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Serological Aspects of Myositis

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1. Introduction

Idiopathic polymyositis is a chronic inflammatory systemic disease with preponderant infestation of the musculature. Dermatomyositis also involves skin participation (Conrad et al., 2001c; Kalovidouris, 1992; Mimori, 1996). Idiopathic, secondary and paraneoplastic forms of the disease can also be observed. The first report about myositis was given in 1863 by Wagner (Wagner, 1863). Also Unverricht (Unverricht, 1887) reported in 1887 about a case about Myositis, and introduced the concept of dermatomyositis in 1891.
In addition, distinct forms of interstitial myositis, marked by an appearing from foci of inflammation in the muscular interstitium and causative organism conditioned Myositis can be observed. The cause-conditioned myositis can be driven by Toxoplasma gondii or Trichinella spiralis infections (parasitcal myositis) and by Clostridium perfringens or staphylococcal infections (bacterial myositis).
Although myositis is a rather rare disease with an annual incidence of 1:100 000- 280.000 inhabitants, this illness belonging to the collagenosis group is, on account of the therapeutic consequences (Glucocorticoides and Immunsuppressiva) and the clinically often observed muscle discomfort, of considerable differential-diagnostic meaning.
Women are more frequently affected than men, the relation being about 2:1. The age distribution is marked by two maxima, for the juvenile form between the 5th and 15th year and the adult form beyond the 5th decade (2004).
The aetiology is unknown. A toxic infectious genesis is discussed among other causes and, in particular with juvenile dermatomyositis, Coxsackie viruses are considered as the cause, an allergic genesis on account of the appearance of a dermatomyositis after taking of antibiotics or sulphonamides and an immunologic genesis on account of the proof of autoantibodies. The illnesses relation with cancer could originate on the base of immunological cross reactions between tumour antigens and skin-muscle antigens or by a myotoxical substance secreted by the tumour tissue (Burmester et al., 2001). A causal connection between malignant and autoimmune disease could be seen in the disappearance or the decline of myositis symptoms after successful treatment of the tumour (in more than 10 % of the observed cases). Various studies show a raised appearance of cancer of the most different kind with patients with diagnosed Myositis (Manchul et al., 1985; Maoz et al., 1998; Zantos et al., 1994).

2. Serological aspects

Myositis can be serologically diagnosed by autoreactivity against a distinct pattern of autoantibodies. Different subsets of autoantibodies targeting distinct groups of antigens

facilitate a differential diagnosis of the subforms of myositis and discrimination to other autoimmune diseases. Many myositis specific antibodies (MSA) and myositis associated antibodies (MAA) have been found and described, as shown in Table 1 and Table 2.

Antibody	**Nature of antigen**	**prevalence [% of IIM]**	**Clinical relevance**
Myositis specific			
a-Jo1	Histidyl-tRNA synthetase(50 kDa)	30 PM 18-46	antisynthetase syndrom
a-PL7	Threonyl-tRNA synthetase(80 kDa)	<5	
a-PL12	Alanyl-tRNA synthetase(110 kDa)	<5	
a-OJ	Isoleucyl-tRNA synthetase(multienzyme)	<5	
a-EJ	Glycyl-tRNA synthetase(75 kDa)	<5	
a-Ks	Asparaginyl-tRNA-Synthetase	<1	Intersititial lung manifestation
a-YRS	Tyrosyl-tRNA Synthetase	<1	
a-Zo	Phenylalanyl tRNA synthetase	<1	Nonspec interstitial lung disesae
a-SRP	Signal Recognition particle	<5	severe PM
a-Mi-2	218 kDa DNA helicase	15-31	DM
a-KJ	Translation factor	<1	PM
a-Fer	Elongation factor 1 α (48 kDa)	<1	Nodular myositis
a-Mas		<1	
a-MDA 5 a-CADM140	melanoma differentiation-associated gene 5	~ 25% in DM	Interstital lung disease with amyopathic DM
a-TIF1-gamma	transcriptional intermediary factor 1-gamma	~ 15% in DM	DM and malignancy
a-p100/p200	unknown	unknown	Necrotising myopathy w/o other specificities

Table 1. Myositis specific antigens (MSA) targeted by the immune system in myositis.

3. Synthetases

T-RNA-synthetases are the most prominent group of autoantigens targeted in myositis. The antibodies here target a group of proteins all having a similar function in the cell: the binding of an aminoacid to its determined tRNA molecule to form the aminoacyl tRNA which afterwards is used by a ribosome in the protein biosynthesis. There are two classes of tRNA synthetases, class 1 and class 2. Aminoacyl tRNA synthetase molecules are differentiated via the different ways of tRNA binding and characteristically structural motives. Class 1 tRNA synthetases have two highly conserved structural motives while class 2 synthetases have three characteristical motives.

Myositis associated			
a-Ku	DNA PK regulating subunit	5-25	PM SSc overlap
a-PmScl	Nuclear protein complex 110-20 kDa	24	PM SSc overlap
a-U2RNP	U2 small RNP(mRNA splicing factor)	<5	PM SSc overlap
a-DNA PKcs	DNA PK katalytic subunit	<5	PM, PM-SSC overlap
a-Ro52	(RBCC) tripartite motif protein ubiquitin-ligase	5-10	antisynthetase syndrom PM/DM
a-U1RNP	U1 small RNP(mRNA splicing factor)	4-17	PM 100% MCTD
Anti Calpastatin	Calpain Inhibitor	24	Often ass.with RA
Anti Annexin	Ca dep. Phospholipid binding protein	10	-

Table 2. Myositis associated antigens (MAA) targeted by the immune system in myositis.

3.1 Jo-1 histidyl-tRNA-synthetase

Antibodies against the Jo-1 antigen are the most frequent antibodies to be found in Polymyositis/Dermatomyositis (PM/DM). They occur with a prevalence of 20-30%, independent of ethnic and geographical population (Nishikai and Reichlin, 1980). The characterisation of Jo-1 as histidyl-tRNA-synthetase was achieved using immunoprecipitation of $tRNA_{HIS}$ together with a 50 kDa protein by Hirkata et al. in 1992 (Hirakata et al., 1992). Patients with serological reactivity against Jo-1 often suffer from Myositis, Polyarthritis, mechanics hands and Raynaud´s phenomenon (Nishikai and Reichlin, 1980). Like mentioned, tRNA-synthetases can be classed into two subgroups, class 1 and class 2 synthetases. Most synthetases targeted by the immune system in myositis belong two the class 2 group of enzymes. The epitope often is the synthetase enzyme itself, not the tRNA. Therefore myositis with reactivities against Jo-1, PL12, PL7, EJ and OJ is often called the synthetase syndrome. Figure 1 shows the three dimensional structure of the Jo-1 Antigen in a monomeric form (Guex and Peitsch, 1997; Peitsch et al., 2000; Schwede et al., 2003; Aberg et al., 1997), figure 2 shows the tetrameric form as the protein occurs in the cell. Structures have been taken from the protein databank (www.pdb.org). The figure shows how the four subunits interdigitate to form an H-like structure. For visualisation the subunits are shown in different colours. Jo-1 can be easily produced recombinantly using the Baculovirus expression system (Hentschel et al., 2002; Schulte-Pelkum, 2005).

3.2 PL7 threonyl-tRNA-synthetase

Anti PL7 autoantibodies, also called TRS-antibodies, bind the tRNA for threonine and an 80 kDa protein of the threonyl-tRNA-synthetase complex. In indirect immunofluorescence microscopy(IIF) a diffuse fine granular cytoplasmic fluorescence can be seen (Conrad et al., 2001a). The clinical manifestations of patients with anti-TRS- antibodies are similar to the clinical manifestations of patients with anti Jo-1 antibodies, but the prevalence of these reactivities is much lower (2-5 %).

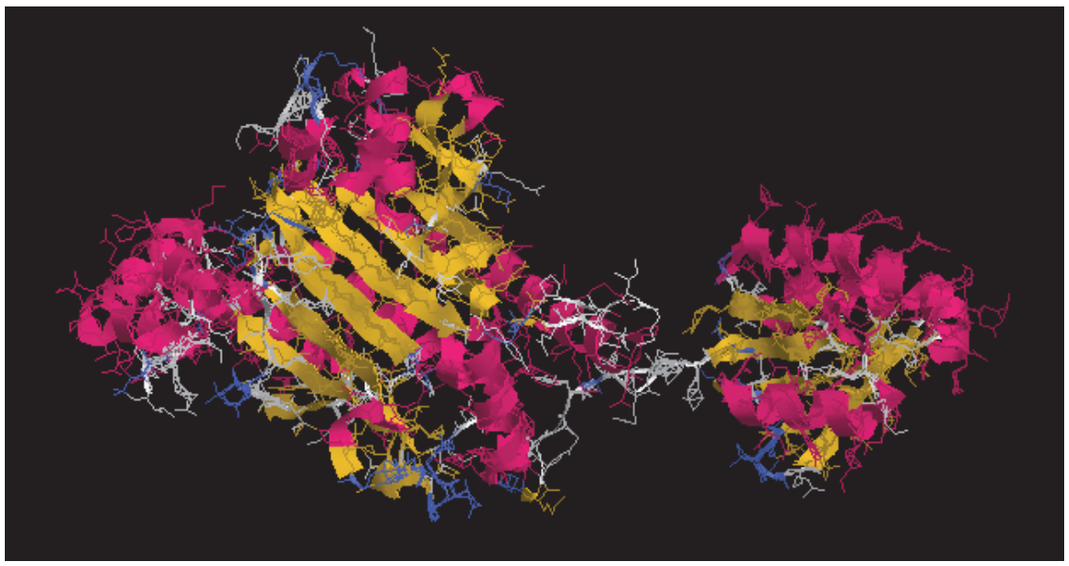

Fig. 1. Histidyl tRNA Ligase monomer, according Aberg et al. (Aberg et al., 1997).

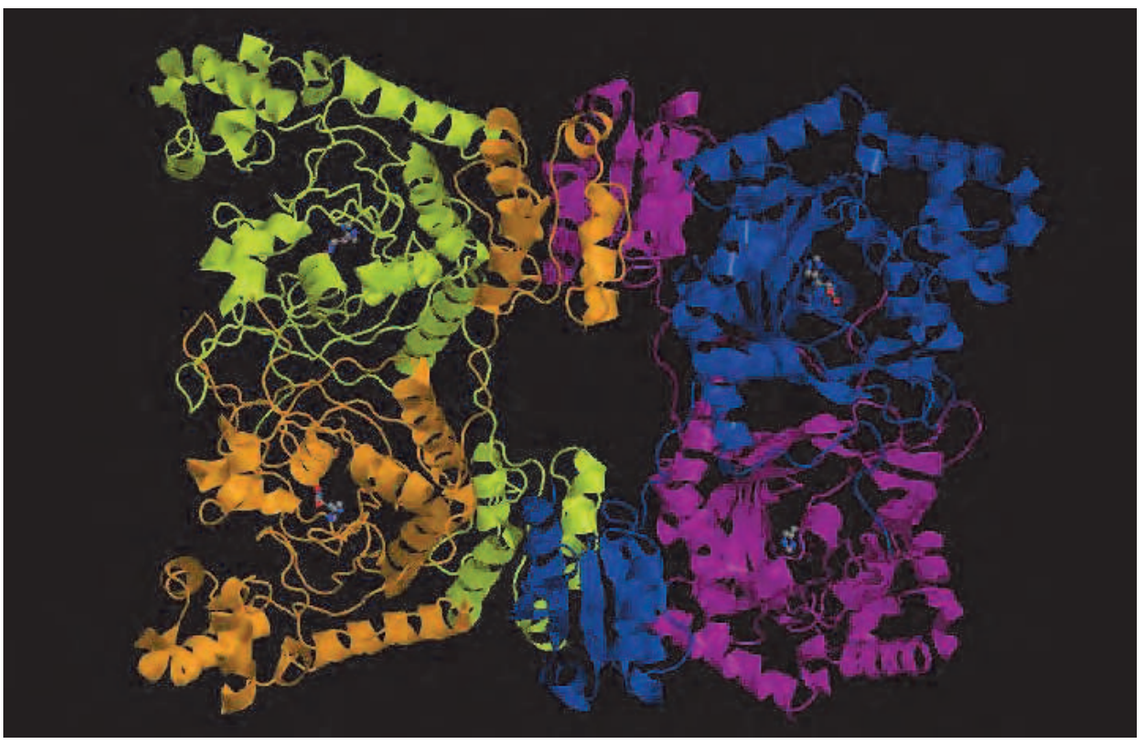

Fig. 2. Histidyl tRNA Ligase tetramer (Aberg et al., 1997).

3.3 PL12 alanyl-tRNA synthetase

Anti-Pl 12-antibodies react with a 110 kDa protein, the alanyl-tRNA synthetase. Sera having this reactivity also contain antibodies directly binding the alanyl aminoacyl tRNA. Next to the relative low prevalence of less than 5 % in myositis, these antibodies are also found in interstitial lung diseases without myositis manifestation (Hirakata et al., 1995).

3.4 EJ glycyl-tRNA synthetase

Anti-EJ-Antibodies bind a 75 kDa-protein of glycyl-tRNA synthetase together with four of the glycyl-tRNAs. This parameter is also of a low frequence. Of interest may be, that anti-EJ antibodies can, like anti Jo-1 antibodies precede the clinical symptoms of myositis (Targoff, 2000). Anti-EJ-antibodies have a prevalence of less than 5 % in myositis patients.

3.5 OJ- isoleucyl-tRNA synthetase

Anti OJ antibodies have Isoleucyl-tRNA synthetases as a main target, but also bind to other synthetases. The main epitope of anti OJ antibodies seems to be directed against a multienzyme complex, containing aminoacyl-tRNA synthetase activity for up to nine different amino acid systems. Anti OJ-antibodies have a prevalence of less than 5 % in myositis

3.6 KS- asparaginyl tRNA-synthetase

Anti KS antibodies bind Asparaginyl tRNA-synthetase. An anti KS-reactivity is not a clear marker for myositis, the majority of patients showing anti KS-reactivity suffers from interstitial lung disease and not from myositis (Hirakata et al., 1999).

3.7 ZO phenylalanyl tRNA synthetase

First described by Betterige (Betteridge et al., 2007) in a patient showing clinical symptoms of an antisynthetase syndrome, but showing no positive serological reaction to the previously identified anti-synthetase autoantibodies. Up to now only one patient has been found with this reactivity.

4. Mi2 antigen: nucleosome remodeling deacetylase

Anti Mi2 Antibodies are well known markers for dermatomyositis with an apparent prevalence of 15-30 % in patients with DM (Conrad et al., 2001b), although the biological function of the Mi2 protein in the cell remained elusive for a long time (Targoff, 2000). Anti Mi2 Antibodies can be found in ca. 20 % of patients suffering from the adult form of dermatomyositis. The function of this protein seems to be to catalyze the unwinding of chromatin structures in chromosomal DNA. The protein possesses one DNA binding domain and one helicase domain (Targoff, 2000; Woodage et al., 1997). It is assumed that the Mi2 complex catalyses an ATP dependand mechanism of Nucleosome remodelling, which makes activated genes accessible on the chromosome. This complex, called Nucleosome Remodeling Deacetylase (NuRD) seems to play a central role in one previously unknown way of gene activation (Zhang et al., 1998). Due to the size of the protein (240 kDa), attempts were made to identify the epitope sequences and to produce a smaller protein for diagnostic purposes. Independently, Mi2 alpha and Mi2 beta were described in 1995 by Ge et al. (Ge et al., 1995) and Seelig et al. (Seelig et al., 1995) wich share a sequential homology of 68 % and have parts of high similarity (Seelig et al., 1996). Sera reacting with the natural form of the Mi2 autoantigen also react with the two different recombinant forms in a highly similar matter. First attempts to solve the three dimensional structure were made by Kwan et al. in 2003 seen in figure 3 (Kwan et al., 2003). The structure of the complex was revealed only lately by Lejon et al. (Lejon et al., 2011a), as shown in figure 4. Mi2 can be easily produced recombinantly using the Baculovirus expression system (Hentschel et al., 2002; Schulte-Pelkum, 2005).

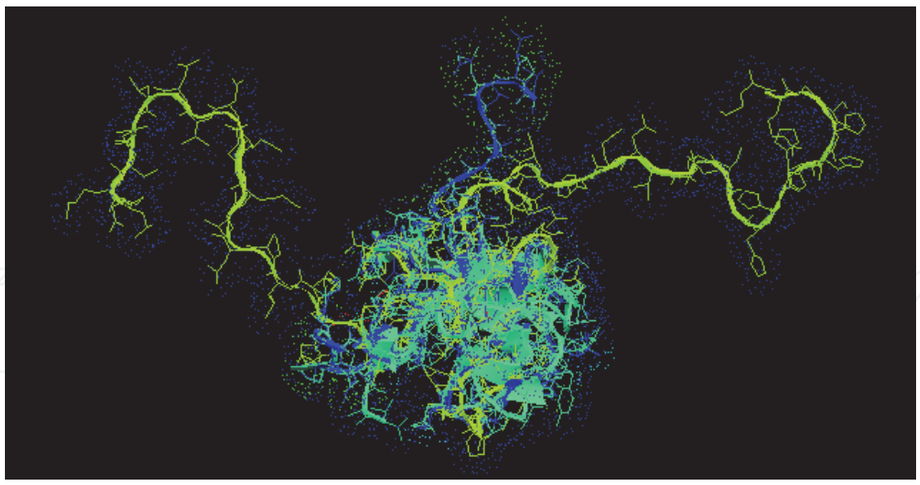

Fig. 3. Chromodomain helicase-DNA-binding protein Mi2 subunit (Kwan et al., 2003).

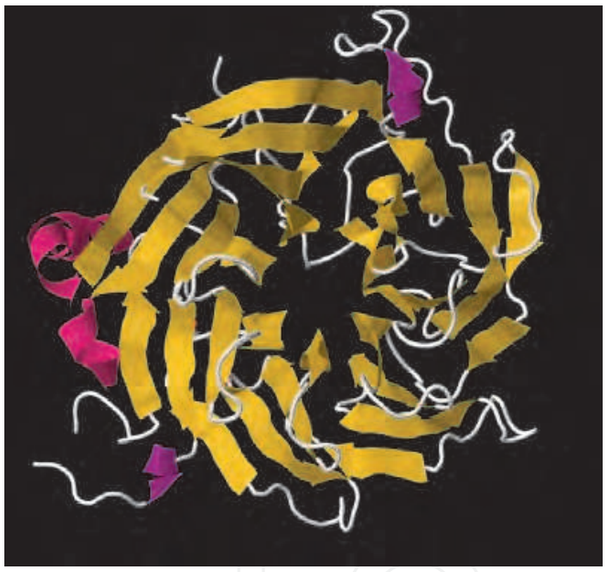

Fig. 4. The NURD complex (Lejon et al., 2011b).

5. PM-Scl- and PM1 Alpha

Although found in high frequency in patients with myositis, autoantibodies against the PM/Scl Antigen are rather myositis associated antibodies (maa) than myositis specific antibodies (msa) (Targoff, 2000). The main antigen, targeted by nearly all anti-PM/Scl positive sera is the PM/Scl 100 protein, which is part of a major protein complex of 11 proteins. Many sera also react with a 75 kDa protein referred to as PM/Scl 75. This protein migrates with an apparent size of 75 kDa in SDS PAGE, but has a calculated size of about 40 kDa, a phenomenon which can be explained by the highly charged carboxyterminal half of the protein. The other proteins of this complex are not targeted by autoantibodies associated with polymyositis. The biological function of the protein complex containing PM/Scl 100 and PM/Scl 75 seems to be analogous to the exosome complex of yeast, in which RNA is

processed. Within this complex the degradation of RNA, the maturation of 5,8 S rRNA and the processing of small nuclear RNAs and AU-rich mRNAs (Raijmakers et al., 2003) is processed. Allmang et al. found out, that size and structure of the yeast exosome complex are the same as the PM/Scl complex in a human cell (Allmang et al., 1999). This complex can be found in the granular parts of the nucleoli and within the nucleoplasma. The PM/Scl 100 protein is the analogue to the yeast Rrp6p-protein, the PM/Scl 75 protein the analogue to the Rrp4p- protein (Van Eenennaam et al., 2002). As there was no three dimensional structure available, Parker and Song published a theoretical structure showing a ring-like structure of the proteins of the exosome complex (Parker and Song, 2004), shown in figure 5.

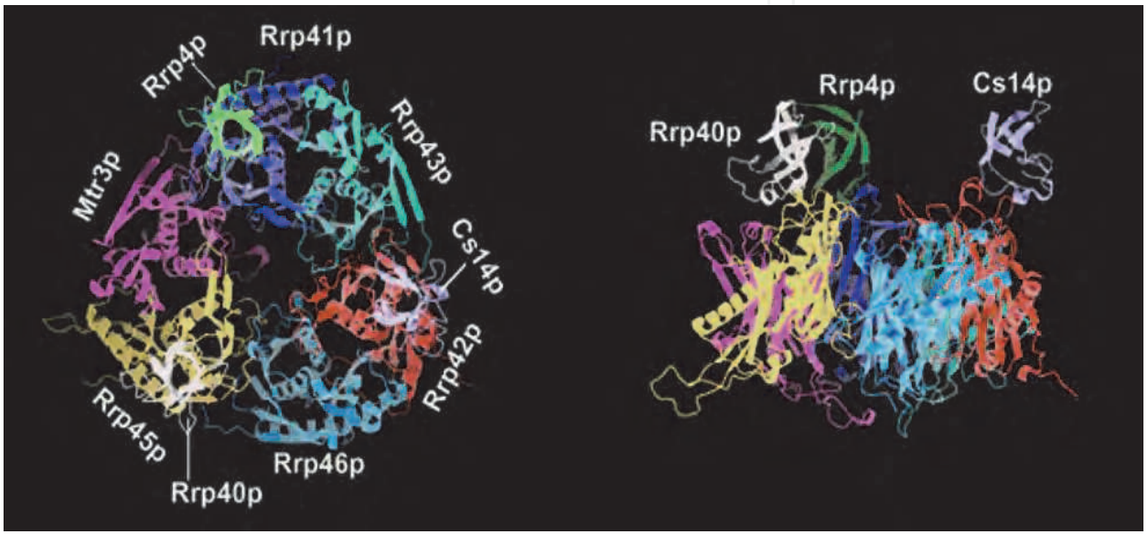

Fig. 5. The hypothetical exosome complex according to Parker et al. (Parker and Song, 2004).

Brouwer et al. (Brouwer et al., 2002) described reactivities towards the exosome complex for patients with idiopathic inflammatory myopathies, overlap syndromes and scleroderma. These reactivities were only found in a combination with reactivity against PM/Scl 100. Initial use of the PM/Scl 100 antigen showed good sensitivity and specificity using a full length 100 kDa antigen (Hentschel et al., 2002). While a debate was going on whether the PM/Scl 75 or the PM/Scl 100 antigen should be used as the preferred antigen for IVD testing (Raijmakers et al., 2004; Mahler and Raijmakers, 2007a; Brouwer et al., 2002), a peptide sequence between amino acids 231 and 245 was found which could be proven as the main site of autoantibody binding in the PM/Scl autoantigen (Bluthner et al., 2000a; Mahler et al., 2003; Mahler and Raijmakers, 2007b). The major epitope of PM/Scl referred to as PM1 alpha, consists of a local alpha helical structure. When an PM1 Alpha ELISA was recently compared to ELISA tests using the recombinant antigens with 75 and 100 kDa respectively, the best discrimination between preselected PM/Scl positive Sera (defined by Immunoblot, indirect immunofluorescence and Immunodiffusion) and control sera was observed with the PM1-Alpha ELISA with an area under the curve, AUC =1.0 compared to the PM/Scl-100 (AUC = 0.98) and PM/Scl-75 ELISA (AUC = 0.85) as revealed by receiver operating characteristics (ROC) analysis. This observation shows an interesting aspect: due to the higher local density of the immunodominant sequence, a peptide can even be the better antigen than the protein sequence it was derived from.

6. Ku –DNA-PK

Antibodies against the Ku-Complex can be found in 1-7 % of myositis patients and in 5 to 25 % of patients suffering from the polymyositis scleroderma overlap syndrome. The Ku autoantigen in its natural form is the regulatory subunit of the DNA phosphokinase complex (DNA-PK). This complex catalyses the non-homologous-end-joining (NHEJ), a repair mechanism for DNA double strand breaks. The complex consists of three subunits: Ku70, Ku80, and the much bigger catalysing subunit. If DNA-double strand breaks occur, e.g. due to ionizing radiation, the Ku-proteins form a dimer around the broken DNA and form a binding site for the 460 kDa catalysing subunit of the DNA-PK complex. The three units form the DNA-PK holoenzyme (Mimori, 1996; Dynan and Yoo, 1998; Wang et al., 1998). This complex also seems to play a central role in the genetic recombination of the different genetic subsequences of antibodies, facilitating the recombination of the different light and heavy chain- coding sequences (VDJ-joining). Here the 75-100 V-genes, the 10-20 D-genes and the 6 J-genes are recombinated freely to form ~12000 different forms of heavy chain genes, which, combined with the 1000 different forms of light (L) chains form up to 10^7 to 10^8 different antibody specificities that form the human immune system. The recombination is catalyzed by enzyme complexes called RAG-1 and RAG-2, the ligation of the DNA strands by the DNA-PK-complex containing the KU-proteins (Manis et al., 1998; Stryer et al., 2002). A defect in the catalytic or regulatory subunit of DNA-PK causes for the severe combined immunodeficiency syndrome as known from SCID-mice. The three dimensional structure of the Ku70/80-DNA binding mechanism was identified in 2001 by Walker et al. (Walker et al., 2001) and shows the spacial interaction of the two Ku-proteins, which, both binding the DNA, mate to form a complex structure, as shown in figure 6. The figure shows the two units in different colours to ease differentiation. The interdigitating structures of the two protein subunits can be clearly seen forming a complex structure surrounding the DNA.

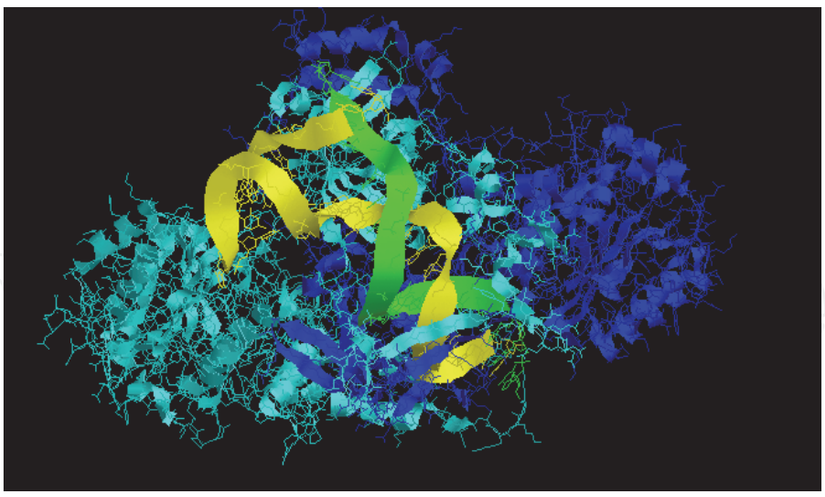

Fig. 6. Ku 70/80 Heterodimer, bound to a DNA molecule (Walker et al., 2001).

The name Ku is derived from the initials of a myositis patient. Anti Ku70/80 antibodies were firstly described by Mimori et al. (Mimori et al., 1981) in a Japanese patient suffering from the polymyositis/scleroderma overlap syndrome. Even in this early stage it was shown, that sometimes autoantibodies against only one of the subunits, but sometimes autoantibodies against both subunits occurred. Antibodies were also detectable against the

whole complex of both regulatory subunits and the catalyzing subunit of DNA-PK. This so called particle antigen was assembled from highly purified native components. Antibodies were found against subunits but also against three dimensional structures of the complete particle antigen (Jafri et al., 2001). The question which one of the two subunits of the Ku antigen offers the higher sensitivity and specificity for myositis diagnosis was raised and Wang et al. (Wang et al., 1997) published a study with showed that about 50 % of the patients showed reactivity against both subunits, 30 % reacted only with the 80 kDa subunit whereas only 3 % showed exclusive reactivity against the 70 kDa Subunit alone. Also of interest in this study was the observation that 18 % of the screened myositis patients had no reactivity against the one or the other subunit, but instead showed antibodies against the heterodimeric form of Ku70/80. For diagnostic purposes a native form of the heterodimeric Ku70/80 complex is the antigen of choice. Experiments showed a far better discrimination using the heterodimeric naitve antigen compared to separately purified subunits, which later were co-coated on an ELISA plate (Schulte-Pelkum, 2005)

7. SRP –Signal recognition particle

Anti Signal recognition particle (SRP, SRP 54) antibodies are rare autoantibodies in myositis with a prevalence of only 5 %, but the anti SRP reactivity coincides with a severe onset of polymyositis (Targoff et al., 1990). Normal corticosteroid treatment usually shows no positive effect on the disease progress on aSRP 54 pos patients. Newer data as described by Hengstman (Hengstman et al., 2006), after conducting an international study with 23 aSRP positive patient samples found anti SRP 54 reactivity as a marker for a necrotising myopathy rather than a classical myositis. The patients symptoms differed only in some cases from the symptoms of the anti-SRP negative myositis control group, but anti SRP pos patients suffered significantly more often from dysphagia and muscle atropy. Also the biopsy samples differed significantly, as there were no myositis specific histological features like inflammatory infiltrates, making anti SRP antibody positive patients a distinct group next to the more classical myositis. Firstly described as an autoantibody by Reeves et al. (Reeves et al., 1986), the SRP is the primary tool for the targeting of the nascent polypeptide chain. proteins which have to be folded and/or glycosylated within the endoplasmatic reticulum have to have a signal peptide sequence on the aminoterminus. The exact structure of this signal sequence seems to be of lesser importance, although all signal-sequences contain repeating motives of hydrophobic aminoacids alternating with serine and threonine residues, which can be found in many different signal sequences moderating the protein targeting. The complex which catalyzes the targeting of the de-novo sequences is the SRP. This complex contains the 7SL-RNA and six proteins of 9, 14, 19, 54, 68 and 72 kDa. The SRP 54 kDa is the protein which directly binds to the signal sequence of the nascent protein. The complex containing ribosome, nascent protein and SRP then binds to the SRP-receptor and to a translocon, a protein on the outside of the rough ER, which then forms a channel inside the ER-lumen. Inside the ER the signal sequence is cleaved by a signal peptidase, while the rest of the protein is now synthesized directly into the lumen of the ER. The three dimensional structure of SRP 54 as shown in figure 7, was determined by Gowda et al. (Gowda et al., 1998; Gowda et al., 1999). The epitopes of SRP 54 showed to be structural epitopes, which is easily understood looking at the structure of the protein, consisting nearly only from Helix-turn-Helix motives. Interestingly Beneviste et al. observed that the aSRP54 antibody titer in a cohort of 8 longitudinally followed patients correlated (Benveniste et al.,

2011) to a high degree with disease activity as measured e.g. by serum creatine kinase activity.

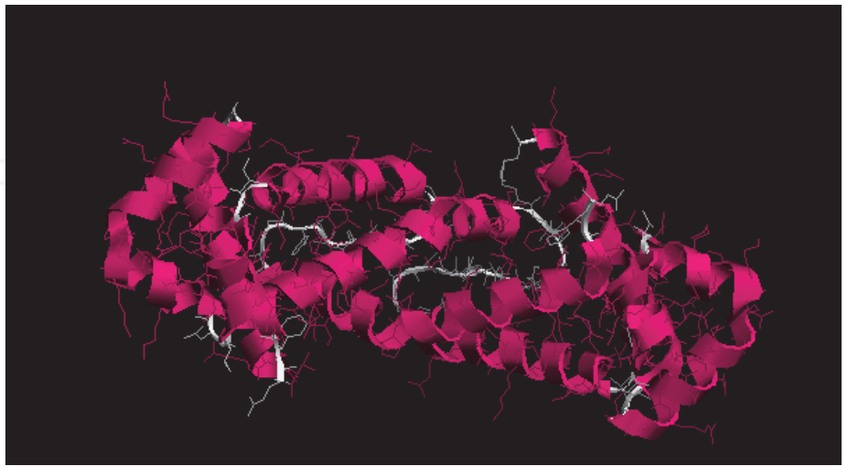

Fig. 7. Structure of SRP 54 (Gowda et al., 1998).

8. CADM140 / MDA 5

Newly shown by Nakashima (Nakashima et al., 2010) the antibody firstly described as a-CADM140 autoantibody recognises the melanoma differentiation-associated Gene 5 protein (MDA 5) which plays a role in innate immune responses. Patients with this reactivity suffer from clinically amyopathic Dermatomyositis (CADM) and have a high risk for life-threatening complications in DM, namely due to the rapidly progressing interstitial lung involvement. After the antibodies were first reported in Japan with a prevalence of around 25 % in DM cohorts (Hoshino et al., 2010), retrospective testing of dermatomyositis groups revealed also in Europe that up to 13 % of DM patients have antibodies against MDA 5, with a clear correlation for severe forms of rapidly progressing ILD and poor prognosis (Labirua and Lundberg, 2010; Fiorentino et al., 2011).

9. TIF1 gamma

First described as the anti P155 antibody the antigen bound by this antibody was revealed to be the TIF1 gamma protein of the tripartite motive family (TRIM 33) like other autoantigens, a zinc finger protein (Targoff et al., 2006a). It is (at the moment) thought to be a transcriptional corepressor. It was described first by Targoff et al. (Targoff et al., 2006b). The clinical manifestations of this reactivity involve high prevalences in dermatomyositis, as reported by Targoff et al., but with a high specificity the occurrence of this MSA correlates with a risk of malignancies as (Kaji et al., 2007). This observation was statistically underlined when Selva O´Canaghan et al. performed a meta analysis for anti TIF 1 gamma antibodies and predictive values for malignancies (Selva-O'Callaghan et al., 2010) and found that anti p155/TIF1 y antibodies have a 70 % sensitivity and a 90 % specificity to detect occult malignancies in DM. The TIF1 gamma protein as described by Venturini et al. shows a strong silencing activity towards gentic promoter sequences. In this promoter sequences, binding affinity of TIF1 gamma is dependant of a single motive (Venturini et al., 1999).

10. U1-snRNP

Antibodies against the U1-RNP complex are, like anti-Ku and anti-PM/Scl antibodies MAA. An association with PM can be found in 4-17 % of myositis cases, whereas these autoantibodies have a prevalence of 100 % in mixed connective tissue disease (MCTD). Absence of this antibodies rules out the diagnosis of MCTD (Conrad et al., 2001a). The U1 RNP consists of three small nuclear ribonuclear proteins (snRNP-"SNURPS") A (34 kDa); C (22 kDa) and the 68 kDa protein. Most prominent is reactivity against the 68 kDa protein. Considering this reactivity the coincidence of an autoimmune disease and a cytomegalo virus infection was discussed (Newkirk et al., 2001), after high rates of coinciding SLE after CMV infections were reported (Newkirk et al., 2001). The U1-snRNP complex belongs to the snRNP protein and is involved in the splicing process of the pre-messenger RNA. In mammalian cells the U1-snRNP binds the 5´splicing site of an intron with a 15 nucleotide consensus sequence of its 165 base long snRNA sequence; the subunits of the U1-RNP then bind to this snRNA. Not all proteins bind directly to the snRNA, RNP-C for example binds with a zinc finger motive to the complex of RNA and the other RNP-proteins (Nelissen et al., 1991). The sequences were published by Sillekens et al (U1-RNP-A), Yamamoto et al. (U1-RNP-C) and by Theissen et al. (U1-RNP-68) (Sillekens et al., 1987; Yamamoto et al., 1988; Theissen et al., 1986). Figure 8 shows the structure of U1-RNP-A bound to RNA (Varani et al., 2000). A scheme of the complete U1 RNP is shown in Figure 9.

11. Ro52

Although Ro52 and Ro60 (SS-A), shown early to be separate proteins (Chan et al., 1991), were initially suggested to be closely related, no direct interaction of the proteins could be conclusively shown. Recent studies indicated that the proteins are even localized in different cell compartments and they perform rather different functions. The 52 kDa Ro antigen was eventually identified as tripartite motif protein (TRIM) 21 ubiquitin-ligase that is over-expressed in peripheral blood mononuclear cells in SjS and SLE patients (Rhodes et al., 2002; Wada and Kamitani, 2006). Ro52 is reported to interact with several different molecules, among them calreticulin and a 78 kDa glucose-regulated protein (GRP78), also known as immunoglobulin heavy chain-binding protein (BIP) and formerly proposed as an early marker for rheumatoid arthritis (Blass et al., 2001). Taking its function into consideration, Ro52 is thought to modify the role or stability of its substrates through ubiquitination, and this modification might result in the Ro52-mediated biological events (Wada and Kamitani, 2006; Gomez-Martin et al., 2008).

12. Association between anti-Ro52 and anti-Ro60 antibodies in different autoimmune diseases

Testing for SS-A/Ro60 and Ro52 with sera from SSA/Ro related autoimmune diseases showed differing prevalences of the two autoantibodies in the different disease entities (see Figure 10). The frequencies of anti-Ro52 antibodies and anti-Ro60 were comparable in all groups except the myositis and scleroderma cohort. The prevalences of anti-Ro52 reactivitiy without anti-Ro60 reactivity varied in the different groups from 14.5 % in SLE to 37.5 % in the myositis group. In the SjS group, 51.7 % of anti-Ro52 sera had also antibodies to Ro60.

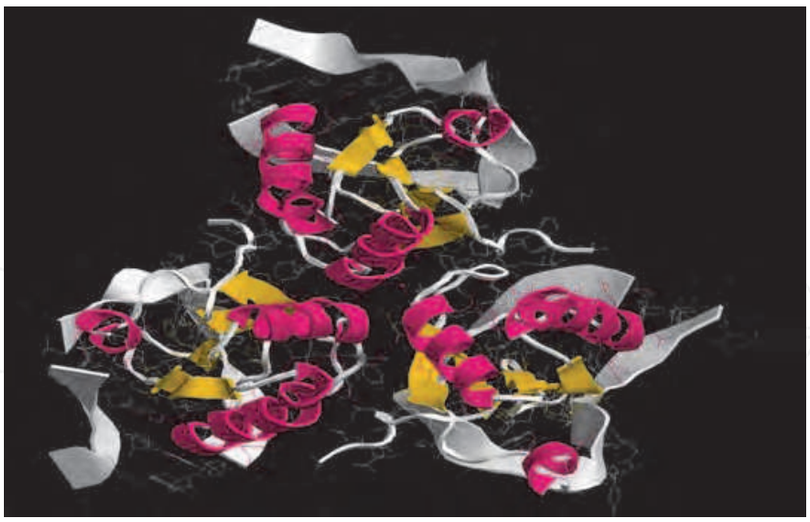

Fig. 8. U1 RNP–A bound to RNA (grey) (Varani et al., 2000).

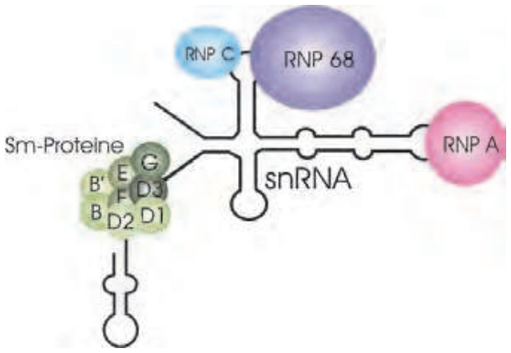

Fig. 9. Schematic view of the snRNP.

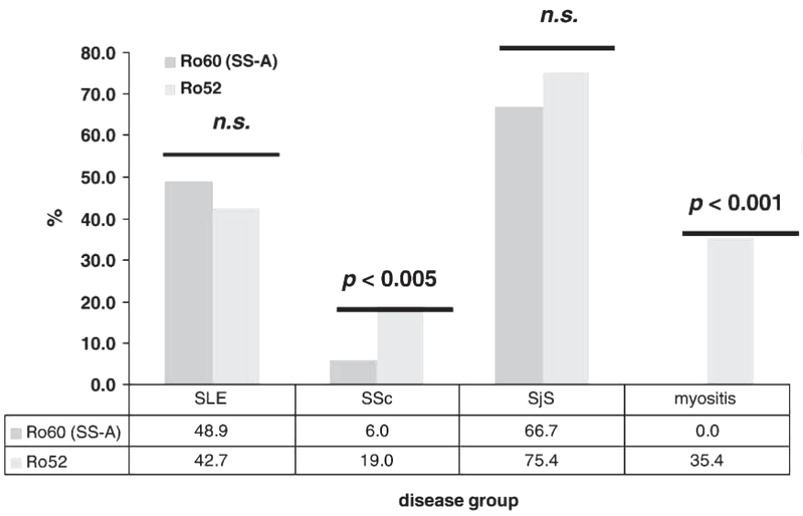

Fig. 10. Anti Ro antibody profiles in different disease groups (Schulte-Pelkum et al., 2008).

13. Coincidence of anti-Ro52 and anti-Jo-1 in patients with polymyositis

A high degree of correlation was found in a group of myositis sera tested for aab against Jo-1 and Ro52: a panel of 43 sera of myositis patients revealed reactivities against Ro52 and Jo-1 in 70 % (p=0.0002, Odds ratio=14.17, kappa=0.54) of Jo-1 positive sera when tested with ELISA (Dr. Fooke Laboratorien) and ALBIA. 22 (24) sera were found positive for anti-Jo-1 by ELISA and ALBIA (numbers in brackets), 16 (17) of these were also found positive for anti-Ro52 (72 % by ELISA, 70.8 % by ALBIA). These observations underline previous conclusions (Peene et al., 2002) that anti-Ro52 is indeed an independent aab in myositis. Rutjes et al. (Rutjes et al., 1997) found anti-Ro52 reactivity in 58 % of Jo-1 positive myositis sera, an observation confirmed in the subsequent years by Rozman et al. (2000), Brouwer et al. (2001) and Koenig et al. (2007) (Rozman et al., 2000; Brouwer et al., 2001; Koenig et al., 2007). In contrast, Langguth et al. (Langguth et al., 2007) indicated that isolated anti-Ro52 reactivity has limited clinical value in a non-obstetric population, a conclusion that could not be confirmed. Our study demonstrated the importance of detecting anti-Ro52 and anti-Ro60 aab separately when considering the diagnosis of patients and in particular myositis patients. This perspective was not included in the study performed by Langguth and colleagues.

It can be concluded that anti-Ro52 clearly differs in reactivity from anti-Ro60 (SS-A): Anti-Ro52 is seen in relatively high frequency in myositis and SSc. Anti-Ro52 has a prevalence of up to 35 % in myositis and in this disease group co-occurs in up to 72 % of anti-Jo-1 positive sera. In our opinion it is strongly recommend that diagnostic assays and kits should test anti-Ro52 and anti-Ro60 (SS-A) separately (Schulte-Pelkum et al., 2008; Schulte-Pelkum et al., 2009).

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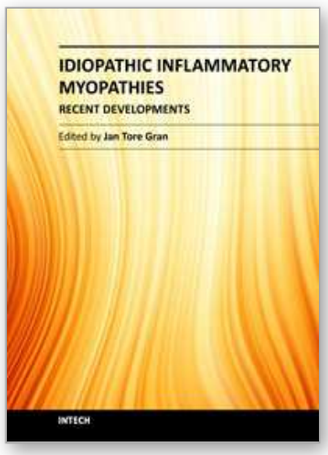

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The term "myositis" covers a variety of disorders often designated "idiopathic inflammatory myopathies". Although they are rather rare compared to other rheumatic diseases, they often cause severe disability and not infrequently increased mortality. 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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