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Triggers of Inflammatory Myopathy: Insights into Pathogenesis

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Abstract

The inflammatory myopathies, which includes dermatomyositis, polymyositis, and the immune-mediated necrotizing myopathies, are a heterogeneous group of autoimmune diseases that manifest with muscle, skin or lung damage. Collectively, these autoimmune diseases result from loss of tolerance to a select group of self-antigens, although the precise mechanism through which this occurs is not known. Infection, malignancy, and certain medications including statins and the immune checkpoint inhibitors used in cancer therapy have been identified as potential immunologic triggers of the inflammatory myopathies. Some of these triggers are classically associated with specific myositis-specific autoantibodies (MSAs). The strong association between certain triggers and MSAs provides insights into how an immunologic event can lead to loss of tolerance to specific self-antigens, resulting in autoimmune disease. In this review, we discuss the proposed triggers of the inflammatory myopathies and their associations with MSAs, and provide insights into how these triggers may result in the inflammatory myopathies.

Introduction

The inflammatory myopathies are a heterogeneous group of diseases that result from an immune-mediated attack on muscle, skin, and/or lung. Common manifestations of myositis include proximal muscle weakness, rashes and interstitial lung disease. The inflammatory myopathies are further subclassified into dermatomyositis (DM), polymyositis (PM), the immune-mediated necrotizing myopathies (IMNM), and inclusion body myositis (IBM) by the presence or absence of specific clinicopathologic features (Lundberg *et al.*, 2017).

The discovery of an expanding list of myositis-specific autoantibodies (MSAs) have further defined the inflammatory myopathies. To date, 16 MSAs have been described, and about 70-80% of patients with myositis have an identifiable MSA. Many MSAs have been discovered only recently, and it is likely that other MSAs will eventually be characterized in patients who today are considered to be autoantibody negative. There is a striking correlation between certain known MSAs and clinical features of disease. For example, patients with autoantibodies targeting histidyl-tRNA synthetase (anti-Jo-1) express features of the antisynthetase syndrome, including myositis, interstitial lung disease, mechanic's hands and arthritis. Similarly, patients with autoantibodies directed against chromodomain

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helicase DNA binding protein 4 (Mi-2) generally have a severe DM rash without significant lung involvement (Betteridge and McHugh, 2016). Despite the clinical relevance of these autoantibodies in classifying patients, their role in the pathogenesis of the inflammatory myopathies remains poorly understood. It is still unknown whether these autoantibodies are pathogenic or are a simply a marker of the disease process itself (Gunawardena *et al.*, 2009).

In this review, we provide a framework for understanding the pathogenesis of the inflammatory myopathies by exploring potential triggers of myositis that may lead to loss of tolerance to self-antigens. We focus on the inflammatory myopathies with a clear autoimmune pathogenesis, which includes dermatomyositis, polymyositis, and the immune-mediated necrotizing myopathies. While largely still unknown, proposed triggers of myositis include viral infections, cancer, and drugs such as statins and the novel immune-checkpoint inhibitors used in cancer therapy (see Table 1).

Viral-induced inflammatory myopathy

Multiple studies have demonstrated a possible link between inflammatory myopathy and infection. Seasonal variation in the onset of myositis by autoantibody has led to the hypothesis that viruses may trigger inflammatory myopathy in some patients (Sarkar *et al.*, 2005) (Manta *et al.*, 1989). Patients with antisynthetase antibodies tend to present in the spring, and patients with autoantibodies targeting signal recognition particle (anti-SRP) seem to cluster in the fall (Leff *et al.*, 2010). A study in a juvenile DM population found that 51% of patients had a clinical history suggestive of an infectious process, most often respiratory, that preceded the onset of myositis (Manlhiot *et al.*, 2008). In an adult myositis population, a preceding gastrointestinal or respiratory illness (but not skin infection) increased the risk of developing inflammatory myopathy (Svensson *et al.*, 2017).

Infectious agents that have been proposed to be triggers of myositis include Coxsackie B virus, parvovirus, enterovirus, human T-cell lymphotropic virus (HTLV-1), and human immunodeficiency virus (HIV). Many of these viruses have a tropism for muscle, and Coxsackie B1 virus is even used as an animal model of myositis (Strongwater *et al.*, 1984). Antibodies against Coxsackie B virus and HTLV-1 are found in greater frequency in patients with inflammatory myopathy compared to healthy controls (Morgan *et al.*, 1989). It is possible that the more frequent viral antibodies in myositis may be explained by immune dysregulation and a higher infection risk from the underlying inflammatory process and immunosuppression. However, Christenson et al. found a higher prevalence of Coxsackie-B virus antibodies in juvenile DM and showed that this was virus- and disease-specific (Christensen *et al.*, 1986), suggesting that Coxsackie B virus may play a unique role in the disease process itself.

One hypothesis for viral-induced autoimmunity is that latent viral infection in muscle may drive the continued immune response against muscle. Despite several studies that identified viral DNA in the muscle of patients with inflammatory myositis (Bowles *et al.*, 1987) (Yousef *et al.*, 1990), other studies have been unable to identify any viral DNA (Leff *et al.*, 1992) (Fox *et al.*, 1994). Chevrel et al. found parvovirus B19 DNA in two sequential muscle biopsies from a patient with polymyositis, but no viral DNA in the third muscle biopsy

obtained from the same patient during a flare (Chevrel *et al.*, 2000) (Chevrel *et al.*, 2003). It is possible that acute viral infection in muscle may trigger immunity against muscle, and this immune response then self-propagates in the chronic phase after the pathogen is cleared. Patients with HIV-associated polymyositis generally have an excellent response to immunosuppression (Johnson *et al.*, 2003), which suggests that the primary driver of muscle damage is an overactive immune response.

Several mechanisms have been proposed for the pathogenesis of inflammatory myopathies triggered by infectious agents (Zampieri *et al.*, 2010). The pathogen may interact with and alter cellular proteins, thereby changing how they are recognized by the immune system. For example, the host tRNA synthetase is used for viral replication, and it is possible that immune tolerance is broken when the tRNA synthetase is presented to the immune system in association with viral protein (Mathews and Bernstein, n.d.). Infectious agents may also break self-tolerance by changing the conformation of cellular proteins and exposing cryptic epitopes, which are epitopes normally hidden from T-cell recognition (Warnock and Goodacre, n.d.). Infections can also induce production of autoantibodies and can expand and activate autoreactive B-cells (Soulas *et al.*, 2005).

Molecular mimicry may also play an important role in autoimmunity induced by infections. Sequence similarities between pathogens and host proteins may lead to cross-reactivity between the pathogen-specific immune response and self-antigens (Albert and Inman, 1999). For example, Massa et al. showed that the immune response in JDM is directed against a homologous sequence shared between group A streptococcal type 5M protein and skeletal muscle myosin (Massa *et al.*, 2002). Another group showed that there is significant homology between the antisynthetase autoantigens histidyl-tRNA synthetase (Jo-1) and alanyl-tRNA synthetase (PL-12) and various proteins on pathogens including Ebstein-Barr Virus (EBV), adenovirus, and influenza. Moreover, there are considerable similarities between the autoantigen PL-12 and both tropomyosin and keratin, suggesting that tissue damage may occur from cross-reactivity of the anti-PL-12 autoantibody with muscle and connective tissue (Walker and Jeffrey, 1986).

Cancer-induced myositis

The striking association between cancer and DM was established in 1992 in a landmark study that demonstrated that 32% of DM patients are diagnosed with cancer at some point during their disease course. There was a strong temporal association between the diagnosis of cancer and DM, with 71% of cancers being diagnosed within 2 years of the onset of myositis. The cancers that are most strongly associated with DM are ovarian, lung, gastric, colorectal, pancreatic, and non-Hodgkin’s lymphoma (Hill *et al.*, 2001). An epidemiologic link between DM and cancer was subsequently confirmed in multiple epidemiological studies.

Several possible mechanisms were initially proposed for the link between cancer and DM, but evidence for a discrete mechanism remained elusive for many years. Immune dysregulation from myositis, or resulting from therapies used in the treatment of myositis, might increase the risk of malignancy (Zintzaras *et al.*, 2005). However, the striking

temporal association between malignancy and cancer, in which the vast majority of malignancies are diagnosed within 3 years before or after the onset of myositis, provided evidence for a causal link between cancer and myositis (Kang *et al.*, 2016). Moreover, reports of cancer-associated myositis that improved or resolved after treatment of the underlying cancer suggested that the tumor itself was directly perpetuating the autoimmune process as a paraneoplastic phenomenon (Osako *et al.*, 2007)(Tagawa *et al.*, 2000).

It is now understood that not all patients with DM are at increased risk for cancer. Certain MSAs are associated with a dramatically increased risk of cancer-associated myositis, while other MSAs are not associated with cancer. Patients with autoantibodies targeting transcriptional intermediary factor 1-gamma (TIF-1γ) and nuclear matrix protein (NXP-2) have a particularly high risk of cancer-associated myositis (Kaji *et al.*, 2007) (Fiorentino *et al.*, 2013) (Tiniakou and Mammen, 2017). In one study, 83% of patients with cancer-associated DM had autoantibodies with specificities for either TIF-1γ or NXP-2 (Fiorentino *et al.*, 2013), and the sensitivity and specificity of the presence of TIF-1γ for cancer-associated myositis in one meta-analysis was 70% and 89%, respectively (Selva-O'Callaghan *et al.*, 2010). Autoantibodies targeting anti-small ubiquitin-like modifier activating enzyme (anti-SAE), a relatively rare autoantibody in myositis, may also be associated with an increased malignancy risk (Muro *et al.*, 2015). Patients with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), an autoantibody that often is associated with statin use, may also in some cases present as a paraneoplastic phenomenon (Allenbach *et al.*, 2016) (Yang *et al.*, 2017) (Kadoya *et al.*, 2016). The presence of other autoantibodies, such as those present in the antisynthetase syndrome including histidyl tRNA synthetase (anti-Jo-1), are not associated with cancer.

The specificity of the relationship between malignancy and certain MSAs in DM provides a basis for understanding a proposed mechanism for cancer-induced autoimmunity. It is now appreciated that malignancies express aberrant proteins, called tumor-specific antigens (neoantigens), which arise from somatic mutations in their DNA (Yarchoan *et al.*, 2017). Foreign proteins expressed by tumor cells can be highly immunogenic, inducing a vigorous immune response that cross-reacts with normal host tissues. This mechanism of cancer-induced autoimmunity is supported by a landmark study of patients with cancer who concurrently developed scleroderma with detectable autoantibodies against RNA polymerase III subunit RPC1. Sequencing of the patients' tumors revealed that many of the cancers had genetic alterations in the gene POLR3A, which codes for RPC1, and these patients had neoantigen-specific T cell immune responses (Joseph *et al.*, 2014). A similar mechanism of autoimmunity in myositis is supported by a recent study of patients with cancer-associated DM and TIF-1γ autoantibodies in which many of the tumors from these patients harbored mutations in the gene coding for TIF-1γ (Pinal-Fernandez *et al.*, 2017). These findings provided strong evidence of a discrete mechanism for cancer-induced autoimmunity in which a T-cell response against a tumor neoantigen cross-reacts with the nonmutated form of the antigen, thereby generating autoimmunity in the host (see Figure 1).

In the setting of malignancy, anti-tumor immunity can also develop against normal host proteins that are highly expressed on tumor cells (tumor-associated antigens, TAAs) as a result of epitope spreading (Yarchoan *et al.*, 2017). Since tumor-associated antigens are not

specific to tumor cells, the loss of tolerance to a TAA may result in host immunity against normal tissues, resulting in autoimmunity. This alternative mechanism for cancer-induced autoimmunity is exemplified by cancer immunotherapies against TAAs that have resulted in immune-mediated toxicity in normal tissues. For example, adoptive therapy of T cells recognizing melanoma-associated antigen 3 (MAGE-A3), which is highly expressed by some malignancies, resulted in severe neurological toxicity related to MAGE-A expression in the brain (Morgan *et al.*, 2013). Cancers that are associated with myositis often highly express myositis-associated antigens, and these same antigens are also highly expressed in regenerating muscle tissue (Casciola-Rosen *et al.*, 2005) (Chushi *et al.*, 2016). It is therefore possible that loss of tolerance to myositis autoantigens on tumor cells may perpetuate myositis through immunity against these same antigens on regenerating muscle cells (see Figure 1).

Not all adult myositis patients with the cancer-associated autoantibodies anti-TIF-1γ, anti-NXP-2, or anti-SAE have an identifiable underlying malignancy. It is not known why only some patients with these autoantibodies either present with or eventually develop a malignancy. In children, autoantibodies targeting TIF-1γ and NXP-2 are among the most common autoantibodies in juvenile dermatomyositis (JDM) and are not associated with malignancy (Morris and Dare, 2010). There may be other mechanisms unrelated to cancer in which the immune system loses tolerance to the TIF-1γ or NXP-2 antigens. It is also conceivable that anti-TIF-1γ and anti-NXP-2 immunity in the juvenile DM population may still be driven by an anti-cancer immune response directed against atypical cells, and the vigorous immune response against these neoantigens may eliminate any subclinical malignancy before it is detected.

Drug-induced myositis

Statins

Anti-HMGCR Ab+ myopathy is one of the most common of the immune-mediated necrotizing myopathies and accounts for approximately 6% of all idiopathic inflammatory myopathies (Christopher-Stine *et al.*, 2010). Anti-HMGCR Ab+ myopathy is strongly associated with statin use, and when it occurs in the setting of statins it is often referred to as statin-associated necrotizing autoimmune myopathy (SANAM). In older adult cohorts, the vast majority of patients (over 90%) with anti-HMGCR Ab+ myopathy report prior or current statin use (Mammen *et al.*, 2011).

SANAM is pathologically distinct from the more common statin intolerance experienced by many patients. Self-limiting statin myopathy can present similarly with myalgias and elevated CK, but it resolves with discontinuation of the statin. In contrast, SANAM is an autoimmune muscle disease in which autoantibodies against HMG-CoA Reductase (HMGCR) are present (Mammen *et al.*, 2012b). The autoimmune process endures even after withdrawal of the statin, and patients often require chronic treatment with immunomodulatory agents.

Several observations have led to possible disease models for anti-HMGCR Ab+ myopathy. HMGCR is the pharmacologic target of statins, which raises the question of whether statins

may trigger autoimmunity through their actions on the HMGCR protein. One proposed mechanism is that statins may change the conformation of the HMGCR protein and trigger autoimmunity by exposing cryptic epitopes (Mammen, 2016). Antigen presentation, whether of cryptic or dominant epitopes, seems to be a critical factor in the development of the disease based on the observation that the presence of the class II HLA allele DRB1*11:01 increases the odds ratio of developing anti-HMGCR autoantibodies by as much as 25-57 depending on patient race (Mammen *et al.*, 2012a) (Limaye *et al.*, 2015). Statins increase the expression of HMGCR in muscle, which may exacerbate autoimmunity against muscle tissues (Morikawa *et al.*, 2005) (Gouni-Berthold *et al.*, 2008).

Anti-HMGCR Ab+ myopathy does not remit even after withdrawal of the statin, which suggests that the immune response self-perpetuates once tolerance to HMGCR is broken. This contrasts with cancer-associated myositis, which can improve (although not always) after the cancer is eliminated. Regenerating muscle cells express high levels of HMGCR, which may provide a continuous source of antigen to propagate the immune response (Mammen *et al.*, 2011). However, it is unclear whether autoantibodies against HMGCR are pathogenic. HMGCR autoantibody titers correlate with disease activity, but remain elevated in some patients even after they achieve clinical remission (Werner *et al.*, 2012). Although the inciting event in most cases of HMGCR Ab+ myopathy seems to be loss of tolerance to HMGCR in the setting of statin therapy, more research is needed to understand how autoimmunity perpetuates after the statin is withdrawn.

Immune Checkpoint Inhibitors

Immune checkpoints are critical regulators of the immune response that help to maintain immune tolerance. Novel cancer immunotherapies target immune checkpoints to unleash the anti-tumor immune response and improve survival in a variety of cancers (Pardoll, 2012). The first immune checkpoint inhibitor approved by the FDA, ipilimumab, is a monoclonal antibody that enhances anti-tumor immunity by binding to the immune checkpoint cluster of differentiation 152 (CTLA-4), which acts as a negative regulator of the T-cell response (Hodi *et al.*, 2010). Another immune checkpoint inhibitor, pembrolizumab, blocks the co-inhibitory interaction of program cell death-1 (PD-1) on T-cells with its ligand (PD-L1) on antigen presenting cells. The immune checkpoint inhibitors have transformed the management of many cancers, and the development of additional immune modulators that can further increase antitumor immunity is a top priority in oncologic research.

The immune checkpoint inhibitors sometimes result in immune-related adverse events (irAEs) that closely resemble sporadic immunity. Colitis, hepatitis, dermatitis, and endocrinopathies are among the most commonly reported irAEs among patients receiving immune checkpoint inhibitors (Postow *et al.*, 2018). DM, PM, and IMNM have also been reported as immune complications of anti-PD-1 and anti-CTLA-4 immunotherapy (Cappelli *et al.*, 2017) (Sheik Ali *et al.*, 2015). Older cancer immunotherapies including interferon-alpha treatment and IL-2 therapy have also been associated with myositis (Dietrich *et al.*, 2000) (Esteva-Lorenzo *et al.*, 1995). irAEs resulting from cancer immunotherapies provide a novel lens in which to study autoimmunity and indicate that many forms of immune

dysregulation, whether through modulating immune checkpoints, cytokines, or other inflammatory pathways, may precipitate myositis.

Although dysregulation of immune homeostasis can precipitate autoimmunity, this does not explain the specificity of organ involvement among the irAEs. For example, patients with checkpoint-induced myositis frequently have muscle and/or skin involvement, but the GI tract or nervous system are rarely involved. It also remains unclear why some organs are more prone to irAEs than others, and why the organs most at risk differ among the classes of immune checkpoint inhibitors. For example, colitis is more common with therapies targeting CTLA-4 and pneumonitis is more common with anti-PD-1 therapy (Spain *et al.*, 2016). To date there have been no studies of whether myositis-specific autoantibodies are present in patients with checkpoint-induced myositis, and if these autoantibodies pre-date the administration of immunotherapy. It is also unclear what role, if any, the cancer may play in irAEs. Preliminary data show that patients with irAEs may have a better cancer response to immunotherapy than patients without autoimmune toxicities (Curti *et al.*, 2017) (Freeman-Keller *et al.*, 2016) (Weber *et al.*, 2012). This suggests that autoimmunity may correlate with anti-tumor immunity, although the cause of this association needs further investigation.

Conclusion

Definite disease triggers can be identified in some patients with inflammatory myopathy. These include environmental factors such as infection, malignancy, and drug toxicities from statins or immune checkpoint inhibitors. Each of these triggers provides a window into how tolerance to a self-antigen can be broken and/or the immune system unleashed to result in chronic autoimmunity.

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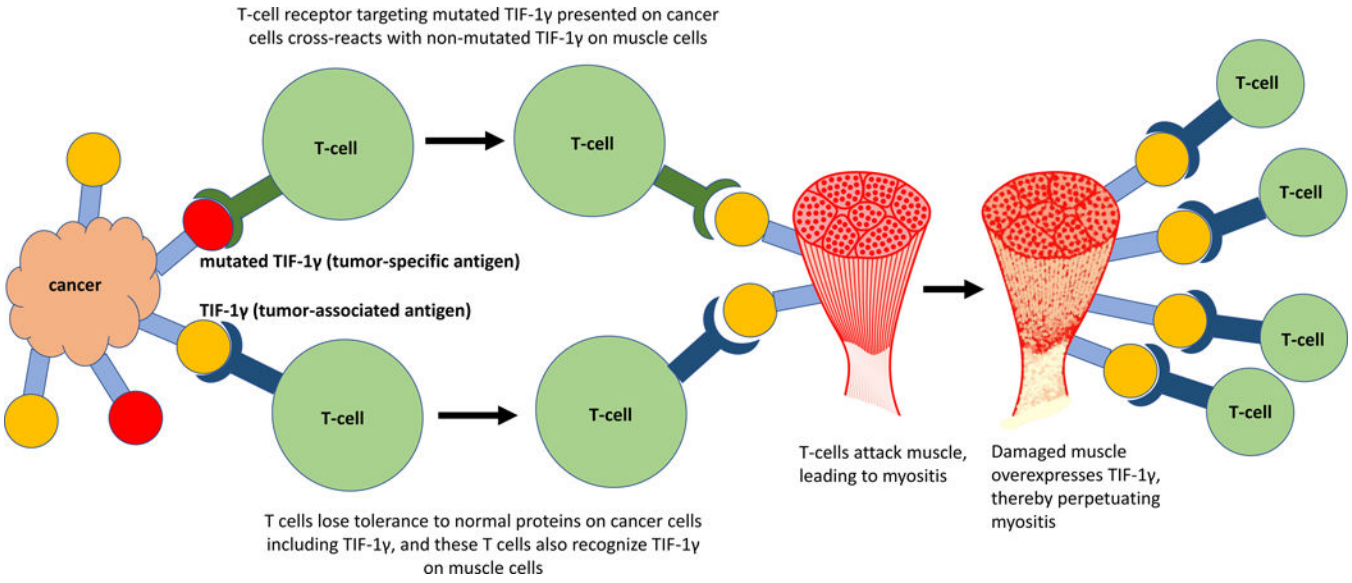

Figure 1.
Proposed model for cancer-induced myositis.

Table 1

Known triggers of myositis and their associated autoantibodies.

Trigger		**Myositis specific autoantibody (MSA)**	**Prevalence of suspected trigger by MSA**
Infection		Proposed: Antisynthetase autoantibodies (Jo-1, PL-7, PL-12, EJ, OJ, KS)	undefined
Malignancy		Transcriptional intermediary factor 1-gamma (TIF-1γ)	38-80%
		Nuclear matrix protein (NXP-2)	24-38%
		Anti-small ubiquitin-like modifier activating enzyme (SAE)	14-50%
		Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)	5-36%
Drug	Statin-associated autoimmune myopathy	Anti-HMGCR	> 90% of patients older than 50 years
	Immune checkpoint inhibitors	Unknown	