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TIF1 autoantibodies in dermatomyositis shed insight into the cancer-myositis connection

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Phenotype-specific autoantibodies are clinically important tools

Across the breadth of autoimmune rheumatic diseases, there is a striking association of specific autoantibodies with distinct clinical phenotypes, making them excellent tools for subsetting patients, predicting disease course and outcomes. Within the myositis spectrum, there are numerous examples of this. Over two decades ago, it was noted that autoantibodies against the aminoacyl tRNA synthetases (the most frequently targeted of which is Jo-1) are found in myositis patients with a constellation of symptoms known as the "synthetase syndrome"[1–2]. These include mechanic's hands, interstitial lung disease, inflammatory arthritis, Raynaud's phenomenon and fever. A more recently described specificity is that of melanoma differentiation-induced gene-5 (MDA-5) – these antibodies are found in dermatomyositis (DM) patients with mild/absent muscle disease, and are frequently associated with rapidly progressive interstitial lung disease[3]. New data continue to further define the clinical phenotype associated with anti-MDA-5 antibodies: in a study of DM patients seen at a Dermatology outpatient clinic, Fiorentino et al demonstrated that this specificity is associated with cutaneous ulcerations and distinctive palmar papules, and confirmed the association with rapidly progressing lung disease[4]. These two examples confirm that autoantibodies in DM patients are of clinical utility.

Autoantibodies against a protein doublet termed "p155/140" (denoting the molecular weights) define another distinct group of DM patients – those with an increased incidence of cancer compared to DM patients without malignancies[5]. A meta-analysis of several studies confirmed that the presence of these autoantibodies has a 70% sensitivity and 89% specificity for identifying patients with cancer-associated DM[6]. This immune response appears specific for DM patients, as it is not found in patients with systemic sclerosis, lupus erythematosus, or healthy individuals. In 1996, p155 was identified as transcriptional intermediary factor (TIF1)-γ by Targoff et al [7], but the identity of the 140 kD specificity remained elusive.

The current study by Fujimoto et al [8] confirms the identify of p155 as TIF1-γ (consistent with Targoff's findings above), and also identifies the 140 kD antibody target as TIF1-α. In addition, the study shows that TIF1-β (100 kD) is also targeted in DM patients, albeit less frequently than the TIF1 –α and –γ counterparts. The TIF1 specificities occurred alone or in various combinations of α, γ and β: of the 78 DM patients studied in this paper, 61.5% were anti-γ/α, 29.5% were anti-γ only, 5% had all 3, 2.5% were anti-γ/β and 1.5% were anti-β only (anti-α alone was not detected in this cohort). Since these proteins are highly

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homologous, and because anti-γ frequently occurs alone but never the anti-α specificity, one possibility is that the epitope is a TIF1-γ sequence, with cross-reactivity of the antibodies to TIF1-α. Interesting in this regard is the fact that TIF1-γ and α share much more sequence similarity to each other than does TIF1-β, perhaps explaining why the latter are so infrequently detected.

These DM-specific antibodies are relatively frequent, being found in 78/456 (17%) of DM patients in this study. They constitute significant subsets in juvenile DM and adult cancer-associated DM (36% and 73%, respectively, in this study); of note, cancer is not a feature associated with juvenile DM. Further careful cross-sectional and longitudinal studies of the phenotypes associated with the various TIF1 antibody combinations may delineate important distinctions in clinical features and outcome. It will also be critical to define whether TIF1 antibodies occur with other known myositis antibody specificities (eg, Jo-1, Mi-2 etc), and if so, to evaluate the relevance of this.

The TIF1 proteins have a variety of important cellular functions

Four members of the TIF1 protein family have been described to date: TIF1-γ (TRIM-33), TIF1-α (TRIM 24), TIF1-β (TRIM 28) and TIF1-δ. All belong to the larger tripartite motif (TRIM) family of proteins that are implicated in a number of important biological processes, including cell proliferation, development, apoptosis, and innate immunity[9]. Members of this subfamily share a common N-terminal TRIM, previously known as a RING–B-box–coiled-coil (RBCC) motif, and a C-terminal chromatin binding unit. The TRIM motif allows these proteins to function as E3 ligases in the ubiquitination pathway to control protein degradation, localization, and function. Due to their C-terminal domains, TIF1 proteins have been implicated in epigenetic mechanisms of transcription regulation involving histone modifiers and heterochromatin-binding proteins. TRIM24 and TRIM33 function as “chromatin readers” to detect multivalent modifications of histones and thus modulate transcriptional activation in only these “marked” areas of the genome[10–11]. TRIM24 has been shown to repress retinoic acid receptor (RAR)-driven transcription, and loss of TRIM24 activity in mice leads to RAR-dependent activation of genes (including many involved in interferon (IFN) signaling) and ultimately hepatocellular carcinoma[12]. However, TRIM24 can also act to increase tumorigenesis, via ubiquitination of p53 in breast cancer cells; in fact, overexpression of TRIM24 is a poor prognostic indicator in breast cancer patients[13]. TRIM33 is also an E3 ligase that modulates TGF-β signaling via ubiquitination of SMAD4 (and disrupting SMAD complexes) and/or acting as a cofactor for phosphorylated SMAD2/3[10]. TRIM33 can also function as a positive regulator of transcription by counteracting RNA polymerase II pausing, and this may function in the regulation of commitment to erythroid (versus myeloid) differentiation[10]. TRIM33 is reported to function as a tumor suppressor for chronic myelomonocytic leukemia as well as pancreatic cancer. Unlike TRIM24 and TRIM33, TRIM28 appears to function largely to promote heterochromatin formation (and transcriptional repression) via interaction with multiple proteins, including histone deacetylase (HDAC) and other components of the NuRD nucleosome remodeling complex[14]. TRIM28 also functions to decrease p53 activity via several mechanisms distinct from its transcriptional repressor activity. Not surprisingly, TRIM28 appears to be implicated in tumorigenesis, and it is overexpressed in liver, gastric, lung, breast, and prostate cancers. Interestingly, TRIM28 is known to bind to STAT1 and to inhibit IFN-driven transcription[15].

What is the glue that binds DM autoantigens?

Why certain antigens (eg, MDA-5, TIF1-γ/α/β, Mi-2) are targeted only in DM and not other forms of myositis or autoimmunity, still remains unknown. With the identification of each

targeted protein, intriguing connections between DM-specific autoantigens are emerging and suggest that several may be involved in common functional pathways essential for chromatin reading and/or structural modulation. This raises the possibility that a particular subnuclear structure (rather than distinct individual antigens) may be the real target of the autoimmune response. For example, TRIM28/TIF1–β binds to Mi-2α, a member of the NuRD complex, and the first DM-specific autoantigen ever described. In addition, TRIM28/TIF1-β is heavily sumoylated, a process which involves a complex set of enzymatic steps mediated by sumoyl activation enzymes (SAE1/2). Interestingly, SAE1 has recently been described as a novel DM-specific autoantigen. NXP-2, another newly identified DM autoantigen, is also a target of SAE1 and allows subnuclear localization of the protein into so-called promyelocytic leukemia nuclear bodies, which are adjacent to subnuclear regions containing TRIM28/TIF1-β[14]. It is tantalizing to speculate that there are both functional and spatial connections between many of these autoantigens, which may be contributing to their immunologic targeting in DM patients.

TIF1-α/γ antibodies, DM and cancer

In an important analysis a decade ago, Hill et al [16] confirmed a strikingly increased risk of cancer in myositis patients compared to that in the general population: 32% of DM and 15% of PM patients had an associated diagnosis of cancer sometime during their illness. The mechanistic nature of this association still remains unclear. It is possible that the anti-TIF1 immune response is simply a marker of patients with cancer and has nothing to do with developing DM. The fact that TIF proteins are overexpressed in many cancer types, along with the fact that an autoimmune response to TRIM28 is a common finding in patients (even without DM) with colorectal carcinoma [17] supports this notion. However, the finding that many juvenile DM patients without a presumed cancer have antibodies against TIF1 (and not patients with other autoimmune diseases), suggests that anti-TIF1 is indeed mechanistically linked with DM.

Tantalizing clues as to how this might come about have come from a study[18], showing that expression of myositis autoantigens is markedly elevated in cancers associated with myositis and in regenerating muscle cells. These authors therefore proposed that autoimmunity may be initiated in the setting of malignancy - that is, there is an adaptive anti-tumor immune response directed against antigens shared with immature muscle cells. When this occurs in the context of non-specific muscle injury (resulting in increased numbers of regenerating muscle cells), muscle – an otherwise innocent bystander – may become the target of tumor antigen-specific responses because it also expresses the relevant antigens. In this way, the propagation phase of autoimmunity is sustained and driven. In this regard, studies to quantitate the levels of TIF1-α and -γ in mature healthy muscle, regenerating muscle and in cancers known to be associated with myositis will be especially informative.

Why, then, is the anti-TIF1 test not 100% specific for cancer? Multiple adult (and all juvenile) DM patients have anti-TIF1 antibodies and no detectable cancer. Do all patients with anti-TIF1 response originally have a cancer, but the immune response is only successful in eliminating that cancer in a subset of patients? This seems unlikely, given that not a single juvenile DM patient with anti-TIF1 antibodies has been shown to harbor a cancer. Perhaps cancer is only one way in which tolerance to TIF1 proteins can be broken, or, a more common process (such as angiogenesis) is the true process that results in the anti-TIF1 response. Further studies addressing why these TIF1 proteins are targets of the immune response should include assessing whether they are overexpressed/induced in certain tissues and microenvironments, and/or modified (eg, post-translational processing, cleavage etc).

Future Directions

It is noteworthy that ~30–40% of myositis patients are autoantibody negative, when assayed using traditional methodologies. The fact that MDA-5 antibodies are poorly detected when screening control cells (or lysates made from these cultures) because robust expression of the protein is only induced after treatment with interferons illustrates the importance of the antigen source used for screening assays. This raises the intriguing (and likely) possibility that additional unidentified myositis antibody specificities exist; detecting these will require screening using appropriate antigen sources. Identification of new, as yet unidentified antibody specificities are certain to yield further fine specificity for use in predicting and monitoring distinct clinical subsets not only in myositis, but also across the spectrum of autoimmune diseases. Systematic, careful screening of large cohorts of sera from patients with different diseases are required to fully understand the diagnostic relevance of anti-TIF1 antibodies, including any mechanistic association with malignancy.

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