Autoantibodies to Aminoacyl-tRNA Synthetases

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The aminoacyl-transfer (t) RNA synthetases are a family of enzymes, each of which catalyzes the formation of an aminoacyl-tRNA from a specific amino acid and its cognate tRNAs. There is a separate, immunologically and enzymatically distinct aminoacyl tRNA synthetase (ARS) in the cytoplasm for each of the 20 amino acids (1). Autoantibodies to six of the synthetases [Jo-1 (histidyl-tRNA synthetase: HisRS) (2, 3), PL-7 (threonyl-: ThrRS) (4), PL-12 (alanyl-: AlaRS) (5), OJ (isoleucyl-: IleRS) (6), EJ (glycyl-: GlyRS) (6), and KS (asparaginyl tRNA-: AsnRS) (7)] have been described in patients with connective tissue diseases, and these antibodies can be found in approximately 25–35% of patients with inflammatory muscle disorders, PM and DM (8–10).

The most common is anti-Jo-1, which occurs four to five times more frequently than any of the other anti-synthetases. Anti-PL-7 (ThrRS) and anti-PL-12 (AlaRS) antibodies are less common, found in 3 to 4% of all patients with PM/DM, while autoantibodies to OJ (IleRS), EJ (GlyRS) and KS (AsnRS) are the least common, occurring in <2% (8–10).

ARSs can be classified into Class I and Class II synthetases based on several properties shared by members of the class, including sequence motifs, molecular structures, and the site of initial aminoacylation (11). Five of 6 anti-synthetases react with Class II synthetases, most of which are found free and uncomplexed in the cell cytoplasm, whereas anti-OJ sera react primarily with isoleucyl-tRNA synthetase, a Class I synthetase that exists as part of a multi-enzyme synthetase complex. The reason for this preference is unknown. The fact that anti-Jo-1 is more common than all other anti-synthetases, clearly indicates that synthetases are not randomly targeted. Possibly, such antigens can be expressed on the surface or presented more easily.

These autoantibodies are unique in having a combination of several important features: 1) they are directed at functionally related enzymes (performing the same function for different amino acids); 2) they are associated with a distinctive clinical syndrome; 3) they are mutually exclusive; individual patients have only a single anti-synthetase; and 4) strong immunogenetic associations have been described (10).

Anti-ARSs have each been associated with a similar distinct syndrome referred to as “anti-synthetase syndrome” disease characterized by myositis with a high frequency of interstitial lung disease (ILD) and arthritis, as well as an increase when compared to the overall myositis population in Raynaud’s phenomenon, fever with exacerbations, and “mechanic’s hands (a hyperkeratosis with fissuring and hyperpigmentation along the radial and palmar aspects of the fingers resembling dirty horizontal lines associated with manual labor)” (8–10).

Although the similarities between patients with different anti-synthetases are prominent, certain differences have been observed. One important difference is that patients with anti-PL-12 are more likely than anti-Jo-1 patients to have ILD either without myositis or with subclinical signs of muscle disease. Clinically significant myositis was seen in 60% of US patients with anti-PL-12 (12, 13), whereas none of 6 Japanese patients with anti-PL-12 antibodies fulfilled criteria for myositis (14). In this issue of the Journal, Handa et al (15) reported a patient with anti-PL-12 antibodies who developed interstitial pneumonia and severe pulmonary hypertension without any clinical symptoms of myositis. With respect to ILD, this patient showed marked elevation of the diaphragm similar to “shrinking lung” and NSIP as confirmed by lung histology, compatible with the features of patients with anti-synthetases. ILD is one of the major features of the anti-synthetase syndrome, and Raynaud’s phenomenon and arthritis, as seen in some anti-PL-12 patients, are also felt to be part of the syndrome. The syndrome associated with anti-PL-12 may be one end of the spectrum of antisynthetases patients. This highlights the clinical importance of looking for such antibodies in patients with ILD even if no signs of myositis or of connective tissue diseases are present. It should be noted that the case reported by Handa et al had pulmonary hypertension with intimal proliferation in the muscular pulmonary arteries in his lung histology (15). Further studies are necessary to clarify the association between anti-synthetases and pulmonary hypertension due to vascular lesion, since the numbers of patients have been limited.

ARS molecules and their proteolytic fragments generated during inflammation and apoptosis have recently been shown to possess chemoattractant properties and generate an ARS-specific autoimmune responses in myositis and ILD (16). However, the association between the pathogenesis and the immune response to these molecules remains unknown, and further studies could provide insight into the etiologic mechanisms of myositis and ILD.
References


