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Autoantibodies and Cancer Association: the Case of Systemic Sclerosis and Dermatomyositis

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Abstract

Several rheumatic diseases have a perplexing association with cancer. Unraveling this mysterious connection is likely to provide deeper understanding regarding mechanisms governing the onset of both autoimmunity and cancer immunity, in addition to providing clinicians much needed guidance around whom and when to screen for occult malignancy. Systemic sclerosis (scleroderma) and dermatomyositis are two diseases in which the association with internal malignancy is well-described and can be considered as models from which to gain important insights that likely have broader applicability. The past 15 years have witnessed a striking acceleration in understanding how these two diseases are related to cancer emergence—an important crack in this inscrutable armor has been the discovery and characterization of disease-specific autoantigens that are closely tied with risk of cancer emergence. The best-described examples of this are antibodies against anti-RNA polymerase III (anti-POL3) and transcription intermediary factor 1-gamma (anti-TIF1γ). Patients with systemic sclerosis and cancer that are diagnosed within a short time interval of each other frequently have anti-POL3 antibodies. Similarly, in the dermatomyositis spectrum, the majority of anti-TIF1γ-associated cancers are detected around the time of DM onset (most often within 1 year). Antibodies against the minor spliceosome complex containing RNA Binding Region Containing 3 (RNPC3) are also associated with increased cancer incidence in SSc. For DM, antibodies against Nuclear Matrix Protein 2 (NXP2) are also potentially associated with increased cancer emergence. The systemic sclerosis/anti-POL3 connection with close cancer onset led to the first experiments directly supporting the concept that rheumatic disease may in fact be a manifestation of cancer. It is now clear that studying these diseases through the lens of autoantibodies can reveal relationships and insights that would otherwise remain obscured. Extending these studies, new findings show that antibodies against RNA polymerase I large subunit are associated with protection against short interval cancers in anti-POL3-positive systemic sclerosis patients. These insights highlight the fact that autoantigen discovery related to cancer emergence remains an important priority; such new tools will enable the testing of specific hypotheses regarding mechanisms governing disease emergence and development of effective anti-tumor responses. Autoantibody phenotype will likely play an

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important role in the development of cancer screening guidelines that are critically needed by clinicians taking care of these patients. In this review we will summarize the current state of knowledge regarding the different ways in which autoantibodies are connected with systemic sclerosis/dermatomyositis and malignancy and highlight potential paths forward.

Keywords

Autoimmunity; cancer; systemic sclerosis; scleroderma; dermatomyositis; autoantibody

Introduction

It has long been recognized that patients with autoimmune rheumatic diseases are at higher risk of cancer than the general population; this is especially true for those with systemic sclerosis (SSc) and dermatomyositis (DM). Why this should be so has been elusive, and there are many potential explanations (not necessarily mutually exclusive). These include the possibility of a common genetic predisposition, or inciting exposure (eg, some environmental influence) that may confer susceptibility to both diseases. Also possible is that tissue damage caused by the autoimmune disease itself may lead to an increased risk of cancer, as may the cytotoxic therapies used to treat these diseases.

An elegant study performed on patients with scleroderma and cancer provided compelling evidence that in some cases, autoimmunity may be initiated by autoantigen mutation in the patient's cancer [1]. That the majority of patients with the same form of SSc and autoantibody response do not manifest a cancer remained an unexplained but important biologic clue. Recent findings following up on this thread now suggest that broader immune (anti-tumor) responses more successfully eliminate any underlying cancers (discussed below). This has put a new focus on the previously under-appreciated role of autoantibodies as unique tools to explore and understand this interface.

In this review, we will focus on SSc and DM and specific autoantibodies to illustrate how they provide a unique opportunity to interrogate the interface of autoimmunity and cancer. New information from these studies will afford important insights into the mechanisms underlying the autoimmune rheumatic diseases, and will enable tools to be developed that can more precisely predict and stratify cancer risk amongst these patient populations. Ultimately, studies at the cancer autoimmunity interface will likely be of broader utility in the general population as this new information will illuminate the natural immune response to human cancers.

Systemic Sclerosis and Cancer

Data generated from multiple epidemiological studies performed over decades has shown that SSc patients have an increased risk of cancer, after adjusting for age and gender, compared to the general population [2, 3, 4]. There is a close temporal relationship between SSc and cancer emergence, with cancers preceding or following SSc diagnosis. That this relationship is likely complex and bi-directional has raised important questions about a possible link between these diseases and has also made study at this interface

challenging. The recent application of simple filters (antibody status, time) has begun to unmask important insights at this interface, with implications that are of potential clinical and mechanistic utility.

In this section of the review, we will focus exclusively on the immune response in SSc patients with or without cancer, highlighting the power of its utility to probe the mechanistic links with cancer. Emerging new insights and potential biomarkers afforded by these studies will be addressed. Ultimately, any phenotypic SSc features that associate with an increased or decreased cancer risk will be of great utility in identifying and risk stratifying those patients who would most benefit from targeted cancer screening. Since it is beyond the scope of this article to discuss studies investigating the epidemiology and types of cancers in SSc, the reader is referred to several recent comprehensive reviews [5, 6, 7].

Autoantibodies against POL3 define co-incident emergence of cancer and SSc

The three most common SSc-specific autoantibodies are anti-topoisomerase1 (anti-topo), anti-RNA polymerase III (anti-POL3) and anti-centromere. These antibodies are clinically useful for evaluating prognosis and risk stratification associated with distinct clinical phenotypes. For example, patients with anti-topo antibodies are at increased risk of diffuse cutaneous disease and interstitial lung disease. In contrast, those with anti-POL3 antibodies frequently have rapidly progressive diffuse cutaneous disease and a higher risk of SSc renal crisis, myopathy, and cardiac disease. For decades, reports across a broad range of tumor types - most notably with breast cancer - have described a co-clustering of cancer emergence and SSc diagnosis [8, 9]. This noteworthy temporal clustering raised the possibility that SSc might be a paraneoplastic disease, at least in some patients.

While clinical phenotypes associated with known SSc-specific autoantibodies were widely recognized, their meaningful association with cancer amongst those patients with SSc was only first illuminated in 2010 [10] in a small but landmark study. This study consisted of 23 finely phenotyped SSc patients, 6 with anti-POL3 antibodies, 5 with anti-topo antibodies, 8 with anti-centromere antibodies and 4 who lacked all 3 of these specificities. When the median duration of SSc at the time of cancer diagnosis was analyzed after applying the filter of autoantibody status, a striking finding emerged: there were significant differences between the antibody groups. Cancer and SSc diagnoses clustered in time in patients with anti-POL3 antibodies (−1.2 years). These findings have subsequently been confirmed in other cohorts across continents [8, 11, 12]. This finding was distinct from those patients with anti-topo and anti-centromere antibodies (+13.4 and +11.1 years, respectively).

An interesting case was recently published [13] describing a patient with multiple primary malignancies occurring within ~2 years of SSc diagnosis. The patient did not have antibodies against POL3 when assayed by ELISA (absent at first visit, and 6 and 13 months thereafter). However, when immunoprecipitation assays were performed, antibodies against POL3 were readily detected. Since ELISA assays are routinely performed to detect POL3 antibodies for clinical use, this raises the question of whether some of the “antibody negative group” with short interval cancer detection may in fact be anti-POL3 positive.

Other antibody specificities associated with short-interval cancer in SSc patients

In addition to anti-POL3-positive patients, other subgroups of SSc patients also have a temporal clustering of SSc diagnosis and cancer emergence. Indeed, Shah et al [10] noted a striking temporal clustering (+2.3 years) of SSc diagnosis and cancer emergence in those patients lacking antibodies against centromere, topo and POL3 ("CTP-negative"). Xu et al [14] used Phage-Immunoprecipitation Sequencing (PhIP-Seq) and Parallel Analysis of in vitro translated Open Reading Frames (PLATO) methodologies in a discovery study designed to address this. The study cohort consisted of 48 extremely well-phenotyped SSc patients. Of these, 32 patients were anti-POL3-positive (both with and without cancer), and 16 were anti-CTP-negative SSc patients with a short interval between SSc onset and cancer diagnosis. Antibodies against the minor spliceosome complex containing RNA Binding Region Containing 3 (RNPC3) were elucidated in the latter group; 25% (4/16) were anti-RNPC3-positive. These authors subsequently confirmed these findings in a larger study of 318 patients with SSc and cancer [15]. They found a short cancer-SSc interval in patients with these antibodies (median 0.9 years). Furthermore, relative to patients with anti-centromere antibodies, those with anti-RNPC3 or anti-POL3 had a greater than 4-fold increased risk of cancer within 2 years of SSc onset.

Several studies have addressed whether cancer-associated SSc-specific (anti-POL3) and myositis-specific (anti-NXP2 and anti-TIF1γ) autoantibodies are found in patients without autoimmune rheumatic disease but with breast [16] or lung [17] cancer. The data showed that these antibodies were rare/absent in cancer patients without autoimmune disease, suggesting that while they are clinically useful as cancer biomarkers in patients with SSc and myositis, they are unlikely to be of utility in improving cancer risk stratification in the general population.

Evidence for a biphasic temporal association between SSc and cancer

Partouche et al [18] recently performed a retrospective study on 55 SSc patients with a least one cancer evaluated at Montpelier University Hospital (a total of 64 cancers were identified for study). The median follow-up time was 11 years. Anti-nuclear antibody, anti-centromere antibody and anti-topo antibody status was known on all patients; unfortunately the anti-POL3 antibody status was not reported as it was not routinely performed on patients at this hospital during the study period. Their findings highlighted two peaks of cancer occurrence: the first occurring within 5 years of SSc diagnosis, and the second following 10 years later. Breast cancers (detected in 9 patients) were the most frequent cancer type in this short-interval set; amongst this group, the SSc/cancer interval was <1 year in 6 of the 9 patients. Overall, in the first cancer peak group, SSc was associated with neither anti-centromere nor anti-topo antibodies, consistent with the findings of Shah et al [10]. Furthermore, 26 of the short-interval cancers were detected in patients with anti-nuclear antibodies but lacking antibodies against topo and centromere. While it is likely that several of these are in patients with anti-POL3 antibodies (see above) and anti-RNPC3 antibodies (see below), it is also probable that there are other as yet unidentified

antibody specificities that associate with a close temporal relationship between SSc and cancer, as discussed above. A second peak of later onset cancers, occurring ~10 years after SSc diagnosis, was also noted in the study performed by Partouche et al [18] most of which were gastrointestinal or lung cancers. Potential reasons for the late emergence are discussed, including the use of immunosuppressants and calcium channel blockers, chronic inflammation, cytokine dysregulation and genetic and epigenetic alterations. The presence of additional autoantibody specificities in these later onset cancers is not known; in light of the recent findings reported by Shah et al [19] and discussed below, it would be informative to address this.

Mechanistic insights: a possible role for genetically altered autoantigens in cancer as initiators of rheumatic diseases.

Several theories have been proposed to explain the occurrence of cancers together with rheumatic diseases. These include the possibility that cancers arise as a consequence of target tissue damage from the autoimmune disease, or from the cytotoxic therapies used to treat aggressive disease, or as a result of a defective immune system that predisposes an individual to developing both autoimmunity and cancer [1, 20]. Studies examining POL3 staining in tumors [10] opened up a new perspective: they demonstrated a unique, robust nucleolar pattern in 4 of the 5 tumors in anti-POL3-positive patients; this nucleolar staining was not detected in tumors from anti-POL3-negative patients. Taken together with the co-occurrence of cancer and SSc in this subgroup, these findings illuminated a new possibility – that genetic alterations in the POLR3A locus in tumors may initiate the autoimmune response.

This concept was addressed in a seminal study of 16 tumors obtained from SSc patients [1]. Importantly, these 16 tumors were obtained from 8 anti-POL3-positive patients, and the remaining 8 were from SSc patients with antibodies against either topoisomerase 1 or centromere. Alterations in the *POLR3A* gene locus were detected in the majority (6/8, 75%) of cancers from the anti-POL3-positive patients, whereas none were found in the tumors from the other 8 patients studied. Interestingly, 3 of the 6 genetic alterations were somatic mutations, and each produced a single amino acid change that was different in each patient. T cells reactive with the mutated neoantigens were found in peripheral blood from 2 of these 3 patients. In the context of how uncommon *POLR3A* mutations are in cancer (0.7% in the Cosmic database, $P<10^{-20}$), these findings (i) are consistent with initiation of the immune response by these mutations and (ii) highlight that even infrequent mutations may initiate autoimmunity if presented to the immune system in the context of the appropriate major histocompatibility complex framework. Loss of heterozygosity (LOH) at the *POLR3A* gene locus was the second type of genetic alteration detected by Joseph et al [1] in this landmark study. This was detected in 5 of the 8 anti-POL3-positive patients, but was not found in the 8 patients lacking this specificity. Such findings suggest that the anti-POL3 immune response may have a role in immunoediting and shaping the genetic characteristics of the tumor [7].

Another key finding was that the anti-POL3 antibodies in the patients with somatic mutations detected both the mutated and the wild-type protein, consistent with a model

of cancer-induced autoimmunity. In such a model, transformation of normal cells may produce the occasional mutation of autoantigens in some of the cancer cells. The immune response is initially raised against the mutated form of the antigen in the cancer (that is, an anti-tumor immune response). Immune effector cells directed against the mutant could kill those cancer cells containing the mutation. The immune response may subsequently spread to the wild-type protein; immune effector cells directed against the wild-type protein would be capable of deleting cancer cells lacking the mutation. They would also be able to cross-react with cells in other tissues. An important aspect of this is that immature cells found in damaged and repairing tissue express high antigen levels. Once autoimmunity has been initiated, such cells can become targets of the immune response because of their robust antigen expression. This sets up an ongoing cycle of tissue damage and repair that sustains and fuels the autoimmune response.

Autoantibodies define cancer-protective immune responses in a subset of SSc patients

In the findings described above, a noteworthy observation is the absence of cancer in the majority (~85%) of patients with SSc and antibodies against POL3. Possible reasons for this include (i) that different mechanisms underlie the development of anti-POL3 immune responses and SSc phenotype in patients with and without cancer, or (ii) similar mechanisms drive the immune response and SSc phenotype in all anti-POL3-positive SSc patients (that is, initiated by mutated *POLR3A* in the cancer), but the groups differ in the efficacy of their anti-cancer immune response. For example, there may be additional immune responses in the patients without cancer, or a differential ability of induced immune responses (eg anti-POL3) to eliminate a cancer. In the context of autoimmunity, the former may be captured in the form of an autoantigen “fingerprint” reading out additional autoantigens targeted by the immune system.

Shah et al [19] addressed whether the breadth of immune response differed between the cancer/no cancer groups in a study performed on 168 anti-POL3-positive SSc patients, 80 of whom had a cancer history, and 88 with no cancer diagnosed after more than 5 years of follow-up. A small subset of each of these groups (17 and 18, respectively) was used in an immunoprecipitation-based discovery approach. In the group without cancer, a 194 kDa protein was enriched; this was subsequently identified as RNA polymerase I large subunit (RPA194). This team went on to show that anti-RPA194 antibodies were significantly more common in anti-POL3-positive patients without cancer (16/88, 18.2%) compared to the anti-POL3-positive group with cancer (3/80, 3.8%; $P = 0.003$).

Emerging data indicate that this phenomenon is found not just in the case of anti-RPA194 antibodies being associated with protection against short interval cancers in anti-POL3-positive SSc patients. In a recent paper, Mecoli et al [21] described the prevalence and clinical characteristics of the 4 most common autoantibodies directed against components of the Th/To complex (POP1, RPP25, RPP30 and RPP40). This case-control study consisted of 804 SSc patients, 401 with no cancer diagnosed after >5 years of SSc onset and 403 with a history of cancer. Autoantibodies against the components were assayed by

immunoprecipitation of ^{35}S-methionine-labeled proteins generated by in vitro transcription and translation. Of those patients with antibodies against 1 or more components of the Th/To complex, 23 had cancer (26 cancers in total, excluding non-melanoma skin cancers). These patients were significantly less likely to manifest a cancer within 2 years of SSc onset compared to patients lacking these antibodies (0% versus 11%; P = 0.009). Amongst the study cohort, there were nine patients with antibodies against one or more of the Th/To complex components and POL3. Interestingly, 0/9 had cancer-associated SSc (that is, a diagnosis of SSc within 3 years of cancer manifesting). In contrast, there was a significantly increased risk of cancer associated SSc amongst the anti-POL3-positive/ anti-Th/To component-negative patients in this study cohort (24% of SSc patients with anti-POL3 had a cancer diagnosed within 3 years compared to 11% without anti-POL3; P<0.0001).

If other studies confirm the association of anti-RPA194 and anti-Th/To component antibodies with decreased cancer incidence/later emergence in a subset of anti-POL3-positive SSc patients, they are likely to be of clinical utility. Thus, the presence of these antibodies at the time of SSc diagnosis may define the subset of anti-POL3-positive patients who do not require extensive workup to detect a malignancy. Further studies are needed to define whether there are additional antibodies (other than those directed against RPA194 and Th/To complex components) that occur with anti-POL3 antibodies; these could be specificities that have already been defined but whose association in this context have never been addressed, or novel antibodies that await discovery. It will also be informative to study whether similar “add-on” specificities are found in the context of other immune responses associated with short-interval cancers in SSc patients (eg, anti-RNPC3), and whether this is also the case with anti-TIF1γ-positive DM patients who do not manifest a malignancy (see DM section below). Finding such specificities would support the hypothesis that orthogonal immune responses directed against additional cellular proteins/complexes are associated with decreased cancer emergence in those patients at higher risk for cancer-associated SSc.

Watad et al [22] recently investigated the relationship between SSc-specific autoantibodies and the survival of SSc patients with cancer in a study that included 2,431 SSc patients and 12,377 age- and sex-matched controls. ANA-positive SSc patients with cancer had a better prognosis than ANA-negatives (P=0.0001), but there was no detectable survival benefit conferred by antibodies against POL3, centromere and topoisomerase 1.

Autoantibodies define cancer risk amongst SSc patients

The body of work investigating cancer risk in SSc performed over the past decade (some of which is discussed above, and see [23]), suggests that important aspects of the cancer-autoimmunity relationship may be hidden in the absence of applying appropriate filters. Such a filtering approach was used by Igusa et al [24] in a recent elegant study designed to examine the overall and site-specific cancer risk at the time of SSc onset, compared to the Surveillance, Epidemiology and End Results (SEER) registry, a representative sample of the general US population. The study cohort consisted of 2,383 well-phenotyped SSc patients (representing 37,686 person-years), with defined phenotypic subsets and antibody profiles

(the latter included: anti-POL3, topoisomerase 1, centromere and CTP-negative). 205 (8.6%) of the study patients had cancer.

When applying the filters of time (cancer diagnosed within 3 years of SSc onset) and antibody status, cancer risk was increased in those patients with anti-POL3 antibodies (SIR 2.84, 95% CI, 1.89 – 4.10), and in the anti-CTP-negative group (SIR 1.83, 95% CI, 1.10 - 2.86). Application of a phenotype filter (limited/diffuse disease) together with an antibody one showed that anti-POL3-positive patients with diffuse disease had an increased risk of cancer (SIR 2.05, 95% CI, 1.44-2.84; $p<0.001$), while those with anti-centromere antibodies and limited disease had a lower risk of cancer during follow-up (SIR 0.59, 95%, CI 0.44 – 0.77). Application of an additional filter (cancer type) showed that cancer-specific risk varied by SSc subtype among anti-POL3-positive patients. That is, those with diffuse SSc had an increased breast cancer risk, while those with limited SSc had a high risk of lung cancer [24].

The data discussed above highlights a previously unrecognized utility of autoantibodies. Together with the judicious application of filters, antibodies may be powerful tools to stratify cancer risk. Ultimately, the goal of this would be to maximize cancer detection by enhancing the screening of high-risk groups (eg, anti-POL3 or -RNPC3-positive SSc patients). This would also minimize the cost and harm of over screening. It will be informative to include and test additional new specificities as they emerge (for example, anti-RNPC3) in such modeling approaches.

Dermatomyositis and Cancer

Perhaps even more so than in the case of SSc, the connection between malignancy and myositis is very robust and has been recognized for over a century [25, 26]. It has now been almost 30 years since the seminal population-based studies in Scandinavia [27, 28, 29, 30] demonstrated this connection definitively and also provided the best evidence that this association is strongest in DM compared to other inflammatory myopathies. As with the case of SSc, this association was suggested before any mechanistic or serologic insights were available. The only clues were that the cancer risk was clearly highest around the time of DM onset, was broadly elevated across multiple cancer types, and was increased in adults but not children with DM [29, 30].

This section of the review will focus on autoantigen targets in DM that are associated with cancer risk, utilizing a similar conceptual framework as that described above for SSc. Given space constraints and the priority for discussing findings with sufficient data, this section will focus on the major DM-specific antigens that define subgroups. We will highlight issues and findings that are also reflected in SSc, as well as observations unique to DM. These may provide further mechanistic insights into the cancer-autoimmunity connection, as well as identify important considerations in the interpretation of autoantibody data with regards to cancer risk. For a more complete overview of the clinical and epidemiologic details regarding cancer risk in DM, the reader is directed to several recent reviews on this subject [31, 32, 33].

TIF1γ is a dominant antigenic target in cancer-associated dermatomyositis

There are five major DM-specific antigenic targets that define relevant DM subgroups. Identified in 1985, Mi2 (Chromodomain Helicase DNA Binding Protein 3/4) was the first of these to be described. It wasn't until the "golden age" of DM antigen discovery between 2005 and 2009 that the other four were described. These include Melanoma Differentiation-Associated Protein 5 (MDA5), Nuclear Matrix Protein 2 (NXP2), Transcription Intermediary Factor 1-Gamma (TIF1γ), and SUMO1 Activating Enzyme (SAE1/2). Since the first description that these autoantibodies define clinical DM subgroups [34], it now a well-accepted tenet that certain clinical features cluster with specific autoantibodies. Despite the obvious connection between DM and malignancy as well as autoantibodies and clinical manifestations, it is noteworthy that none of these antigens were discovered as a result of a systematic search for specificities associated with malignancy prevalence. This is despite the fact that rationale for such a search was provided in a seminal study in 2005 with the demonstration that the Mi2 autoantigen is overexpressed in cancers as well as specifically in DM target tissue--in this case, regenerating muscle fibers [35]. It is this study that provided the first data supporting the notion that at least some cases of DM could be the result of an adaptive anti-cancer immune response whose targets are shared by both tumor and diseased tissues.

First identified in 2006 [36, 37] with the antigenic target defined several years later [38], antibodies against Transcription Intermediary Factor 1γ (TIF1γ, or TRIM33) identify a family of related autoantigens targeted in DM that also includes TIF1α (TRIM24) and, less commonly, TIF1β (TRIM28). It is now clear that, in every racial group or geographic area examined, DM patients with anti-TIF1γ antibodies have an increased prevalence of cancer compared to their anti-TIF1γ-negative DM counterparts with an overall odds ratio (OR) of 9.37 (95% CI 5.37–16.34) [39]. However, the magnitude of this association appears to vary by patient population, with cancer prevalence in the anti-TIF1γ serogroup highest in Asian populations compared to the United States [39]. As is the case with anti-POL3 in scleroderma, the majority of anti-TIF1γ-associated cancers emerge in a narrow 1-year window around the time of DM onset, with two studies from Japan and the United Kingdom suggesting that malignancies beyond a 3-year window are rarely seen in this serogroup [40, 41]. Interestingly, at least in European patients, these anti-TIF1γ-associated cancers are enriched for ovarian cancer [40], which may explain the preponderance of ovarian cancers seen in the original Scandinavian population-based studies.

Cancer risk associated with antibodies other than anti-TIF1γ in DM

Despite the fact that anti-TIF1γ antibodies are the most consistently associated with cancer in DM, the question of whether other DM-specific antibodies are also associated with increased cancer risk remains unresolved. This is because, due to lack of power, most studies have looked at relative cancer prevalence within the DM population, which will not provide information regarding absolute risk compared to a healthy population. The data on prevalence of malignancy-associated DM associated with each antibody relative to without that particular antibody is summarized in Table 1. It is important to note, however, when using a relative scale, some groups will by definition have a lower associated cancer

risk, which may mask a true absolute association. Another problem with pooling multiple DM serotypes as the reference population is that some of these serotypes may confer an increased cancer risk. Consequently, the risk of the entire comparator population may be raised to such an extent that a potential cancer association with the specificity being studied is obscured.

As a benchmark, anti-TIF1γ antibodies are associated with a standardized incidence ratio (SIR) of 17.3 (95% CI = 11.9-24.1) in a study in Chinese patients. Interestingly, this is the only study to date to report an SIR for cancer risk in anti-TIF1γ-positive patients [42]. Antibodies targeting NXP2 have variably been associated with increased relative prevalence of cancer amongst DM patients, although the only two studies estimating risk over matched controls (performed in the U.S. and China) both demonstrated an elevated SIR of 3.7 and 8.1, respectively [42, 43]. Patients with anti-SAE1 antibodies are not typically thought to have high cancer risk, but the only population-based study to date in China demonstrated an SIR of 12.9 (95%CI=3.2-32.9) [42]. It is presently unknown if these data reflect a unique cancer association in Asian patients for this serotype. Antibodies against Mi2 have traditionally been thought to identify patients at a relatively lower prevalence of cancer within the DM population, but a large study in Europe recently demonstrated an increased relative cancer prevalence compared to anti-Mi2-negative patients (OR=2.1., 95% CI 1.2-3.6) [44], while a French study reported an increased SIR of 5.1 (95%CI=3.0-8.6) [45]. The only other study comparing cancer risk in patients with anti-Mi2 antibodies to the general population was performed in China. This study did not demonstrate an increased absolute risk, although that might be explained by lack of power given the rarity of anti-Mi2 antibodies in the Asian population [42]. Thus, although anti-TIF1γ antibodies are most strongly associated with increased cancer risk, data suggest that several other serotypes might also be associated with increased incidence of malignancy when compared to the general population.

Mention should be made regarding other antibodies described in DM patients that, although not specific for myositis, may be associated with cancer. A recent study identified antibodies targeting heat shock factor 1 (HSF1) in 69/581 (11%) of patients with inflammatory myopathies, of which DM patients comprised over 80% of the cohort [46]. These antibodies were found in a similar percentage of SSc and rheumatoid arthritis patients but in only 3%of healthy controls. Anti-HSF1 antibodies were associated with anti-TIF1γ antibodies in 69% of patients, but nonetheless anti-HSF1 antibodies independently associated with cancer emergence. In another study, antibodies against calreticulin were found in 18% (62/351) of DM patients [47]. They were also found at a similar frequency in patients with other inflammatory myopathies, SLE, SSc, and rheumatoid arthritis, but rarely (1%) in healthy controls. None of the other connective tissue disease patients with anti-calreticulin antibodies had a cancer diagnosis, although they were also found in 25% of non-DM patients with solid tumors.

Mechanistic links between the anti-TIF1γ immune response and cancer

As is the case in SSc, one framework to explain the connection between DM and cancer is that in some instances malignancy engenders an adaptive anti-cancer response (with

corresponding autoantibodies) that is subsequently directed at relevant tissues to confer rheumatic disease. Even in this scenario, it is likely that mechanisms for initiation of the immune response in tumors are varied and complex. One possible mechanism involves overexpression of antigen in the tumor. A recent study demonstrated that expression levels of TIF1γ, although variable, tend to be higher in the tumor than in the surrounding non-cancerous tissue. Interestingly, these levels do not appear to vary between DM and non-DM related tumors, nor between DM-associated tumors from patients with or without anti-TIF1γ antibodies [48].

Another mechanism for induction of autoimmunity is via acquired mutations, although the case for tumor-associated somatic mutations in DM autoantigen genes is less robust than that for SSc. One study [49] identified a single tumor (out of 7 patients with anti-TIF1γ antibodies) with a non-synonymous somatic mutation in the TRIM33 coding region; no mutations in 3 patient tumors without anti-TIF1γ antibodies were identified. Complicating interpretation of this data was the fact that 1 tumor from each group also showed loss-of-heterozygosity (LOH) at the TRIM33 locus. A more recent study revealed multiple genomic alterations in the TRIM33 locus, but suffered from lack of validation of the mutations as well as no controls to demonstrate that the mutations were enriched specifically in patients with anti-TIF1γ antibodies [50].

Other mechanisms for induction of autoimmunity to TIF1γ exist. The fact that TIF1γ is directly involved in cancer pathogenesis, with roles as a tumor suppressor as well as in DNA repair and cell cycle control, also brings up the possibility that initiation of anti-TIF1γ autoimmunity may be a direct consequence of the role of TIF1γ in tumor biology. It is interesting to note that cancers from patients with anti-TIF1γ autoantibodies typically present at an advanced stage, simultaneously with onset of DM, suggesting that anti-TIF1γ autoimmunity (with resultant DM symptoms) may be a direct consequence of tumor aggressiveness that is associated with alteration in TIF1γ structure, binding partners and/or localization.

Beyond the tumor mutational studies described above, other data support the concept that anti-TIF1γ antibodies can reflect an immune response to cancer. First, TIF1γ antibody titers decrease with successful treatment of tumors but not in advanced, untreatable cancers [51]. Second, cases of DM induced by immune checkpoint inhibitors (ICI) have been reported that are associated with anti-TIF1γ antibodies, suggesting that the latter can be a reflection and/or byproduct of enhanced immune surveillance of tumors. Third, IgA antibodies against TIF1γ are found in early lung and colon cancers in patients without DM [52, 53]. In this context, it is interesting that multiple studies suggest that IgG anti-TIF1γ antibodies are not a general feature of breast, lung, and other solid cancers [16, 17, 54, 55].

Does heterogeneity in cancer timing and outcomes reflect efficacy of the anti-cancer immune response?

If indeed some cases of DM are initiated by an anti-tumor immune response, the clinical presentations of these patients might differ in predictable ways. For example, tumors from DM patients with more effective anti-cancer responses would be expected to grow more

slowly and take longer to reach clinical presentation (e.g. beyond the 1 year window from DM onset). In a similar vein, they might be expected to be less aggressive and/or advanced. Interestingly, a study from Korea demonstrated that cancers developing near the time of DM onset presented at a more advanced stage and were associated with a worse overall survival than those cancers that were diagnosed well after onset of DM disease [56]. Since most cancers associated with anti-TIF1γ antibodies present around the time of DM onset [40, 41], the question remains whether cancers that arise at a later time are reflective of other, non-TIF1γ antibody subsets. Findings from two large studies in the UK and Japan suggest that patients with anti-TIF1γ antibodies do indeed have a shorter DM-cancer time interval than the anti-TIF1γ-negative population [40, 41], although another from China did not appear to find such an association [42]. It is interesting that the study from Japan also showed that tumors from patients with anti-TIF1γ antibodies present at a more advanced stage than those from the anti-TIF1γ-negative group [41], consistent with the notion that the anti-TIF1γ immune response might be weakly effective in terms of anti-cancer efficacy. However, even in the anti-TIF1γ population, there still exist patients in whom cancer does not emerge until well after the 6-month window around DM onset. It is tempting to speculate that the delayed emergence of cancers may, in some cases reflect additional orthogonal immune responses that restrain cancer growth. Future studies will be required to identify if there are specific, “add-on” autoantibodies that are enriched in cancers that emerge at a later time.

Another prediction relating to differentially effective anti-cancer immune responses associated with DM is that there may exist antibodies that are enriched in anti-TIF1γ-positive patients in whom a cancer never emerges, presumably marking more successful anti-cancer immune responses. As discussed above, this phenomenon has been confirmed in SSc with the observation that anti-POL3-positive SSc patients without cancer are enriched for additional antibodies against RPA194 and/or the Th/To complex [19, 21]. This concept is relevant in DM because, despite the connection between anti-TIF1γ antibodies and malignancy, in some populations ~80% of patients with anti-TIF1γ antibodies never manifest a cancer [57]. The risk of cancer emergence in this group varies by geographic location of the study population as well as by increasing age [39, 40, 57]. Although these cancer-negative cases could reflect successful anti-tumor immunity, DM (and anti-TIF1γ antibodies) might also be triggered by factors other than cancer, including pregnancy [58].

If identical antibody specificities are found associated with both lack of and delayed cancer emergence, this may suggest that these specificities mark effective anti-cancer immune responses, and that some DM cases are initiated by tumors that are ultimately eliminated by the immune system. Defining such specificities is of high priority as these might identify patients (i) at greater risk for cancer emergence well after DM diagnosis, and (ii) in which repeat cancer screening is justified. Thus, studying malignancy in DM through the filters of cancer prevalence, timing, stage and autoantibodies provides a path forward with testable hypotheses using the framework of cancer immunoediting, in which cancers can have multiple fates: elimination, equilibrium, and emergence.

Stratifying DM patients for cancer risk: the path forward

Given the fact that most DM patients will not be diagnosed with an associated cancer, accurate identification of those at high risk and for whom it is appropriate to perform costly screening, is an urgent priority. To date, key clinical characteristics associated with increased cancer risk in DM have been identified; these include increasing age, male sex, cutaneous necrosis, and dysphagia, while Raynaud's, arthritis, and interstitial lung disease are associated with relative protection from cancer [59]. It is unclear which of these factors modulate risk independent of the DM autoantibodies, although it appears that age is one of them [57]. However, no predictive models have been proposed (let alone validated) that utilize these risk factors in developing evidence-based guidelines regarding whom and when to screen for cancer. It seems likely that this will only come from a combination of clinical, genetic and demographic features using the unique lens of the autoimmune response. For example, early data suggest that anti-SAE1 antibodies are more highly associated with malignancy in Asian versus Caucasian patients [60]. Furthermore, within the Asian population, these antibodies may be uniquely enriched in tumors of the GI tract when compared to patients with anti-TIF1γ antibodies [60].

There likely exists further nuance that could optimize the use and interpretation of autoantibodies with regards to cancer risk in DM. For example, a recent study suggests that a high titer of the IgG2 isotype of anti-TIF1γ antibodies is uniquely associated with increased risk of cancer in DM patients [61]. While the explanation for this observation is unclear, it is possible that this isotype may reflect an environment in which anti-TIF1γ directed B cells are stimulated that is associated with tumor emergence (for example, high or sustained levels of IFNγ within a tumor [62]). Alternately, it may represent repetitive antigen exposure mirroring inefficient elimination of tumor cells harboring the altered autoantigen. Using the construct that cancer is one of many triggers of autoimmunity in DM, different initiating environments may be reflected in subtle differences in epitopes, isotypes, and T cell receptors for the same antigen. Knowledge of this may ultimately help clinicians identify DM patients in whom cancer was the initiating event.

As with SSc, it is likely that additional novel autoantibody specificities will be described that are associated with decreased risk of cancer emergence, even in high-risk antibody groups. In this way, identification of further axes of immunologic heterogeneity will continue to refine cancer risk stratification. Some of these responses may be less effective in halting cancer growth than others, resulting in delayed "breakthrough" cancers. Thus, patients harboring these less effective "autoantibody fingerprints" might be those selected for repeat cancer screening even many years after DM onset.

Finally, an important consideration in interpretating autoantibody data regarding cancer risk is the assay used to identify the autoantibody. For example, our group recently found that cancer risk in anti-TIF1γ-positive patients was highest when the assays were performed by line blot, intermediate when detection was by immunoprecipitation, and lowest when assayed by a commercially available ELISA [2]. While the mechanistic basis for this observation is presently unclear, it highlights that universal use of a standardized assay platform should be a critical component of larger, collaborative studies seeking to quantify

test performace regarding cancer risk that will ultimately be the basis for cancer screening guidelines in the DM population.

Can autoantibodies inform cancer screening guidelines?

Knowing how and when to screen an asymptomatic patient with DM or SSC for cancer remains a controversial subject. It is generally agreed that the most important positive outcome of a cancer screening protocol is a reduction in patient morbidity and/or mortality. However, cancer screening in DM or SSC adds additional complexity as eradication of cancer may provide the additional benefit of reduction of rheumatic disease morbidity, mirrored by the observation that some DM patients experience disease remission following cancer treatment. However, there are still several important and potentially negative outcomes of screening—these include medical side effects of some screening procedures or the cancer therapies themselves as well as wasted resources and unnecessary patient anxiety from either cancer overdiagnosis (e.g. diagnosing a cancer that would have otherwise had no clinical impact) or a false positive screening test with its attendant follow-up evaluations. Thus, evidence-based guidelines on cancer screening would ultimately need to result from long-term prospective studies that have shaped other cancer screening guidelines over the past several decades.

In the absence of that data, however, it will be important to initially develop guidelines based on evidence that is perhaps more readily obtained. The first variable to define is the malignancy prevalence in a given patient—this will impact not only decisions around screening aggressiveness but will also impact the predictive value of any screening modality. The concept of risk stratification will be critical in constructing an effective cancer screening strategy. In DM and SSc, cancer risk will depend upon with geographic location, patient demographics, the specific type of malignancy, and other clinical and serologic risk factors, at the very least. Many clinical characteristics that positively or negatively impact risk of cancer have been defined in SSc and DM. Additional complexity is introduced as it is likely that many of these factors interact. For example, the cancer risk associated with a particular autoantibody may depend on the race of the patient, and this interaction may in turn influence which type of cancer is most likely present. Given the dramatic effects of some of these variables, developing screening guidelines for the “average” DM or SSc patient may be of limited utility, unlike currently formulated cancer screening guidelines for the general population. Beyond cancer risk, relative performance of different screening modalities in these diseases must be compared. In DM, data suggest that PET-CT scans may be as effective as a combination of multiple other modalities (including CT) [63, 64] and actually associated with lower costs [65]. There is currently a formal, international effort to construct cancer screening guidelines for the inflammatory myopathies (including DM) which is organized under the auspices of the International Myositis Assessment and Clinical Studies group (IMACS)—the first step of performing a meta-analysis of data pertinent to this subject has recently been published [59].

What might such guidelines look like? As discussed, the first critical step will likely be risk stratification. It is our opinion that autoantibody status will play a large role in this effort—optimally this would require standardized, validated, and universally adopted assay

platforms. A clinician might then match low, medium, and high-risk patients (e.g. with zero, one, or greater than one clinical risk factor, respectively) with basic (age-appropriate), enhanced and comprehensive cancer screening, respectively, as previously suggested [66]. At the very least, a basic cancer screening strategy consisting of physical examination, CBC, liver function tests, urinalysis, and age-appropriate cancer screening should be implemented for all patients diagnosed with SSC or DM, particularly within the first 3 years of disease onset. For the higher risk patient, what might these "enhanced" screening modalities look like? Data from two retrospective studies in DM suggest that age-appropriate screening will miss a significant number of occult cancers and that thoracoabdominal computed tomography (CT) scans identify the majority of these occult cancers [67, 68]. Thus, one might imagine that a medium or high-risk patient at least be given consideration for CT scanning of the thorax and abdomen/pelvis, while a higher risk patient might be appropriately screened with PET-CT or CT scanning paired with additional directed testing if there are specific cancers to consider based upon the interaction of the clinical risk factors discussed above. For example, given the increased association of anti-TIF1γ antibodies with ovarian cancer in Caucasian women [40], this subgroup might be considered for follow-up pelvic ultrasound studies. Finally, timing and frequency of testing may also depend on autoantibody profile—for example, the fact that most cancers in patients with antibodies targeting TIF1γ antibodies occur within a one-year window of onset of DM symptoms suggests that group of patients may not need aggressive follow-up screening. Finally, in the absence of evidence-based guidelines, it will be critical for the clinician to have a shared-decision making approach with the patient after a discussion of what is known regarding their unique risk for cancer balance with the risks and costs associated with aggressive screening. All of these elements are critical for a cancer screening strategy that is consistent with the concept of "high value care" [69] which eschews a prescriptive, one-size-fits-all algorithm for cancer detection.

Concluding Remarks

Studies performed in recent years have illuminated the complex, intertwined interface of autoimmunity and cancer. Research to be carried out over the next decade will surely focus the beam and tie up many of the tantalizing emerging clues. Thoughtful use of large, well-phenotyped cohorts of patients with autoimmunity (SSc and DM are the poster children), standardized assays to read out autoantibodies and new research technologies and computational tools, will likely yield important understanding about the origins of autoimmunity. In turn, this may also provide critical insights into natural anti-tumor immunity and its potential use in treating cancers.

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Table 1:

Summary of autoantibodies and relative malignancy risk in DM (modified from Oldroyd et al, ref 57)

Antigen	RR (95% CI)[1]	GRADE certainty[2]	Number studies	Total cancers in antibody group
TIF1-γ	4.68 (3.37-6.48)	High	18	240
NXP2	1.16 (0.73-1.87)	Moderate	11	34
Mi-2	1.05 (0.28-3.92)	Low	6	19
SAE1/2	1.59 (0.33-7.74)	Low	3	9
MDA5	0.17 (0.02-1.28)	Low	5	4

[1] Risk of cancer-associated myositis (cancer within 3-5 yrs of DM onset) estimated against study's comparator DM patients

[2] Grading of Recommendations, Assessment, Development and Evaluations certainty rating: very low (the true effect is probably markedly different from the estimated effect), low (the true effect might be markedly different from the estimated effect), moderate (the authors believe that the true effect is probably close to the estimated effect), and high (the authors have a lot of confidence that the true effect is similar to the estimated effect). RR: Risk Ratio; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; TIF1-γ: Transcriptional Intermediary Factor 1-gamma; NXP2: Nuclear Matrix Protein 2; SAE1/2: small ubiquitin-like modifier-1 activating enzyme; MDA5: melanoma differentiation-associated gene 5.