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Aminoacyl-tRNA Synthetases in Idiopathic Inflammatory Myopathies: An Update on Immunopathogenic Significance, Clinical and Therapeutic Implications

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1. Introduction

Polymyositis and dermatomyositis, the most important disease subsets in idiopathic inflammatory myopathies (IIMs), are heterogeneous conditions classically defined by a wide clinical spectrum including proximal skeletal muscle weakness, skin lesions and systemic organ involvement, particularly interstitial lung disease, in conjunction with biochemical and histopathological background of varying degrees of muscle inflammation (Gunawardena et al., 2008; Gunawardena et al., 2009; Mimori et al., 2007).

Although the exact etiology is still controversial, there is increasing evidence of aberrant autoimmunity in both entities, closely linked to different patterns of myositis-specific (MSAs) and myositis-associated autoantibodies (MAAs) (Gunawardena et al., 2009; Mimori et al., 2007).

Currently recognized as disease biomarkers, myositis-specific autoantibodies have been identified as key players in IIMs, promoting several pathogenic pathways as they target cytoplasmic and nuclear proteins involved in basic cellular processes (protein synthesis, nuclear transcription and translocation), but also being directly connected to phenotype disease profiles (Betteridge et al., 2007; Gunawardena et al., 2008; Gunawardena et al., 2009; Mimori et al., 2007).

While several subsets of myositis-specific autoantibodies targeting both classic (aminoacyl-tRNA synthetases, ARSs, signal recognition particle, SRP, and Mi-2) and newly identified (MJ, PMS1, CADM140, p-155/p-140, SAE) autoantigens have been fully described in polymyositis and dermatomyositis (Gunawardena et al., 2009; Hengstman et al., 2004; Suber et al., 2008), the most widespread group of myositis-specific autoantibodies is represented by anti-aminoacyl-tRNA synthetase autoantibodies (Gunawardena et al., 2008; Gunawardena et al., 2009).

Advancing knowledge in the field of synthetases, either antigenic or non-antigenic subtypes, has been reflected in critical association between genotype, serotype, clinical phenotype and

therapeutic potential in IIMs (Gunawardena et al., 2008; Gunawardena et al., 2009; Mammen, 2010).

In this review we emphasize current concepts regarding the pathogenic role, clinical significance and potential therapeutic implications of aminoacyl-tRNA synthetases and their specific autoantibodies in idiopathic inflammatory myopathies.

2. Aminoacyl-tRNA synthetases and their specific autoantibodies

New findings on classical and novel aminoacyl-tRNA synthetases and their corresponding autoantibodies are analyzed in this section.

2.1 Aminoacyl-tRNA synthetases (ARSs)

The aminoacyl-transfer (t) RNA synthetases (ARSs), one of the major targets for autoimmune response in IIMs, represent a distinct group of cytoplasmic enzymes that catalyze the binding of specific aminoacids to their cognate transfer RNAs (tRNAs) in an energy-dependent manner (Hirakata, 2005; Mimori et al., 2007; Wikipedia, 2011).

The ARSs are functionally-related, ubiquitously expressed enzymes involved in protein synthesis (Betteridge et al., 2007; Gunawardena et al., 2009, Shirakawa et al. 2005). A unique, immunologically and enzymatically distinct aminoacyl-tRNA is characteristically assigned to each of the currently known 20 aminoacids (Hirakata, 2005; Mammen, 2010), transferring the appropriate aminoacid to an elongated polypeptide chain (Mammen, 2010).

Eight autoantigenic synthetases have been identified so far. Six out of eight are recognized as classical ARSs and are represented by Jo-1 (histidyl-tRNA synthetase: HisRS), PL-7 (threonyl-tRNA synthetase: ThrRS), PL-12 (alanyl-tRNA synthetase: AlaRS), EJ (glycyl-tRNA synthetase: GlyRS), OJ (isoleucyl-tRNA synthetase: IsoRS) and KS (asparaginyl-tRNA synthetase: AsnRS) (Hirakata, 2005; 7, Mimori et al, 2007; Shirakawa et al., 2005).

Additionally, two novel subsets of synthetases have been recently described as being autoantigenic, including Zo (phenylalanyl-tRNA synthetase: PheRS) and YRS or Ha (α and β chains of tyrosyl-tRNA synthetase: TyrRS), respectively (Betteridge et al., 2007; Mimori et al., 2007).

Specific autoantibodies targeting the aforementioned synthetases have been commonly encountered in connective tissue disorders, particularly in 25 to 35% of patients with polymyositis and dermatomyositis (Hirakata, 2005; Mimori et al., 2007; Park et al., 2008).

Based on distinct enzymatic properties, sequence motifs, molecular structure and the site of initial aminoacylation, ARSs can be divided in two main classes (Betteridge et al., 2007; Hirakata, 2005; Woese et al., 2000; Wikipedia, 2011). Class I ARSs comprises a multi-enzymatic complex with anti-synthetasic specificity for nine different amino acids, whereas Class II ARSs are typically found free and uncomplexed in the cellular cytoplasm. Since OJ or isoleucyl-tRNA synthase is part of such multi-enzyme complex, specific anti-OJ antibodies can react also against multiple synthetases; however, the specific anti-OJ pattern is not shaped (Betteridge et al., 2007; Hirakata, 2005; Woese et al., 2000). On the other hand, five classical synthetases, both Jo-1 and non-Jo1 subtypes (PL-7, PL-12, EJ and KS), are further classified as Class II members.

It is widely accepted that not all synthetases are autoantigenic in patients diagnosed with either polymyositis or dermatomyositis (Hirakata, 2005). Besides, ARSs are not randomly targeted as several autoantibodies like anti-Jo-1 are more prevalent than the others

(Hirakata, 2005; Mimori et al., 2007), perhaps directly related to their accessibility and expression on the cell surface (Hirakata, 2005).

2.2 Anti-aminoacyl-tRNA synthetases auto-antibodies

Overall, eight different autoantibodies reacting with autoantigenic ARSs have been recognized, specifically described as anti-Jo-1 and anti-non Jo-1 antibodies. The anti-non-Jo-1 subtypes refer to us as anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, anti-KS, anti-Zo and anti-YRS or anti-Ha antibodies (Hirakata, 2005; Mimori et al., 2007; Solomon et al., 2011).

Several characteristics of these anti-ARSs autoantibodies have been emphasized (Betteridge et al., 2009; Hirakata, 2005; Solomon et al., 2011; Targoff, 2008):

- they focus on functionally related protein enzymes (synthetases) implicated in normal vital cellular cycle, specifically targeting muscle and lung tissue;
- they are highly selective, each autoantibody being directed to only one synthetase;
- they are mutually exclusive in a given patient, with a few exception only a single anti-synthetase being typically found;
- they are generally associated with particular phenotypes, a characteristic clinical syndrome being known as "anti-synthetase syndrome", although distinct profiles are defined for each autoantibody; and
- they are associated with particular genotypes.

Even thought to represent only disease biomarkers, it seems that anti-synthetase autoantibodies are active players in the immunopathogenesis of polymyositis and dermatomyositis. However, if the anti-ARSs autoantibodies are simply epiphenomena or directly linked to disease mechanisms remain an open question. Several fascinating paradigms have been effectively anticipated to explain why and how certain intracellular proteins, widely originating in all cellular types, are selectively and specifically targeted in IIMs (Betteridge et al., 2009).

Anti-ARS autoantibodies are associated with anti-synthetase syndrome (ASS), classically defined by several characteristic clinical features including myositis, interstitial lung disease (ILD), arthritis, fever, Raynaud's phenomenon and "mechanic's hands", in addition to other typical skin lesions such as Gottron's papules and heliotrope rash (Betteridge et al., 2007; Betteridge et al., 2009; Gunawardena et al., 2009; Hirakata, 2005). Moreover, distinct associations between certain anti-synthetases profile and corresponding clinical pattern have actually been up-dated.

Specific anti-synthetase autoantibodies detected in polymyositis and dermatomyositis and their target are listed in Table 1.

Anti-synthetase antibody	Target autoantigen (aminoacyl-tRNA synthetase)	Frequency in IIMs (%)
Anti-Jo-1	Histidyl-tRNA synthetase	15 - 20
Anti-non-Jo-1		
• **anti-PL-7**	Threonyl- tRNA synthetase	5 – 10
• **anti-PL-12**	Alanyl- tRNA synthetase	< 5
• **anti-OJ**	Glycyl - tRNA synthetase	5 – 10
• **anti-EJ**	Isoleucyl - tRNA synthetase	< 5
• **anti-KS**	Asparaginyl- tRNA synthetase	< 5
• **anti-Zo**	Phenylalanyl-tRNA synthetase α and β chains	< 1
• **anti-YRS (anti-Ha)**	tyrosyl- tRNA synthetase	< 1

Table 1. Anti-synthetase autoantibidies in IIMs: targets and frequencies.

3. Immunopathogenic significance of aminoacyl-tRNAs in myositis

Recent evidences have highlighted the role of autoantigenic aminoacyl-tRNA synthetases and their specific autoantibodies in the initiation and progression of myositis. Although the exact sequence of events still remains under debate, several pathways are actually proposed including (i) enhanced expression of aminoacyl synthetases in different target tissues, particularly in muscle and lung, (ii) potential role of proteolytic cleavage fragments of aminoacyl-tRNA synthetases generated during inflammation and apoptosis in lesional tissues (muscle and lung), and (iii) autoantigen signaling through chemokine receptors with subsequent amplification of the inflammatory and autoimmune response (Hirakata, 2005).

A detailed insight into the ethiopathogenic mechanisms of myostis, along with genetic susceptibility and adjuvant environmental triggers will be further discussed in this section.

3.1 Enhanced aminoacyl-tRNA synthetase expression in lesional tissues

Increased synthesis of specific antibodies subsets targeting restricted series of autoantiogens in myositis has been extensively debated. Recent findings have suggested that the modification of biochemical structure of different proteins with consecutive augmented antigenicity is essential in guiding their selection as targets (Howard et al, 2003).

Moreover, posttranslational modification of proteins as well as proteolytic cleavage of autoantigens by the direct intervention of either caspases or granzyme B leading to proteolytic fragments with enhanced autoantigenicity might contribute to the initiation and propagation of autoimmunity (Casciola-Rosen et al., 1999; Darrah & Rosen, 2010; Gunawardena et al., 2009; Howard et al, 2003).

It can be hypothesized that up-regulation of certain autoantigens in specific target tissues as muscle and lung play a key role in myositis induction, as the main source of antigens (Betteridge et al., 2009; Mimori et al., 2007). Additionally, based on augmented expression of autoantigens in the lung and skeletal muscle, it has been emphasized the potential significance of distinct microenvironments in determining the specific autoimmune response in IIMs with or without lung involvement (Betteridge et al., 2009; Levine et al., 2007).

Current reports have indicated increased expression of autoantigens, both myositis-specific and myositis- associated subgroups, in muscle fibers from patients with IIMs, particularly in damaged and regenerating cells (Casciola-Rosen et al., 2005). While most autoantigens are frequently expressed in a tissue-restricted manner, aminoacyl-tRNA synthetases are targeted only in autoimmune myositis and, therefore, markedly expressed in injured muscle (Betteridge et al., 2009; Gunawardena et al., 2008; Gunawardena et al., 2009; Mimori et al., 2007).

Enhanced ARSs expression was mainly described for histidyl-tRNAsynthetase (Jo-1), supporting the hypothesis that the presence of challenger autoantigens during reparative myogenesis promotes aberrant autoimmune response (Betteridge et al., 2009; Gunawardena et al., 2008; Gunawardena et al., 2009; Mimori et al., 2007).

Concomitant up-regulation of major histocompatibility complex (MHC) class I has been already reported in the affected muscle cells, while either very low or normal levels of

myositis-specific and associated antigens are detected in normal skeletal muscle (Betteridge et al., 2009; Mimori et al., 2007).

3.2 Proteolytic granzyme B cleavage of aminoacyl-tRNA synthetase and intervention in interstitial lung disease

It is well known that the autoantigenic fragments resulted by the specific intervention of granzyme B serine protease on aminoacyl-tRNA synthetase substrates are actually essential for myositis induction and development during IIMs (Betteridge et al., 2009; Casciola-Rosen et al., 1999; Darrah & Rosen, 2010; Levine et al., 2003; Levine et al, 2007).

Besides, it has been demonstrated that the susceptibility of these antigenic synthetases to cleavage by granzyme B is highly predictive of autoantigen status in myositis (Casciola-Rosen et al., 1999). Not only histidyl-tRNA, but also two other synthetases, isoleucyl-tRNA and alanyl-tRNA synthetases, are cleaved by granzyme B leading to the release of autoantigenic epitopes (Betteridge et al., 2009; Casciola-Rosen et al., 1999; Levine et al, 2007).

Current reports support also the hypothesis that the expression of different autoantigens is not uniformly defined across all tissues and may be modified in disease-specific milieu such as inflamed muscle and lung in patients with polymyositis and dermatomyositis (Levine et al, 2007).

Interestingly, two isoforms of autoantigenic His-RS with different susceptibility to cleavage by proteolytic enzymes, and, subsequent, distinct immunogenic properties have been recently identified (Katsumata et al, 2007; Levine et al, 2007; Mammen, 2010); the granzyme B cleavage site has been detected only in the novel described conformation. Furthermore, although the overall expression of His-RS/Jo-1 in specific target tissues (muscle, lung) is the same, the novel isoform is highly expressed in the epithelium of the lung and may be one factor that generates auto-immunity at this level (Labirua & Lundberg, 2010; Lundberg & Grundtman, 2008; Mammen, 2010). Cleavage with granzyme B result in the generation of cryptic Jo-1 fragments with increased antigenicity and subsequent immune response (Shirakawa et al., 2005).

As a consequence, the aforementioned paradigm that distinct microenvironments may influence disease expression was highlighted with the identification of high expression of this new Jo-1 conformation resulted by proteolytic cleavage in the lung (Casciola-Rosen et al., 1999; Darrah & Rosen, 2010; Labirua & Lundberg, 2010; Levine et al, 2007; Lundberg & Grundtman, 2008).

Furthermore, it has been proposed that the initiating target tissue for the autoimmune response in the anti-Jo-1 syndrome is the lung with secondary attack of muscle (Gunawerdana et al., 2009). In addition, a modification of aminoacyl-tRNA synthetases in the lung could lead to production of autoantibodies (antisynthetase antibodies), a second, event being required for the immune reaction to direct against muscle or other organs (Gunawardena et al., 2008). How the anti-Jo-1 immune response originating in the lung might be redirected to skeletal muscle cells still remain an open question (Mammen, 2010).

3.3 Pro-inflammatory and chemo-attractant properties of autoantigenic aminoacyl-tRNA synthetases

Aminoacyl-tRNA synthetases and their proteolytic fragments as a result of inflammatory and apoptotic processes seem to hold chemo-attractant properties, inducing specific autoimmune response in IIMs (Hirakata, 2005).

Recent works have demonstrated that enhanced expression of autoantigenic ARSs as well as specific cytokines and chemokines pattern are broadly involved in the initial recruitment

and amplification of muscle-specific inflammatory response, since ARSs exhibit significant pro-inflammatory and specifically chemo-attractant potential (Betteridge et al. 2007; Betteridge et al. 2009; Howard, 2006).

Furthermore, the chemo-attractant properties of ARSs might contribute to their selection as targets in myositis, not only in muscle but also in lung tissue (Howard et al., 2002). This may therefore suggest a role for tRNA synthetases in the pathogenesis of myositis and interstitial lung disease itself (Betteridge et al., 2007, Betteridge et al., 2009; Howard, 2006).

Advanced studies on the ability of aminoacyl-tRNA synthetases to induce leukocyte migration have revealed distinct profiles according to the ARSs subset (Howard et al, 2003).

Therefore, histidyl-, asparaginyl- and tyrosyl-tRNA syntetases feature chemo-attractant properties and promote CD4+ and CD8+ lymphocytes, interleukin (IL)-2-activated monocytes and immature dendritic cells migration through the intervention of CCR5 and CCR3 receptors. Indeed, while His-RS specifically functions as a nonchemokine chemo-attractant for cells expressing CCR5 (Howard et al, 2003; Mammen, 2010), Asn-RS is known to generate the migration of CCR3-bearing cells (Howard et al, 2003; Kron et al., 2005).

Additionally, both aminoacyl-tRNA synthetases hold the potential to attract immature dendritic cells, participating in the initiation of an adaptive immune response with subsequent autoantibody synthesis and perpetuation of autoimmune-mediated muscle damage (Howard et al, 2003; Mammen, 2010). In fact, most autoantigens are chemotactic for immature dendritic cells, enhancing their ability to connect the innate and the adaptive immune systems (Howard, 2006).

Further, both His-tRNA and Asn-tRNA synthetases induce the activation and subsequent migration of newly cells expressing their chemokine receptor. In turn, these leukocytes perpetuate the vicious circle by releasing a wide range of other chemokines and activating other immune cells leading to magnification of inflammatory process during IIMs (Howard, 2006).

Conversely, neutrophils, mature dendritic cells and unstimulated monocytes are not influenced by the presence of ARSs (Gunawardena et al., 2009; Howard et al, 2006).

On the other hand, non-antigenic aspartyl- and lysyl-tRNA synthetases do not exert proinflammatory chemo-attractant properties, as such ARSs do not activate chemokine receptors (Gunawardena et al., 2009; Howard et al, 2003; Howard et al, 2006).

Finally, there is now increase evidence that the local abundance of pro-inflammatory autoantigenic ARSs (perhaps liberated from damaged and regenerating muscle cells) may not only provide the reason for autoantibody synthesis, but also may expand the inflammatory process and immune-mediated muscle damage (Howard et al, 2003; Kron et al., 2005; Mammen, 2010).

3.4 Anti-Jo-1 autoantibodies

It was already emphasized that not only antigenic synthetases, but also their specific autoantibodies might contribute to IIMs pathogenesis (Gunawerdana et al., 2008). This model has been validated for anti-Jo-1 autoantibodies, particularly for the association between anti-SSA/Ro-52 (and not anti-SSA/Ro-62) and anti-Jo-1, recognized as endogeneous type 1 IFN-inducer (Betteridge et al., 2009; Gunawerdana et al., 2008; Labirua & Lundberg, 2010).

The co-existence of anti-SSA/Ro with anti-Jo-1 has been reported in up to 60% of anti-Jo-1 positivity cases and seems to be essentially involved in promoting IFN synthesis (Betteridge et al., 2009; Eloranta et al., 2007; Gunawerdana et al., 2008). Moreover, up-regulation of type-1 IFN-induced genes has been depicted in IIMs (Betteridge et al., 2009; Walsh et al., 2007).

On the other hand, it is well known that IFN type 1 plays a role in the pathogenesis of myositis, being fundamentally related to disease propagation (Betteridge et al., 2009).

3.5 Cancer, myositis and anti-aminoacyl-tRNA synthetases

Since the relationship between myositis, particularly adult dermatomyositis, and cancers is well establish, there is increasing evidence for the role of the members of aminoacyl-tRNA synthetases family as autoantigenic targets in malignancies (Betteridge et al., 2009; Chinoy et al., 2007; Mimori et al., 2007); while most studies concentrate on the contribution of hystidil-tRNA, tyrosyl-tRNA, isoleucyl-tRNA, phenylalanyl-tRNA and glycil-tRNA synthetases in malignancy-associated myositis, recent data focus on preferential expression of the alpha-chain of phenylalanyl-tRNA synthetase not only in interstiatial lung disease and solid lung tumours, but also in acute myeloid leukaemia (Betteridge et al., 2009). In addition, Jo-1 is highly expressed in lung and breast adenocarcinoma (Betteridge et al., 2009; Mimori et al., 2007).

Furthermore, it has been suggested that there may be a relative increased expression of the proteolytic enzymes such as granzyme B in carcinoma cells, with subsequent increase in autoimmune fragments and cryptic epitopes, and aberrant autoimmune response in skeletal muscle (Betteridge et al., 2009; Mimori et al., 2007). Additionally research is mandatory to support the cross-reactivity to tumor-related antigens in muscle (Betteridge et al., 2009; Mimori et al., 2007).

3.6 Environmental factors

It is widely accepted that myositis occurs in genetically susceptible recipients and that external antigens could trigger an aberrant immune response in target tissues such as lungs or skeletal muscle (Gunawardena et al., 2009; Mimori et al., 2007). Besides, the paradigm of myositis with or without interstitial lung disease has been extensively highlighted based on the link between immunogenetic profiles, autoimmune targets and clinical phenotype (Betteridge et al., 2009; Labirua & Lundberg, 2010; Targoff, 2008).

Additional evidence is directed towards the key role of infection in the development of muscular damage, particularly the interaction between myogenic RNA viruses with tRNA-like structures and ARSs, with consecutive abnormal autoimmunity face to cryptic epitopes (Betteridge et al., 2009; Gunawardena et al., 2009; Mimori et al., 2007).

Molecular mimicry between myositic autoantigenic ARS substrates and viral proteins with increasing antigenicity represents an attractive hypothesis that may modulate the immune response and the development of autoimmune myositis (Mimori et al., 2007).

Also, current data support the role of several geoclimatic variables and seasonal patterns in the development of specific serologic myositis subsets; thus, in patients with anti-ARS autoantibodies, particularly anti-Jo-1 positive cases, the onset of myositios seems to peak in spring (Gunawardena et al., 2009; Sarkar et al., 2005).

4. Clinical significance of aminoacyl-tRNA synthetases and management of anti-synthetase syndrome

Considerable progress focusing on the striking association between serotype and clinical phenotype has been made in myositis.

Whereas highly selective, mutually exclusive and associated with particular genotypes with few exceptions, anti-synthetase autoantibodies are strongest associated with the anti-

synthetase syndrome, a disease subset characterized by a broad clinical spectrum including varying degrees of (i) interstitial lung disease (ILD), (ii) myositis, (iii) non-erosive (poly)arthritis, (iv) fever, (v) Raynaud's phenomenon and (vi) "mechanic's hand" meaning hyperkeratosis with fissuring and hyperpigmentation along the radial and palmar aspects of the fingers (Betteridge et al., 2007; Hirakata, 2005; Mimori et al., 2007; Solomon et al., 2011).
More detailed clinical features, investigations and specific management of patients with anti-ARS antibodies have been described in several recent reports (Betteridge et al., 2009; Hirakata, 2005; Koenig, 2007; Solomon et al., 2011).
Current findings on autoantibodies in anti-synthetase syndrome have already provided important information about clinical phenotypes, course and prognosis related to anti-ARSs status (Lundberg & Grundtman, 2008; Labirua & Lundberg, 2010).
Therefore, data about antibody profile may predict the clinical course of interstitial lung disease in patients with polymyositis and dermatomyositis (Yoshifuji et al., 2006; Labirua & Lundberg, 2010; Mimori et al., 2007); anti-ARSs positive patients had significantly higher frequency of lung involvement than negative cases (70-95% versus 40%) (Mimori et al., 2007). 70% or more of the anti-ARSs positive cases have ILD and only 40-50% muscle pathology, milder than in anti-ARSs negative patients and even subclinical (Labirua & Lundberg, 2010; Lundberg & Grundtman, 2008). Moreover, in the majority of anti-ARSs positive disease, ILD was diagnosed at the same time or before the onset of myositis (Mimori et al., 2007). There is increasing evidence that ILD is commonly associated with anti-non-Jo-1 positivity, particularly with the presence of anti-PL-7 and anti-PL-12 antibodies (Labirua & Lundberg, 2010; Targoff, 2008).
Anti-ARSs positivity in patients with ILD and myositis showed more favorable clinical outcomes with better response to first-line corticosteroids, but developed significant higher recurrence rate versus anti-ARSs negative cases (Labirua & Lundberg, 2010; Mimori et al., 2007). Conversely, it seems that the 2-year prognosis of pulmonary function was not different based on anti-ARSs status (Mimori et al., 2007).
The detection of anti-ARS antibodies is an important predictor for late-onset skeletal muscle pathology in patients with ILD and the clinical course of ILD in myositis (Mimori et al., 2007).
Although patients with anti-synthetase syndrome typically develop common clinical signs and symptoms, there is increasing evidence that autoantibody profile is associated with particular clinical subgroups (Labirua & Lundberg, 2010; Mimori et al., 2007; Sato et al., 2007; Targoff, 2008). However, the exact mechanisms responsible for this clinical diversity are still unknown.
Detailed insights into clinical picture of distinct anti-synthetase syndrome are further presented and summarized in table 2.

4.1 Anti-Jo-1 positive anti-synthetase syndrome

Anti-Jo-1 (anti-HisRS) autoantibody. Anti-Jo-1 was the first discovered and characterized autoantibody from the eight currently described anti-synthetases and, in the mean time, the most common anti-ARSs antibody (Betteridge et al., 2009; Solomon et al., 2011). Most anti-Jo-1 positive patients have been diagnosed with polymyositis (20-30%), while only 5 to 10% of cases have dermatomyositis; overall, nearly 75% of all anti-ARS cases present with anti-Jo-1 positivity (Labirua & Lundberg, 2010; Mileti et al., 2009) and anti-Jo-1 is found in 15 to 20 % of all myositis patients (Mimori et al., 2007).

Anti-ARSs antibody	Anti-synthetase syndrome cinical spectrum	Clinical subsets
Anti-Jo-1	**Myositis**	Arthritis (75%); Raynaud (50%); mechanic's hand (20%)
Anti-PL-7	**Lung involvement** interstitial pneumonia	Interstitial lung disease (up to 100%); infrequent myositis (40%); polymyositis/ scleroderma overlap syndrome
Anti-PL-12	**Skin involvement** mechanic's hands Gottron's papules	Interstitial lung disease (70-100%); pulmonary hypertension; myositis (0-50% to 60-100%); amyopatic ASS (60%); Raynaud (40-100%); rare mechanic's hand
Anti-OJ	**Joint involvement** non erosive (poly)arthritis	Interstitial lung disease (95%); rare myositis or Raynaudphenomenon
Anti-KS	**Fever**	Interstitial lung disease
Anti-Zo	**Raynaud phenomenon**	Severe non-specific interstitial pneumonia, proximal myopathy, Raynaud and arthralgia
Anti-YRS/Ha		Skin rash, muscle weakness, interstitial lung disease and arthritis

Table 2. Anti-aminoacyl-tRNA synthetase antibodies, anti-synthetase syndrome and particular clinical phenotipes.

Certain genotypic, immunological, histopathological and clinical characteristics have been demonstrated among anti-Jo-1 positive patients, with particular relevance for their prognosis (Solomon et al., 2011; Zampieri et al., 2005).
Recent studies on the association between anti-Jo-1 levels and myositis activity have shown the presence of a direct correlation, even if modest, with creatine kinase levels, myositis, articular and pulmonary disease status (Gunawardena et al., 2009; Stone et al., 2007). Furthermore, it seems that anti-Jo-1 positivity is the strongest predictor of ILD in polymyositis and dermatomyositis, over 70% of those patients featuring lung disease (Solomon et al., 2011). The true incidence of myositis in anti-Jo-1 anti-synthetase syndrome is difficult to evaluate, since either biochemical or clinical significant disease might be reported (Mileti et al., 2009; Solomon et al., 2011).
A particular subset of anti-Jo-1 positive anti-synthetase syndrome has been described in patients with the association between anti-Jo-1 and anti-SSA/Ro-52; the clinical phenotype of such patients showed severe extensive lung pathology (interstiytial lung fibrosis), with higher activity and damage scores and adverse outcomes, even with aggressive immunosupresive therapy (Labirua & Lundberg, 2010)

4.2 Anti-Jo-1 negative anti-synthetase syndromes

Anti-PL-7 (anti-ThrRS) autoantibody. Clinical characteristics of anti-PL-7 positive anti-synthetase syndrome have also been described. Compared to anti-Jo-1 positive ASS, patients

with anti-PL-7 positivity appear to have a higher incidence of pulmonary disease (up to 100%) associated with a lower incidence of myositis (about 40%) (Labirua & Lundberg, 2010; Mimori et al., 2007; Solomon et al., 2011). Lower serum muscle enzymes (creatinine kinase) and milder muscle pathology in Japanese cases, as well as polymyositis–scleroderma overlap syndrome with idiopathic interstitial pneumonitis, arthritis and sclerodactyly have been also reported in patients with anti-PL7 autoantibodies (Gunawardena et al., 2009; Mimori et al., 2007; Sato et al., 2007).

Anti-PL-12 (anti-AlaRS) autoantibodys. It should be noted that the clinical spectrum of anti-PL-12 positive anti-synthetase syndrome varies from interstitial lung disease (70-100%) to myositis (earlier reports 60-100%, but recent ones with a smaller proportion of 0-50%) and Raynaud's phenomenon (40-100%), but rare mechanic's hand (Hirakata, 2005; Kalluri et al., 2009; Labirua & Lundberg, 2010; Solomon et al., 2011; Tzioufas, 2001).

Moreover, compared to anti-Jo-1 positive anti-synthetase syndrome, patients with anti-PL-12 positivity account for higher incidence of lung and lower incidence of muscle pathology (Gunawardena et al., 2009; Hervier et al., 2010). In the mean time, anti-PL-12 antibodies were also revealed in up to 60% of cases presenting with amyopatic anti-synthetase syndrome and non-specific interstitial pneumonia (Gunawardena et al., 2009; Hirakata, 2005; Solomon et al., 2011).

Reports of higher pulmonary hypertension with hystologically proven intimal proliferation in the pulmonary arteries, and esophageal involvement have been registered in a limited number of cases (Hirakata, 2005; Labirua & Lundberg, 2010; Solomon et al., 2011). Finally, prognosis seems to depend on severity of ILD and the response to immunosuppressive therapy is variable (Solomon et al., 2011).

Anti-OJ (anti-IsoRS) autoantibody. Anti-OJ antibodies are found in up to 2% of polymyositis and dermatomyositis patients (Sato et al., 2007; Solomon et al., 2011). It is classically accepted the association between interstitial pneumonia and non-Jo-1 anti-ARS antibodies including anti-OJ, the reported prevalence being as high as 95%; furthermore, it seems that patients with lung disease in the absence of clinically apparent myositis are closely related to anti-OJ subset (Betteridge et al., 2009, Gunawardena et al., 2009; Mimori et al., 2007).

Additionally, one study conducted in Japanese patients has recently concluded that the presence of anti-OJ antibodies may distinguish a subtype of anti-ARS syndrome that is more closely associated with ILD than myositis or Raynaud's phenomenon (Mimori et al., 2007; Sato et al., 2007). Moreover, anti-OJ was found to be useful for the diagnosis of patients with ILD with or without myositis (Sato et al., 2007).

Anti-KS (anti-AsnRS) autoantibody. Clinical and immunogenetic characteristics have recently focused on interstitial pneumonia that may predominate in ASS with non-Jo-1 anti-ARS antibodies including anti-KS (Gunawardena et al., 2009; Mimori et al., 2007), but also on stronger association with ILD than myositis (Hirakata et al., 2007; Sato et al., 2007).

Anti-Zo (anti-PheRS) autoantibody. The newly identified anti-Zo antibodies directed against autoantigenic alpha and beta chains of PheRS have been recently detected in only one patient with typical features of ASS, namely severe non-specific interstitial pneumonia, proximal myopathy, Raynaud's phenomenon and arthralgia (Betteridge et al., 2009, Mimori et al., 2007; Solomon et al., 2011), by using proteomic analysis of immunopprecipitation and immunoblotting.

Anti-YRS or anti-Ha (anti-TyrRS) autoantibody. Another novel antibody targeting TyrRS has been identified in one case of typical clinical pattern of ASS, particularly the association

between skin rash, muscle weakness, interstitial lung disease and arthritis (Hashish et al., 2005; Mimori et al., 2007).

4.3 Therapeutic consideration

Latest findings have clearly demonstrated the association between aminoacyl-tRNA synthetases and their corresponding specific autoantibodies profiles in patients with IIMs with clinical and therapeutic implications. Moreover, the prevalence, course and severity of interstitial lung disease are significantly influenced by the autoantibody pattern. Accordingly, it seems that crucial decision on possible therapeutic options and subsequent disease outcomes and prognosis are fundamentally guided by the presence of different antibodies subsets (Baer, 2006; Labirua & Lundberg, 2010).

Classically, high doses of steroids, as first-line therapy, in association with second-line immunosuppresors including azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil or tacrolimus could be effective in such patients (Baer, 2006; Hervier et al., 2009; Labirua & Lundberg, 2010). Aggressive therapy such as intravenous immunoglobulins or newer biological are controversial, as there are no data to define firmly long-term disease outcomes in such conditions. Furthermore, advancing knowledge about the potential benefits of rituximab, an anti-CD20 monoclonal antibody, in life threatening antisynthetase syndrome provide conflicting data (Ball et al., 2010; Labirua & Lundberg, 2010; Sem et al., 2009; Vandenbroucke et al., 2009).

An attractive therapeutic approach fundamentally based on antagonists of the targeted chemokine receptors has already been proposed, but not yet validated; the design of such intervention was suggested by the paradigm of chemokine receptor mediated cell migration triggered by autoantigens like aminoacyl-tRNA synthetases (Howard, 2006).

5. Conclusion

There is now emerging evidence supporting the fundamental role of specific aminoacyl-tRNA synthetases and their corresponding autoantibodies in the initiation, propagation and expression of myositis spectrum.

Furthermore, detailed insights into the pathways of myostis emphasizes the critical contribution of up-regulated synthetase expression in target tissues, particularly in muscle and lung, proteolytic cleavage fragments generated during inflammation and apoptosis in specific microenvironments and autoantigen signaling through chemokine receptors with subsequent amplification of the inflammatory and autoimmune response.

The paradigm of distinct anti-aminoacyl-tRNA synthetase autoantibody pattern shaping the clinical features and course of the generic anti-synthetase syndrome to specific phenotypes is actually wide accepted.

Considerable progress focusing on the striking association between serotype and clinical phenotype may be the fundamental for further development of more specific therapeutic options.

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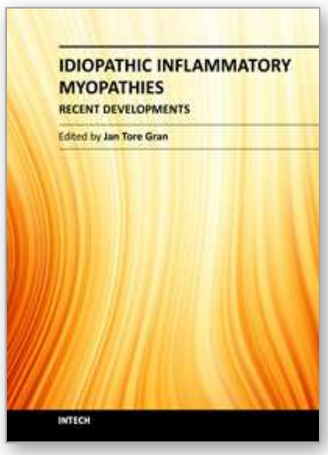

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The term "myositis" covers a variety of disorders often designated "idiopathic inflammatory myopathies". Although they are rather rare compared to other rheumatic diseases, they often cause severe disability and not infrequently increased mortality. The additional involvement of important internal organs such as the heart and lungs, is not uncommon. Thus, there is a great need for a better understanding of the etiopathogenesis of myositis, which may lead to improved treatment and care for these patients. Major advances regarding research and medical treatment have been made during recent years. Of particular importance is the discovery of the Myositis specific autoantibodies, linking immunological and pathological profiles to distinct clinical disease entities. A wide range of aspects of myopathies is covered in the book presented by highly qualified authors, all internationally known for their expertice on inflammatory muscle diseases. The book covers diagnostic, pathological, immunological and therapeutic aspects of myositis.

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