

Title	A Combination of Autoantibodies Predicts the Fate of Cancer-Associated Dermatomyositis
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Citation	Arthritis and Rheumatology. 2023, 75(7), p. 1085–1087
Version Type	АМ
URL	https://hdl.handle.net/11094/91343
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Editorial

A combination of autoantibodies predicts the fate of cancer-associated dermatomyositis

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Word count: 1,403 words

References: 15

Address correspondence to Manabu Fujimoto, MD Department of Dermatology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0781, Japan E-mail: <u>fujimoto@derma.med.osaka-u.ac.jp</u> ORCID ID: 0000-0002-3062-4872 Idiopathic inflammatory myopathies (IIMs), including dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, inclusion body myositis, polymyositis, and overlap myositis, are a heterogeneous group of autoimmune disorders with varying clinical manifestations [1]. In the past two decades, the discovery of several novel myositis-specific autoantibodies (MSAs) brought great advances in the field of IIMs [2]. MSAs are almost exclusively found in patients with IIMs, and thus are useful for diagnosis. Moreover, MSAs are strongly associated with distinct clinical phenotypes and, therefore, serve as powerful tools to identify more homogeneous subgroups for predicting organ manifestations and prognosis, and designing therapies. In addition, MSAs may provide insights into disease mechanisms.

Dermatomyositis itself is also a heterogeneous disease. Besides muscle weakness and prototypic rash, malignancies and interstitial lung disease often determine the prognosis. Currently, five disease-specific autoantibodies have been established in dermatomyositis: anti-Mi-2, anti-melanoma differentiation-associated gene 5 (MDA5), anti-transcriptional intermediary factor 1 (TIF1), anti-nuclear matrix protein 2 (NXP2), and anti-small ubiquitin-like modifier activating enzyme (SAE) autoantibodies [2], in addition to antisynthetase antibodies, which are detected in antisythetase syndrome including those who can be clinically diagnosed as dermatomyositis (Figure 1). While anti-NXP2 and anti-SAE antibodies are also potentially associated with increased cancer emergence, anti-TIF1 antibodies have been shown to have a strong association with malignancy and are considered a potent serological marker for cancer-associated dermatomyositis [3, 4]. Approximately 70% of dermatomyositis patients positive for anti-TIF1 antibodies have cancer, mostly at the time of DM diagnosis. By contrast, 20-30% of patients with juvenile dermatomyositis also possess anti-TIF1 antibodies, although they do not usually have cancers. Thus, there is heterogeneity within anti-TIF1-positive dermatomyositis.

In this issue of Arthritis and Rheumatology, Fiorentino, Mecoli, et al. assessed

the clinical characteristics of patients with autoantibodies against cell division cycle and apoptosis regulator 1 (CCAR1) [5]. This is an extension of their prior study [6], in which they identified 10 previously undescribed autoantibodies in sera from anti-TIF1- γ positive dermatomyositis patients without cancer, in comparison with those with cancer. Among them, 6 antibodies were found in multiple patients in two independent cohorts. Notably, they observed a decreased cancer risk with an increasing number of concurrent autoantibodies. Among them, anti-CCAR1 antibodies were the most frequent. Anti-CCAR1 positivity was negatively associated with cancer emergence within 3 years of dermatomyositis onset.

In the current study, Fiorentino, Mecoli, and colleagues expanded their study to the whole population of adult dermatomyositis to clarify the disease specificity, clinical phenotype, and cancer associations of anti-CCAR1 autoantibodies [5]. They determined that the N-terminal region is the major epitope of anti-CCAR1 autoantibodies, and developed a new ELISA system for anti-CCAR1 autoantibodies.

Anti-CCAR1 positivity was strongly associated with the presence of anti-TIF1- γ antibodies, whereas it was relatively rare in anti-TIF1- γ -negative dermatomyositis patients (80/252 [32%] v.s. 14/186 [8%], p<0.001) [5]. Anti-CCAR1 antibodies in the sera from anti-TIF1-g-negative patients tended to be detected at low-moderate titer. Moreover, these antibodies were not detected in the healthy control sera and were present at very low frequencies in other rheumatic diseases, including anti-3-hydroxy-3-methylglutaryl-coA reductase (HMGCR)-positive necrotizing myopathy, inclusion body myositis, and systemic lupus erythematosus. Therefore, anti-CCAR1 antibodies were largely restricted to anti-TIF1- γ antibody-positive dermatomyositis.

While their prior analysis evaluated cancer risk within time windows around (before and after) dermatomyositis onset, they took a more clinically relevant approach to start with a patient that has already experienced dermatomyositis onset and to estimate subsequent cancer incidence relative to the general population, using two independent cohorts [5]. As is already well described, the observed number of cancers diagnosed in anti-TIF1- γ -positive patients was significantly greater than expected in both cohorts, with standardized incidence ratios (SIRs) of 3.49-4.54 in the two cohorts. By contrast, in patients who were anti-TIF1- γ -positive/anti-CCAR1-positive, the SIRs decreased to 1.61-1.78. Thus, the concomitant presence of anti-CCAR1 antibodies with anti-TIF1- γ antibodies attenuates cancer risk to levels comparable to those in the general population.

Clinically, anti-CCAR1-positive patients showed significantly lower CK levels and were significantly less likely to have an elevated CK over longitudinal follow-up as well as cutaneous ulcerations. Importantly, these features are associated with contemporaneous cancer in a recent meta-analysis [4], consistent with attenuated cancer risk in anti-CCAR1-positive patients.

It is intriguing that autoantibodies against a transcription factor, specificity protein 4 (Sp4), recently reported by Hosono et al. [7] have similar features to anti-CCAR1 autoantibodies. Anti-Sp4 autoantibodies were specific for dermatomyositis: they were present in 10.5% of patients with dermatomyositis but were rarely found in healthy individuals or other diseases. Moreover, among patients with DM, anti-Sp4 autoantibodies were found almost exclusively in those with coexisting anti-TIF1- γ autoantibodies [7]. Similar to the study by Fiorentino, Mecoli, et al [5], the prevalence of cancer was relatively decreased in those with coexisting anti-Sp4 autoantibodies and anti-TIF1g autoantibodies.

The mechanisms of how cancer and certain rheumatic diseases are connected have long been debated. When a rheumatic disease precedes cancer, tissue damage by chronic inflammation is likely to result in an increased risk of cancer. However, there needs another explanation when cancer is found around the same time as the onset of rheumatic diseases, as in dermatomyositis. One of the currently leading hypotheses, originally proposed in anti-RNA polymerase antibody-positive systemic sclerosis [8], is that genetically altered autoantigens, i.e. neoantigens, in cancer initiate autoimmune responses in rheumatic diseases [9]. TIF1 proteins, TIF1- α , TIF1- β , TIF1- γ , and TIF1- δ , form a subfamily of the large, highly conserved tripartite-motif (TRIM) family of E3 ligases. TIF1 proteins have diverse functions, including transcription, cell differentiation, DNA repair and mitosis, all of which can be altered in tumorigenesis [10]. TIF1 proteins exhibit both oncogenic and tumor-suppressive roles depending on the context, but increasing evidence has indicated that TIF1 proteins contribute to the maintenance of genome stability [10]. Tumors from paraneoplastic anti-TIF1-y-positive patients showed an increased number of genetic alterations, such as mutations and loss of heterozygosity, in TIF1- γ genes compared with tumors from anti-TIF1- γ -negative myositis patients [11]. TIF1- γ overexpression in tumors [10] may also enhance the response. Supporting this hypothesis, anti- TIF1-y-positive dermatomyositis developing after immune checkpoint inhibitor therapy has been reported. Importantly, anti-TIF1 antibodies are usually not detected in just cancer-carrying patients, but only in dermatomyositis patients with cancer (and also without cancer), suggesting that anti-TIF1 immune response may not be an epiphenomenon. Indeed, TIF1- γ immunization can induce myositis in mice [12]. B celldeficient mice mounted a similar response but CD8 T cell-deficient mice failed to develop myositis, suggesting that, while the humoral immune response may be dispensable, the immune response against TIF1- γ can directly develop myositis [12]. Although precise mechanisms of how intracellular TIF1- γ can be targeted need to be elucidated, regenerated muscle tissue overexpresses TIF1- γ [13], which may amplify the muscle damage.

CCAR1 (also known as CARP-1) is a 130-kDa peri-nuclear protein, acting as a co-activator of steroid/thyroid nuclear receptors, β -catenin, Anaphase Promoting Complex/Cyclosome (APC/C) E3 ligase, and tumor suppressor p53 [14]. While contradictory reports exist on the CCAR1 functions as either tumor promoters or suppressors, like TIF1, depending on cancer types, several studies have indicated the critical roles of CCAR1 in tumorigenesis and metastasis. Upregulation of Sp

transcriptional factors, Sp1, Sp3, and Sp4 is associated with the transformation of normal cells to cancer cells [15]. Collectively, identification of these autoantibodies provides further evidence that complex cancer protective immunity forms autoimmune responses causing dermatomyositis, and indicates that the diversity and potency of anti-tumor response may influence cancer progression.

Currently, the classification of autoantibodies present in IIMs is straightforward: MSAs and myositis-associated autoantibodies (MAAs). A major feature of MSAs is that they are almost mutually exclusive. Now it appears appropriate to include anti-CCAR1 and anti-Sp4 autoantibodies into myositis-specific autoantibodies based on their specificity. Therefore, MSAs may need to be categorized into two hierarchies: those that are mutually exclusive and those that coexist with other specific antibodies. Anti-CCAR1 and anti-Sp4 autoantibodies belong to the latter as they are likely to appear in association with anti-TIF1- γ antibodies and define a cancer-unrelated subgroup within them (Figure 1).

In summary, the study by Fiorentino, Mecoli, et al. [5] is of clinical importance in that combination of autoantibodies can predict cancer risk with more accuracy. At the same time, this study will give an insight into the pathomechanisms of how anti-tumor activity may shape autoimmunity in dermatomyositis. Further investigations on anti-CCAR1 and other autoimmune responses in cancer-unrelated anti-TIF1- γ -positive patients, especially in juvenile dermatomyositis, will provide further information on how autoimmune response is mounted in dermatomyositis. Moreover, it is intriguing to know whether anti-CCAR1 activity only acts against tumors or also contributes to the development of dermatomyositis positively or negatively.

References

 Lundberg IE, Fujimoto M, Vencovsky J, Aggarwal R, Holmqvist M, Christopher-Stine L, Mammen AL, Miller FW: Idiopathic inflammatory myopathies. *Nat Rev Dis Primers* 2021, 7(1):86.

- McHugh NJ, Tansley SL: Autoantibodies in myositis. Nat Rev Rheumatol 2018, 14(5):290-302.
- Fujimoto M, Hamaguchi Y, Kaji K, Matsushita T, Ichimura Y, Kodera M, Ishiguro N, Ueda-Hayakawa I, Asano Y, Ogawa F *et al*: Myositis-specific anti-155/140 autoantibodies target transcriptional intermediary factor 1 family proteins. *Arthritis Rheum* 2012, 64:513-522.
- Oldroyd AGS, Allard AB, Callen JP, Chinoy H, Chung L, Fiorentino D, George MD, Gordon P, Kolstad K, Kurtzman DJB *et al*: A systematic review and metaanalysis to inform cancer screening guidelines in idiopathic inflammatory myopathies. *Rheumatology (Oxford)* 2021, 60(6):2615-2628.
- 5. Fiorentino D, Mecoli CA, Igusa T, Albayda J, Paik JJ, Tiniakou E, Adler B, Mammen AL, Shah AA, Rosen A *et al*: Anti-CCAR1 autoantibodies are specific for anti-TIF1g-positive dermatomyositis and decrease cancer risk relative to the general population. *Arthritis Rheumatol* 2023:in press.
- Fiorentino DF, Mecoli CA, Rosen MC, Chung LS, Christopher-Stine L, Rosen A, Casciola-Rosen L: Immune responses to CCAR1 and other dermatomyositis autoantigens are associated with attenuated cancer emergence. J Clin Invest 2022, 132(2).
- 7. Hosono Y, Sie B, Pinal-Fernandez I, Pak K, Mecoli CA, Casal-Dominguez M, Warner BM, Kaplan MJ, Albayda J, Danoff S *et al*: **Coexisting autoantibodies against transcription factor Sp4 are associated with decreased cancer risk in patients with dermatomyositis with anti-TIF1gamma autoantibodies**. *Ann Rheum Dis* 2022.
- Joseph CG, Darrah E, Shah AA, Skora AD, Casciola-Rosen LA, Wigley FM, Boin F, Fava A, Thoburn C, Kinde I *et al*: Association of the autoimmune disease scleroderma with an immunologic response to cancer. *Science* 2014, 343(6167):152-157.
- 9. Fiorentino DF, Casciola-Rosen L: Autoantibodies and Cancer Association: the Case of Systemic Sclerosis and Dermatomyositis. *Clin Rev Allergy Immunol* 2022, **63**(3):330-341.
- 10. McAvera RM, Crawford LJ: **TIF1 Proteins in Genome Stability and Cancer**. *Cancers (Basel)* 2020, **12**(8): 2094.
- Pinal-Fernandez I, Ferrer-Fabregas B, Trallero-Araguas E, Balada E, Martinez MA, Milisenda JC, Aparicio-Espanol G, Labrador-Horrillo M, Garcia-Patos V, Grau-Junyent JM *et al*: Tumour TIF1 mutations and loss of heterozygosity related to cancer-associated myositis. *Rheumatology (Oxford)* 2018, 57(2):388-

396.

- 12. Okiyama N, Ichimura Y, Shobo M, Tanaka R, Kubota N, Saito A, Ishitsuka Y, Watanabe R, Fujisawa Y, Nakamura Y *et al*: Immune response to dermatomyositis-specific autoantigen, transcriptional intermediary factor Igamma can result in experimental myositis. *Ann Rheum Dis* 2021, 80(9):1201-1208.
- 13. Mohassel P, Rosen P, Casciola-Rosen L, Pak K, Mammen AL: Expression of the dermatomyositis autoantigen transcription intermediary factor 1gamma in regenerating muscle. *Arthritis Rheumatol* 2015, **67**(1):266-272.
- 14. Muthu M, Cheriyan VT, Rishi AK: CARP-1/CCAR1: a biphasic regulator of cancer cell growth and apoptosis. *Oncotarget* 2015, 6(9):6499-6510.
- 15. Safe S, Abbruzzese J, Abdelrahim M, Hedrick E: Specificity Protein Transcription Factors and Cancer: Opportunities for Drug Development. *Cancer Prev Res (Phila)* 2018, 11(7):371-382.

Figure 1. Disease-specific autoantibodies detected in dermatomyositis. Patients with dermatomyositis can be clinically classified into those with malignancy (red; left), those with interstitial lung disease (yellow; right), and those with neither (blue; center). Disease-specific autoantibodies are represented by rounded rectangles, of which the size is roughly proportional to their frequency. Antisynthetase antibodies (dotted round rectangle) are not specific for dermatomyositis but are detected in non-dermatomyositis patients. They are closely associated with clinical phenotype and mutually exclusive, although anti-cell division cycle and apoptosis regulator 1 (CCAR1) and anti-Sp4 antibodies are present in association with anti-transcriptional intermediary factor 1 (TIF1) antibodies. MDA5, melanoma differentiation-associated gene 5; NXP2, nuclear matrix protein 2; SAE, small ubiquitin-like modifier activating enzyme.