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Myositis autoantibodies

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Abstract

Purpose of review—To review recent advances in our understanding of autoantibodies associated with dermatomyositis and the autoimmune necrotizing myopathies.

Recent findings—Autoantibodies preferentially associated with dermatomyositis include those recognizing Mi-2, MDA5, TIF1 γ, and NXP-2. Each of these is associated with a distinct clinical phenotype. Autoantibodies found in patients with autoimmune necrotizing myopathies recognize SRP and HMG-CoA reductase. The latter are found in patients with statin-associated autoimmune muscle disease.

Summary—As these are helpful both diagnostically and prognostically, a rheumatologist should be familiar with autoantibodies found in patients with dermatomyositis and the autoimmune necrotizing myopathies.

Keywords

Autoantibodies; autoantigens; myositis; dermatomyositis; necrotizing myopathy

INTRODUCTION

In the autoimmune myopathies (i.e., myositis), autoantibodies are diagnostically and prognostically useful because they are frequently associated with specific clinical subgroups. This review will focus on recent progress in our understanding of autoantibodies associated with dermatomyositis (DM) and the necrotizing autoimmune myopathies, the majority of which have only been identified and characterized in the last decade. In contrast, antibodies targeting the antisynthetases (e.g., Jo-1) have been recognized for more than thirty years and many up-to-date reviews are already available (see (1)).

DERMATOMYOSITIS-ASSOCIATED AUTOANTIBODIES

While anti-Mi2 antibodies have long been recognized to associate with DM, findings from recent studies have highlighted melanoma differentiation-associated gene 5 (MDA5), transcriptional intermediary factor 1 γ (TIF1γ, previously known as p155/140) and nuclear matrix protein 2 (NXP2) as additional DM-specific antibodies. Each of these specificities, and associated clinical features, are detailed below.

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CONFLICT OF INTEREST
Drs. Casciola-Rosen and Mammen have a patent for an anti-HMGCR antibody test.

Mi2 autoantibodies

Mi2 autoantibodies are associated with characteristic DM skin lesions and disease features suggesting that this specificity defines a distinct disease subgroup. Hallmark cutaneous features may include heliotrope rash, shawl rash, cuticular overgrowth, Gottron's papules and V-sign. In general, DM patients with anti-Mi2 antibodies have a better disease prognosis, as well as a more favorable response to steroid treatment and a lower incidence of cancer compared to other DM patients (reviewed in (1)).

Mi2, a prominent component of the nucleosome-remodeling deacetylase complex, is a DNA-dependent nucleosome-stimulated ATPase which regulates gene transcription (2,3). Studies performed in several different systems have shown that Mi2 has a role in regulating developmental processes; this function may play an important role in the pathogenesis of DM. For example, a tissue-specific knockout mouse model has demonstrated that Mi2 is a key participant in repairing the basal cell layer of skin epidermis (4), a prominent target of the immune response in DM skin disease.

Recent data strongly suggests that autoantigen expression in the target tissue in rheumatic diseases plays an important role in amplifying and sustaining the ongoing tissue injury which characterizes this spectrum of diseases. Several features of Mi-2 are particularly relevant in this regard. For example, although Mi2 is a ubiquitously expressed protein, expression levels may change in response to certain stimuli, or may vary in different tissues and/or in cells in defined stages of differentiation. When levels of Mi2 were quantitated by immunoblotting using lysates prepared from muscle biopsies obtained from patients with DM or PM, or control individuals, very low levels were detected in PM and normal biopsy lysates, whereas expression was robust in DM biopsy lysates (5). Immunohistochemistry performed on DM muscle biopsies showed that Mi2 expression was elevated in the centralized nuclei of small muscle fibers that express regeneration markers (6). Furthermore, when Mi2 levels were monitored during differentiation of cultured human myoblasts by immunoblotting, regenerating muscle cells were found to express high levels of Mi2 (and other myositis autoantigens). These studies demonstrate that Mi2 is expressed in regenerating muscle cells in DM, which provide the antigen source that sustains/drives the propagation phase of the disease. Also noteworthy in this regard is the finding that Mi2 levels are rapidly elevated in cultured keratinocytes after UVB irradiation (7). Interestingly, only the Mi2 component of the nucleosome-remodeling deacetylase complex was induced, possibly providing the antigen source in UV-induced dermatitis, and consistent with the fact that only this component is targeted by the autoimmune response. Taken together, these studies pinpoint the tissue repair process as an important source of Mi-2 in skin and muscle in DM, which creates the potential for a feedforward damage loop. Thus muscle and epidermal injury induces repair. The repairing cells express high levels of Mi-2, and are therefore the targets of further immune attack, which generates injury, and the need for ongoing repair.

MDA5 Autoantibodies

Antibodies against MDA5 (originally termed "anti-CADM-140" antibodies) were first described in 2005 (8). In studies performed on several Japanese cohorts and a US cohort, these DM-specific autoantibodies have been detected in 13–35% of DM patients (9–11), with the US frequency being on the lower end of this spectrum, perhaps reflecting different methodologies used to detect these antibodies, or population differences. The initial studies showed that patients with these antibodies typically have absent/mild muscle disease, and are at increased risk for developing rapidly progressive interstitial lung disease (9,10). New data continues to expand the clinical phenotype associated with anti-MDA5 antibodies. Fiorentino et al (11) recently described characteristic mucocutaneous features frequently

found in DM patients with this specificity (in addition to the clinical features noted above). These consist of skin ulceration and/or tender palmar papules, with typically affected areas including the lateral nailfolds, Gottron papules and elbows. They also noted that patients with MDA5 autoantibodies had a higher risk of experiencing oral pain/ulceration and arthritis/arthralgia. The prominent involvement of skin and lung, with minimal muscle involvement suggests that the pathogenesis of this syndrome differs from the more classic DM in which muscle disease is more prominent. It has been proposed that perhaps viewing the MDA5-associated syndrome as a "dermato-pulmonary syndrome" rather than an amyopathic DM would be useful to improve recognition of this syndrome clinically (12).

MDA5 is a cytoplasmic RNA-specific helicase that recognizes single-stranded RNA viruses (13). It belongs to a family of retinoic acid-inducible gene I-like receptors that function as cytoplasmic sensors of pathogen-associated molecular patterns within viral RNA. These proteins drive type I interferon production and anti-viral gene expression, thus mediating the intracellular immune response to control virus infection. Substantial evidence has accumulated implicating type I interferons in the pathogenesis of DM (14). It is therefore noteworthy that MDA5 is both type I interferon inducible, and a frequent target of the immune response in DM. Also intriguing is the observation by Fiorentino et al that Ro52 antibodies (another IFN-induced autoantigen) are found in 30% of anti-MDA5 antibody positive patients (11). Quantitative studies evaluating whether MDA5 expression is increased in relevant affected tissues in DM will be informative and may highlight the possible utility of anti-interferon therapeutics in this disease spectrum. Why the lung is so prominently targeted with patients with MDA5 antibodies raises the possibility that this organ (rather than muscle) may be the initiation site in the anti-MDA5 antibody positive DM disease subgroup (15).

TIF1γ Autoantibodies

Several years ago, autoantibodies against a 155 kD protein and a 155/140 kD doublet (thought to be the same protein) were described in DM patients (16,17). Both studies showed that the antibodies were DM-specific, and were detected in patients with an increased risk of malignancy. Trallero-Araguas et al (18) recently performed a systematic literature review and a meta-analysis to determine the diagnostic value of these antibodies for detecting cancer-associated DM. Their analysis was performed using data from 6 published studies (a total of 312 adult DM patients), with all assays to detect the antibodies involving immunoprecipitation from either K562 or HeLa whole cell lysates. A technically complex assay, the readout of antibody status is neither standardized nor objective, possibly explaining the range (14–31%) in the percent of antibody-positive patients in the different cohorts. This comprehensive analysis showed that patients with anti-155 kD antibodies had an 89% specificity and a 78% sensitivity for diagnosing cancer-associated DM, with positive and negative predictive values of 58 and 95%, respectively.

In 2006, soon after the specificity was described, Targoff et al reported that the target of the 155 kD autoantibodies was transcription intermediary factor 1γ (TIF1γ) (19). Since then, the assumption has been that anti-155/140 and anti-155 kDa antibodies are the same. Fujimoto et al (20) recently used a combination of immunoblotting and immunoprecipitation to show that anti-155/140 antibodies target the family of TIF1 proteins (α,β and γ with the 140 kDa antigen of the 155/140 doublet being TIF1α and TIF1β being a band of ~100 kDa often detected in immunoprecipitations performed with anti-155/140 positive sera using cell extracts. In their cohort of DM patients, these authors found that 78/456 (17%) had one or more anti-TIF1 antibody, with the most frequently observed combination of antibodies being anti-TIF1 α and γ (the so-called anti-155/140 specificity) found in 48/62 (62%) patients. Reactivity against TIF1α alone, or with anti–TIF1α and β in the absence of γ reactivity was not detected in this cohort.

The TIF1 family is a subgroup of the tripartite motif (TRIM)-containing proteins consisting of several members, including TIF1β (TRIM28), TIF1α (TRIM24) and TIF1γ (TRIM33). These play a role in various key cellular functions and pathways, especially carcinogenesis. TIF1γ monoubiquitinates Smad4, thereby inactivating it and thus suppressing TGFβ signaling and enhancing cell growth and differentiation (21). TIF1α ubiquitinates p53, the tumor suppressing gene (22), and activates other genes associated with tumor development and cellular proliferation (23). TIF1β enhances p53 ubiquitination and inhibits its acetylation, thus having an anti-apoptotic effect (24). Interestingly, Ro52 belongs to the same TIF1 family (Ro52 is also known as TRIM21), and it ubiquitinates IRF8 (25). Although the levels of TIF1 family member expression in various tumors and myositis muscle is not known, it is intriguing to speculate that autoantibodies against TIF1 family proteins are generated during anti-tumor responses (ie, initiation phase of autoimmunity is an anti-cancer response). Consistent with a scenario proposed by Casciola-Rosen et al in 2005 (5), this response may cross-over to tissues expressing high levels of such antigens (for example, in the setting of damage, drugs or virus) thereby sustaining the autoimmune response and enabling the propagation phase to continue in a cycle of antigen expression/ focus of immune mediated damage/enhanced antigen expression in regenerating cells.

NXP2 Autoantibodies

Another 140 kDa specificity, originally called “anti-MJ” was found in 18% of patients in a JDM cohort study (26). Nuclear matrix protein 2 (NXP2) was subsequently identified as the autoantigen target (27). This specificity was associated with severe muscle weakness, polyarthritis, joint contractures and intestinal vasculitis. Further studies performed on JDM cohorts in the UK (28) and Argentinia (29) reported that these antibodies were found in 23–25% of patients, with a higher incidence of calcinosis also being detected amongst those in the UK.

More recently, the frequency and clinical associations of NXP2 antibodies have been studied in 2 different adult myositis cohorts. Ceribelli et al (30) studied 58 Italian DM/PM patients, and detected NXP2 antibodies in 8/27 (30%) of DM and 2/25 (8%) of PM patients. These antibodies were associated with younger ages of both disease onset and first visit, calcinosis, no internal involvement and good response to therapy. In another study, Ichimura et al (31) examined a cohort of 507 adult Japanese patients (445 with DM and 62 with PM), and detected anti-NXP2 antibodies in 7/445 (1.6%) of DM and 1/62 (1.6%) of PM patients. All of the anti-NXP2 antibody positive patients were noted to have significant muscle weakness and elevated creatine kinase levels. Associated cancers (detected within 3 years of myositis diagnosis) were present in 38% of the anti-NXP2 antibody positive patients in this Japanese cohort; while this observation is intriguing, the number of anti-NXP2 positive patients involved is small and additional studies will be needed to confirm this in larger groups. Further studies in other adult DM cohorts are also needed to assess whether the differences in anti-NXP2 antibody frequency in these 2 adult DM populations (30% in Italian, 1.6% in Japanese) are due to methods used to detect the antibodies, and/or genetic or environmental factors.

ANTIBODIES ASSOCIATED WITH NECROTIZING AUTOIMMUNE MYOPATHIES

The presence of inflammatory cells is common in patients with autoimmune myopathies. However, some patients with immune-mediated muscle disease have abundant myofiber degeneration, regeneration, and necrosis without prominent chronic inflammatory cell infiltrates. The best understood examples of this include those with antibodies recognizing

either the signal recognition particle (SRP) or the anti-HMG-CoA reductase (HMGCR) enzyme.

Anti-Signal Recognition Particle Autoantibodies

The signal recognition particle (SRP) is a ubiquitous cytosolic ribonucleoprotein consisting of a 7SL RNA molecule and six polypeptides with molecular weights of 9, 14, 19, 54, 68, and 72 kDa. The SRP complex binds the amino-terminal signal sequences of newly translated proteins and targets them to the endoplasmic where a protein-conducting channel translocates them across the organelle's membrane. In 1986, Reeves and colleagues first reported the presence of autoantibodies recognizing the 54 kDa subunit of SRP in a single patient described to have "typical polymyositis" (32). Autoantibodies recognizing all six polypeptides as well as the 7SL RNA have been described since then (33).

The unique clinical features of anti-SRP subjects have been documented in several case series. In 1990, Targoff and colleagues described the first cohort, a collection of 13 anti-SRP positive subjects (34) with some features of "classic adult PM". However, the anti-SRP subjects often had more severe disease with a very rapid onset. Furthermore, unlike many other patients with autoimmune myopathy, anti-SRP subjects did not appear to have frequent skin involvement, interstitial lung disease, Raynaud's phenomenon, arthritis, or overlap syndromes with other connective tissue diseases. Given these differences, these authors proposed that anti-SRP antibodies are associated with a distinct subgroup of adult PM.

In 2002, Miller and colleagues provided detailed clinical features of seven anti-SRP subjects. This study confirmed that these patients have a rapidly progressive, severe myopathy with dysphagia and very high CK levels that is frequently responsive to steroids (35). They also described the typical muscle biopsy features of anti-SRP positive subjects: abundant degenerating and regenerating muscle fibers with little or no inflammation (i.e., a necrotizing myopathy). Although these subjects did not have rashes or perifascicular atrophy, anti-SRP muscle biopsies were notable for having some "DM-like" features, including a reduced number of capillaries, enlarged capillaries, and complement deposition on the remaining capillaries. Most of these clinical and pathological features have been confirmed by other groups (36–38). However, not all investigators have detected complement deposition on capillaries (37). There is also some discrepancy regarding the prevalence of cardiac involvement in anti-SRP autoimmune myopathy. Whereas palpitations, arrhythmias, EKG abnormalities, and/or cardiomyopathy were reported in more than half of 42 combined subjects in three studies (34,37,39), cardiac abnormalities were found in only 3 of 50 combined subjects in three others (35,36,40). The reasons for this are not clear.

Most case series have emphasized that patients with anti-SRP myopathy are difficult to treat and often require multiple immunosuppressive medications to control. Interestingly, a recent report by Suzuki and colleagues suggests that those with a subacute presentation respond better to therapy than do those with a chronic presentation (40). Among 27 anti-SRP positive subjects, 22 were defined as having a subacute presentation (i.e., they were seen by a physician within 6 months of symptom onset) and 5 were defined as having a chronic presentation (i.e., they were first examined only 8 or more months after symptom onset). Assessing neurological outcomes using the modified Rankin Scale, these authors found that almost all patients with a subacute presentation either recovered or had mild residual deficits. In contrast, 2 of the 5 subjects with chronic presentations had severe residual deficits and none of them recovered fully. Although this study raises the possibility that two distinct forms of anti-SRP myopathy may exist, there were important limitations to this study. First, it may be that delay of diagnosis and treatment resulted in worse outcomes for

the “chronic” subjects. Second, the interval between diagnosis and assessment of outcomes was not reported in either group, making it difficult to interpret the comparison between these two groups.

As with other antibodies associated with autoimmune myopathy, the pathologic role of anti-SRP antibodies remains in question. Although anti-SRP antibodies from patient sera can inhibit the function of the SRP complex (41), it is unclear how these antibodies would access the cytosolic compartment in undamaged cells where their target is located. Nonetheless, two recent case series demonstrate that anti-SRP autoantibody levels do correlate with markers of disease activity in individual patients (38,42). Consequently, some authors have suggested that following anti-SRP levels may be a useful measure of disease activity in individual patients. Further studies will be required to determine whether monitoring antibody levels provides any additional benefit over monitoring CK levels.

Anti-HMG-CoA Reductase Autoantibodies

In 2010, our group published a study designed to identify novel autoantibodies in patients with necrotizing myopathies who had no known autoantibodies or other clear explanation for their muscle biopsy findings (e.g., muscular dystrophy) (43). By performing immunoprecipitations from radioactively labeled HeLa cells, we found that 16 of 26 sera from subjects with idiopathic necrotizing myopathies recognized a pair of proteins with molecular weights of 200-kd and 100-kd. The anti-200/100-kd antibodies were only found in 1 of 187 patients without prominent myofiber necrosis on muscle biopsy, suggesting they are very specific for patients with this muscle biopsy feature.

Patients with anti-200/100 antibodies had a typical clinical phenotype including proximal muscle weakness, mean maximum CK values over 10,000 IU/L, an irritable myopathy on electromyography, and either a partial or complete response to treatment with immunosuppressive agents. Interestingly, 63% of these subjects were noted to have had statin exposure prior to developing muscle weakness, which was significantly higher than the prevalence of statin exposure in patients with either DM (15.2%) or PM (18.4%). The statistically significant association was maintained when comparing statin exposure in anti-200/100 subjects over the age of 50 (83%) with age-matched DM (25%) or PM (37%) subjects. Given the high prevalence of statin exposure, we noted that the statin-exposed anti-200/100-kd positive subjects were phenotypically similar to those previously reported by others to have developed a statin-associated immune-mediated necrotizing myopathy (44,45). Importantly, in all three studies, muscle weakness and CK levels continued to progress in patients despite prolonged discontinuation of the offending medication.

Based on our observation that the 200-kd and 100-kd proteins are up-regulated in cultured cells exposed to statins, we identified the 100-kd autoantigen as HMG-CoA reductase (HMGCR), the pharmacologic target of statin medications (46). In all patients tested to date, autoantibodies have been directed against the intracellular carboxy terminal catalytic domain of HMGCR. Additional experiments indicate that the 200-kd autoantigen is the dimeric form of HMGCR.

Using an ELISA to screen sera collected from 750 subjects at the Johns Hopkins Myositis Center, we found that 45 (6%) were anti-HMGCR positive, making it the second most prevalent autoantibody (after anti-Jo-1) in our cohort of patients with myopathy. As expected, most of these subjects had predominantly necrotizing muscle biopsies. However, 20% did have significant inflammatory infiltrates noted on biopsy, indicating that the presence of cellular infiltrates does not exclude a diagnosis of anti-HMGCR associated autoimmune myopathy.

In order to more precisely define the phenotype of patients with anti-HMGCR autoantibodies, we screened a large number of subjects with and without statin exposure, including those with the more common mild form of statin intolerance. First, we determined the prevalence of anti-HMGCR autoantibodies in a large cohort of patients without known muscle disease who were enrolled in the community-based Atherosclerosis Risk in Communities (ARIC) Study (47). Among 763 current statin users, 322 with prior statin use, and 881 without a history of statin use, 14 subjects had anti-HMGCR titers which were greater than 3 standard deviations higher than the mean of the entire population. However, none of these patients had anti-HMGCR antibodies that immunoprecipitated purified HMGCR protein, indicating that these were ELISA false-positives. We also screened samples obtained from 51 subjects with familial hypercholesterolemia and mild forms self-limited statin intolerance characterized by myalgias, subjective weakness, and/or modestly elevated serum CK levels. None of these subjects were anti-HMGCR positive. Taken together, these studies demonstrate that anti-HMGCR antibodies are not found in the majority of patients with statin exposure, including those with self-limited musculoskeletal complaints. Rather, anti-HMGCR antibodies appear to be specific for those with an autoimmune myopathy.

As with other myositis-specific antibodies, certain immunogenetic factors are associated with either an increased or decreased risk of developing anti-HMGCR autoantibodies (48). Specifically, we found that the HLA class II antigen DRB1*11:01 was strongly associated with anti-HMGCR autoantibodies in both white (odds ratio 24.5; $p = 3.2 \times 10^{-10}$) and African American (odds ratio 56.5; $p = 3.1 \times 10^{-6}$) subjects. In contrast, the class II alleles DQA1 and DQB6 were decreased in frequency among white autoantibody positive subjects compared to healthy controls ($p = 5.5 \times 10^{-4}$ and 2.1×10^{-5}, respectively). The DRB1*11:01 allele was associated with anti-HMGCR autoantibodies in both statin-exposed and statin-unexposed subjects.

Although both statin-exposed and -unexposed anti-HMGCR myopathy patients present with proximal muscle weakness, irritable myopathy on EMG, necrotizing muscle biopsies, and similar immunogenetic risk profiles, there are significant differences between the two groups. For example, we found that statin-exposed anti-HMGCR subjects were more likely to be white (87 vs. 47%), older (59 vs. 37 years old), and to have lower serum CK levels (7881 vs. 13,392) than statin unexposed subjects (46). We have also noted that anti-HMGCR antibody levels at first visit to the Johns Hopkins Myositis Center were correlated with CK levels and strength only in statin-exposed subjects (49). Interestingly, in a two year follow-up analysis, statin-exposed subjects seemed to respond better to immunosuppressive therapy than those without statin exposure.

Although the mechanisms underlying the initiation and maintenance of anti-HMGCR autoimmunity remain unclear, some clues have emerged. First, we and others have noted that HMGCR protein expression is up-regulated in cultured cells exposed to statins. Second, we found that HMGCR protein is expressed at low levels in normal muscle, but at high levels in regenerating muscle cells in biopsy specimens from patients with anti-HMGCR-associated necrotizing myopathy. These observations suggest a model in which anti-HMGCR autoimmunity can be initiated in immunogenetically susceptible individuals by HMGCR over-expression in the context of statin use and persists (despite statin discontinuation) due to elevated levels of HMGCR in regenerating muscle cells which are the target of the immune response. This attractive model awaits experimental validation.

The correlation between antibody levels and indicators of disease activity (i.e., serum CK and strength) suggests a potential pathologic role for anti-HMGCR antibodies. However, it is important to note that anti-HMGCR antibody levels remain markedly elevated even in

subjects who have normalized their strength and serum CK levels (49). This argues that anti-HMGCR autoantibodies do not directly damage normal muscle cells. Rather, they may only be a byproduct of the disease process. Nonetheless, anti-HMGCR antibody testing may help clinicians distinguish between those who have a statin-triggered autoimmune myopathic process requiring immunosuppressive therapy to resolve and those who have self-limited statin intolerance which only requires cessation of the offending medication.

CONCLUSION

Testing for most of the autoantibody specificities discussed in this review is already commercially available. For those that are not, clinical assays are likely to soon become commercially available. Testing for selected antibodies will be helpful in establishing the diagnosis and prognosis of patients with suspected autoimmune muscle disease.

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KEY POINTS

- Anti-MDA5 antibodies are associated with unique mucocutaneous features, severe lung disease, and minimal muscle involvement.
- Patients with anti-TIF1γ autoantibodies have an increased risk of malignancy.
- Children with anti-NXP-2 antibodies are more likely to experience calcinosis.
- The anti-SRP autoantibody level may be a clinically useful marker of disease activity.
- Anti-HMGCR autoantibodies are found in those with statin-associated autoimmune myopathy requiring immunosuppression but not in the vast majority of those with statin exposure, including patients with mild self-limited statin intolerance.