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Cancer and systemic sclerosis: novel insights into pathogenesis and clinical implications

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Abstract

Purpose of review—Most epidemiologic studies have demonstrated an increased risk of cancer in scleroderma patients. Reasons for this risk increase have been poorly understood and often attributed to cytotoxic therapies or damage from scleroderma. Recognition that some patients have a close temporal relationship between cancer diagnosis and scleroderma clinical onset has focused attention on the possibility that scleroderma may be a paraneoplastic syndrome in a subset of patients. This review will discuss the latest epidemiologic data linking cancer and scleroderma and explore a model for the development of paraneoplastic scleroderma.

Recent findings—New investigations have demonstrated an association between RNA polymerase III autoantibodies and a close temporal relationship between cancer diagnosis and the development of clinical scleroderma. A unique nucleolar RNA polymerase III expression pattern has been identified in malignant tissue from these scleroderma patients suggesting that autoantigen expression in the cancer and the autoantibody response are associated. Similar data in inflammatory myositis have illustrated that disease-specific autoantigens may be expressed in cancers and damaged target tissues (muscle) undergoing regeneration.

Summary—These data suggest a model of paraneoplastic autoimmunity in which cross-reactive immune responses may target autoantigens that are expressed in both cancers and diseased autoimmune target tissues.

Keywords

autoantibodies; cancer; paraneoplastic; systemic sclerosis

Introduction

The majority of epidemiological studies probing the link between systemic sclerosis (SSc) and cancer provide compelling evidence that patients with SSc have an increased risk of malignancy compared with the general population [1•,2–8]. As in inflammatory myositis, the significance and meaning of the association between SSc and cancer has remained a puzzle and source of debate [9]. Observations of a close temporal relationship between cancer diagnosis and SSc onset, and reports of cancer therapy halting SSc progression, suggest that SSc may be a paraneoplastic syndrome in some patients [10–16]. Most investigations probing the connection between SSc and cancer have been hampered,

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Conflicts of interest

There are no conflicts of interest.

however, by small samples of SSc patients, limited characterization of the SSc clinical phenotype, lack of data on important confounders, a narrowed focus on particular cancers, or lack of information about the timing of cancer diagnosis relative to SSc clinical onset. In particular, few studies have investigated the population of patients with concurrent cancer and SSc onset, a subset of patients that may provide valuable and unique insights into biological events that may link antitumor immune responses and autoimmunity. This review will discuss the epidemiology of cancer in SSc, outline potential mechanisms linking the two entities, and explore a model of how SSc might be a paraneoplastic autoimmune phenomenon in a subset of patients.

Epidemiologic clues to disease mechanism

The majority of epidemiologic studies investigating the link between SSc and cancer demonstrate an increased risk of a wide array of malignancies in SSc compared with the general population [1•,2–8]. In the largest population-based cohort study of malignancy in SSc to date, Olesen *et al.* [1•] examined cancer risk using the Danish National Registry of Patients and the Danish Cancer Registry. Among 2040 SSc patients followed for over 16 000 person-years, 222 cancer cases were identified. Scleroderma patients had an increased risk of cancer compared with the general population [standardized incidence ratio (SIR) of 1.5], and men with SSc were at higher risk (SIR 2.2). Scleroderma patients had higher risks of cancers typically associated with alcohol or smoking (SIR 1.6) and hematological malignancies (SIR 2.5). Other smaller studies have similarly detected increased cancer risks for lung, esophageal, oropharyngeal, nonmelanoma skin, primary liver, and hematologic sites.

Many theories have been postulated to explain this increased cancer risk in SSc, but the supporting data to date are contradictory or inconclusive. Cytotoxic immunosuppressive therapies used to treat SSc, or chronic inflammation and repair because of the SSc disease process, may predispose cells to malignant transformation. This mechanism may play an important role in the development of late lung cancers and esophageal adenocarcinomas in the setting of pulmonary fibrosis and longstanding gastroesophageal reflux disease, respectively. An alternative hypothesis is that cancer therapy may result in the development of SSc. For example, multiple chemotherapeutic agents have been implicated as potential causes of SSc, scleroderma-like disease, or severe Raynaud's phenomenon [17–21]. Radiation therapy may trigger severe skin thickening in patients with SSc [22] or localized scleroderma in patients without a prior connective tissue disease history [23]. Other possible explanations for the increased cancer risk in SSc include a unique genetic susceptibility to both malignancy and the development of autoimmune disease, or a common inciting exposure. Definitive studies addressing these potential mechanisms are lacking to date.

Perhaps the most compelling and interesting aspect of the relationship between SSc and cancer is the temporal link between the two entities. As in dermatomyositis, a close temporal relationship between cancer diagnosis and the clinical onset of SSc has been described repeatedly and in a variety of cancers, most commonly breast, lung, and ovarian carcinomas and in lymphomas [10,13–15,24•,25–27]. In one particular series of SSc patients with breast cancer, over 60% of patients had a less than 12-month interval between cancer diagnosis and SSc onset [14]. Reports of successful cancer therapy halting the SSc disease process suggests that in these unique cases, the malignancy may drive the expression of SSc, possibly through the provoked immune response [11,12,16,28]. The study of other paraneoplastic autoimmune syndromes provides important insights into possible paraneoplastic mechanisms in SSc.

Insights from the study of other paraneoplastic autoimmune syndromes

Autoimmune inflammatory myopathies are associated with an increased risk of cancer, particularly adenocarcinomas in dermatomyositis [29–34]. The majority of cancer diagnoses occur within 1 year of the clinical onset of myositis [29–31,33,34], and a significant number of cancer cases cluster shortly before the diagnosis of myositis [31–33], suggesting that the risk increase is not solely attributable to heightened surveillance and detection bias [31]. Dramatic improvement in dermatomyositis with cancer therapy and relapse of muscle weakness with cancer recurrence further support the possibility that dermatomyositis is a paraneoplastic disease in a subset of patients [35,36]. The strong association between highly specific autoantibodies and unique clinical phenotypes in myositis prompted a team of investigators to use autoantibodies and autoantigen expression as tools to probe this temporal clustering between malignancy and myositis [37•]. This study demonstrated that myositis autoantigens are expressed at low levels in normal breast, lung, and liver tissues but are markedly enhanced in cancers associated with myositis: breast and lung adenocarcinomas and hepatocellular carcinoma [37•]. Expression levels of these same myositis autoantigens were low in control muscle biopsies but were dramatically increased in autoimmune myositis, particularly in regenerating muscle cells rather than mature myotubes [37•,38]. These data suggest that tumors are an antigen source in myositis that may be critical in disease initiation and that injured and repairing tissue populated by stem cells or other differentiating cells may be an ongoing antigen source that contributes to disease propagation.

As in rheumatic diseases, the paraneoplastic neuro-degeneration syndromes (PNDs) are conditions in which distinct clinical phenotypes associate with stereotypical autoantibody profiles. For example, Yo/CDR2 autoantibodies are found in patients with breast and ovarian cancers who develop paraneoplastic cerebellar degeneration [39], whereas anti-Ri/NOVA antibodies are detected in patients with paraneoplastic opsoclonus–myoclonus ataxia in the setting of small-cell lung, breast, and ovarian tumors [40,41]. To gain insight into these strong antibody–phenotype associations, onco-neural antigen expression has been evaluated in varied PNDs. In one study [42•], gynecologic tumors from patients with anti-Purkinje cell antibodies and paraneoplastic cerebellar degeneration were shown to highly express Purkinje-cell antigens unlike control gynecologic tumors obtained from neurologically normal patients [42•]. Affinity-purified antibodies to Purkinje-cell antigens reacted specifically with tumor tissue in patients with paraneoplastic cerebellar degeneration [42•]. In other PNDs, onconeural antigens are widely expressed in tumors, and it is the immune response to these antigens that associates with neurodegenerative phenotypes [43]. For instance, antigen-specific cytotoxic T cells have been shown to lyse target cells expressing onconeural antigens in paraneoplastic cerebellar degeneration [44]. In another PND, anti-Hu antibodies have been detected in neuronal nuclei in the central nervous system, suggesting a pathogenic role for these autoantibodies [45]. Interestingly, patients who develop PNDs have better cancer prognoses than those who do not [46,47], suggesting that patients who develop paraneoplastic autoimmune syndromes have successful antitumor immune responses resulting in spontaneous regression of tumors [47].

Similar findings have been made in melanoma, in which survival rates are significantly higher among patients who develop vitiligo compared with patients who do not [48,49]. Vitiligo developing during or after immunotherapy treatment of melanoma is associated with improved melanoma response rates, suggesting that a robust, successful antitumor immune response may trigger autoimmunity [50–52]. Indeed in melanoma patients who developed vitiligo after treatment with experimental dendritic cell vaccinations, vaccine-induced T cells invaded both tumor and vitiligo lesions, thereby directly linking vitiligo to the immunotherapy intervention [53]. Melanocytes and malignant melanoma cells share

melanocyte differentiation antigens, and immune responses to these antigens have been detected in both vitiligo and malignant melanoma [50,54].

The models of inflammatory myositis, paraneoplastic neurodegenerative syndromes, and vitiligo in melanoma suggest a paradigm in which autoantigens are expressed in malignancies and trigger antitumor immune responses that may cross-react with autoimmune target tissues, leading to specific clinical phenotypes. Although the autoantibodies are highly phenotype-specific, their involvement in pathogenesis is less clear. It is likely that the autoantibodies recognize the same antigenic targets as other immune effector pathways, and that cytotoxic T-cell immune responses play important roles in controlling tumor growth and inducing autoimmune tissue damage. Whether a cancer is detectable in patients with these immune responses ultimately depends on the effectiveness of the antitumor immune response. Therefore, it is possible that SSc and myositis phenotypes may manifest even in the absence of a detectable tumor, as has been demonstrated in the PNDs.

RNA polymerase III is overexpressed in cancer tissue from systemic sclerosis patients with RNA polymerase III antibodies

To begin to probe the relationship between malignancy, autoantigens and SSc, we investigated 23 SSc patients with malignancy and available sera and cancerous tissue [24•]. When examining the temporal relationship between SSc and malignancy onset by autoantibody status, we discovered that patients with RNA polymerase III antibodies had a unique close temporal relationship between cancer diagnosis and SSc onset compared to patients with anticentromere or antitopoisomerase I antibodies (Fig. 1). Patients in the anti-RNA polymerase III positive subset had both cancer diagnosis and SSc onset occur within 2 years of one another, typically with cancer shortly preceding the development of SSc. On the basis of these initial intriguing findings, we investigated RNA polymerase III expression in cancerous tissue from SSc patients with and without RNA polymerase III antibodies. Scleroderma patients with RNA polymerase III antibodies had a unique nucleolar pattern of RNA polymerase III expression in their tumors compared to patients with other SSc autoantibodies (Fig. 2), suggesting that the expression of SSc antigens in tumors may associate with SSc-specific autoantibody responses.

These initial findings and recent confirmation that RNA polymerase III autoantibodies associate with coincident cancer and SSc [55] have raised numerous interesting questions about the relationship between malignancy and SSc. One possible paradigm for this association is that SSc-associated antigens are expressed in tumor cells. Most SSc autoantigens are nucleolar in origin and play a critical role in ribosome synthesis and mitogenesis. These proteins are very likely to be relevant in rapidly proliferating malignant cells. Genetic mutations or posttranslational modifications could produce conformationally altered protein products that accumulate in malignant tissue and create novel epitopes [56]. These neoantigens may gain exposure to the immune system by several mechanisms, particularly release during tumor cell death. The resulting immune response may include the generation of antigen-specific T and B cells, and in many circumstances, successful tumor immunity and eradication may result. Interestingly, immune recognition of mutated gene products may trigger autoimmune phenomena and tumor immunity by cross-recognition of nonmutated and normally silent epitopes [57•]. A mechanism by which this could translate into the SSc clinical phenotype is similar to what has been suggested in inflammatory myositis. In a subset of patients, distant tissues (e.g. muscle, skin, and kidney) that have been damaged from a variety of potential causes (e.g. ischemia reperfusion injury, stress, toxins, infection, and chemotherapeutic agents) may express these novel autoantigens during

repair and regeneration, thereby reactivating immune responses initially formed in the antitumor immune response and perpetuating the autoimmune phenotype (Fig. 3).

Conclusion

Although the preliminary data and models of paraneoplastic autoimmune phenomena are intriguing, proving the paraneoplastic theory in SSc will be challenging and will require extensive investigation of the biology and epidemiology of cancer in SSc. Important questions that need to be addressed include whether tumor autoantigen expression is unique in SSc patients; whether SSc autoantigen expression is prevalent across tumors but autoantibody production is unique to SSc; or whether tumor autoantigen expression and autoantibody production are seen in many cancer patients but other factors confer susceptibility to the clinical expression of SSc. From a biological perspective, examination of whether autoantigen expression levels and patterns in tumors are unique in SSc and whether the autoantibody response is tumor-specific, histology-specific, or SSc-specific will be very informative. If autoantigen expression levels or patterns are specific to SSc patients' tumors or particular histologies, the impact of cancer therapy (i.e. removal of the antigen source) on SSc or cancer outcomes merits further study. If SSc autoantigen expression is widespread among tumors, it will be important to investigate whether the autoantibody response is specific to SSc or is a tumor-specific immune response seen widely across patients with cancer. In these scenarios, it would be important to define and compare tumor size at discovery and tumor outcomes between patients with and without the immune response. Definition of antigenic epitopes, identification of SSc-antigen specific T cells capable of lysing tumor cells, and examination of SSc-antigen expression in target tissues such as the skin, vasculature, and kidney are important next steps to probe the paraneoplastic model.

Robust epidemiologic study will be an important tool to guide these mechanistic studies. For example, defining other autoantibodies that associate with a clustering of cancer and SSc may inform which antigens are overexpressed or altered in malignant tissue. A prior study [58] in patients with preexisting SSc demonstrated increased topoisomerase I titers and recognition of novel, distinct epitopes at the time of lung cancer diagnosis; these data suggest that examination of whether autoantibody responses change with cancer diagnosis and treatment may also provide unique insights into underlying pathological mechanisms. Identification of phenotypic features and SSc autoantibodies that are markers of cancer risk may guide research investigating the impact of risk factor modification or heightened cancer surveillance on both SSc and cancer outcomes. Lastly, it will be important to define novel biomarkers and techniques to discover subclinical malignancy as this may have a direct impact on early cancer detection and hopefully improve cancer and SSc outcomes.

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 621).

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Key points

- Study of the close temporal relationship between cancer diagnosis and the clinical onset of SSc may yield unique insights into SSc pathogenesis.
- Scleroderma patients with cancer and RNA polymerase III autoantibodies have a close interval between cancer diagnosis and the onset of SSc symptoms and a unique nucleolar pattern of RNA polymerase III expression in their cancers.
- The models of inflammatory myositis, paraneoplastic neurodegenerative syndromes, and vitiligo in melanoma suggest a paradigm in which autoantigens are expressed in malignancies and trigger antitumor immune responses, which cross-react with target tissues leading to autoimmune-mediated damage and specific clinical phenotypes.
- Robust epidemiologic study of the link between cancer and SSc will be an important tool to guide mechanistic studies probing the paraneoplastic model.

Figure 1. Scleroderma duration at cancer diagnosis by autoantibody status

Scleroderma patients with cancer and RNA polymerase III autoantibodies (anti-RNA pol I/III) had a close temporal relationship between cancer diagnosis and systemic sclerosis clinical onset compared to patients with other antibody types. Reproduced with permission from [24•].

Figure 2. RNA polymerase III staining is prominent in cancerous tissue from scleroderma patients as compared with normal tissues

Paraffin sections from cancerous breast tissue from a scleroderma patient (a) and from normal breast tissue (b) stained with antibodies against RNA polymerase III. Brown shows RNA polymerase III staining; blue shows nuclei (Mayer's hematoxylin counterstain). Original magnification $\times 40$. Reproduced with permission from [24].

Figure 3. Conceptual framework for the paraneoplastic model – tumors and distant tissues may share antigens that are targets of the immune response

Transformed cells may expose self-antigen through varied mechanisms and trigger an antitumor immune response. This primes the immune system. Injured distant tissues may expose these same self-antigens during repair and regeneration mechanisms (e.g. differentiation of cell types involved in repair) and be a target of the immune response. Thus, the immune response initiated against tumor antigens may be propagated against the same antigens in target tissues.