kinase levels and ILD and decreased with treatment. Moreover, a recent study showed that serum IFN-α and BAFF levels were significantly increased in patients with anti-MDA5 DM. In patients with anti-MDA5 DM and ILD with elevated IFN-α levels, BAFF levels were correlated with IFN-α and the disease severity of ILD.[4] Therefore, the increase of BAFF levels caused by excessive IFN-α production may play an important role in the pathogenesis of anti-MDA5 DM with ILD.

NETs are extracellular structures made up of granular proteins and chromatin that kill bacteria. In addition to resistance to pathogens, NETs have also gained attention for its role in autoimmune diseases.[10] A recent study found that significantly increased levels of NETs were detected in serum of patients with anti-MDA5 DM.[8] This suggests that NETs may also play an important role in the pathogenesis of anti-MDA5 DM with ILD. It has been shown that in autoimmune diseases such as systemic lupus erythematosus, type I IFN initiates neutrophils to release NETs, which in turn further activate plasmacytoid dendritic cells to produce high levels of IFN-α via DNA and Toll-like receptor 9. This creates a permanent loop of positive feedback between type I IFN and NETs. In anti-MDA5 DM, the high levels of type I IFN and NETs suggest that this positive feedback may also play an important role in the pathogenesis, which needs further verification.

Type I IFN can induce the production of a variety of associated proteins, including myxovirus resistance protein A (MxA). Under normal circumstances, MxA induced by type I IFN plays an antiviral role. However, recent studies have shown that the expression of MxA is increased in various subtypes of DM. In all patients with DM, the sensitivity and specificity of sarcoplasmic MxA expression were 77% and 100%, respectively. In addition, some anti-MDA5 DM samples showed a scattered staining pattern of MxA. In view of the high sensitivity and specificity of MxA in diagnosis, it can be considered as a pathological marker of DM.[9]

Abnormal complement activation also plays an important role in the pathogenesis of DM. It leads to destruction of capillaries, resulting in ischemia and microinfarction, hypoperfusion, and perifascicular atrophy. However, this abnormal immune activation sequence has not been fully defined and needs to be further studied.

In summary, anti-MDA5 DM has been widely concerned because of its unique clinical characteristics and high mortality. Although the pathogenesis of anti-MDA5 DM is not yet clear, great progress has been made in recent years. Genetic factors, environmental factors, and immune factors may be involved in its pathogenesis. Type I IFN plays a crucial role in the pathogenesis of anti-MDA5 DM, and its pathogenic effects may occur mainly through the BAFF pathway, NET pathway, and the release of type I IFN-associated proteins. It is of great clinical significance to understand the pathogenesis of anti-MDA5 DM. Future studies are expected to further reveal the important roles of anti-MDA5 antibody, virus, and type I IFN in its pathogenesis.

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Conflicts of interest

None.

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