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The Expanding Role of Anti-Ku in Autoimmune Disorders

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Abstract

Anti-Ku antibodies, directed against the Ku heterodimer (p70/p80), have emerged as significant biomarkers in a spectrum of autoimmune diseases, including systemic lupus erythematosus (SLE), polymyositis/dermatomyositis (PM/DM), and mixed connective tissue disease (MCTD) [1]. This review explores the expanding clinical implications of anti-Ku, its role in immune system dysregulation, and its association with organ-specific manifestations—particularly in muscular, pulmonary, and cutaneous involvement [2]. The presence of anti-Ku is increasingly linked to overlap syndromes, interstitial lung disease, and resistant forms of inflammatory myopathies [3]. Despite its diagnostic potential, challenges remain regarding its pathogenic relevance and therapeutic targeting [4]. Advances in detection methods, clinical cohort analyses, and immunopathological correlations underscore the need for further research to clarify anti-Ku's role as a prognostic and therapeutic biomarker in systemic autoimmune disorders [5].

Keywords: Anti-Ku antibodies; Autoimmune diseases; Myositis; Interstitial Lung Disease (ILD); Connective tissue disorders

Introduction to Autoimmune Disorders

Autoimmune diseases are characterized by a pathological immune response, which can present with the development of autoantibodies [6]. Autoantibodies can be involved in the development of tissue damage, in the pathogenesis of disease, or can just be epiphenomena that do not affect the overall clinical picture. Anti-Ku conditions belong to the heterogeneous family of autoimmune diseases targeting the nuclear antigen Ku, a heterodimer involved in essential cellular mechanisms such as DNA repair, endocytosis, and gene expression [7]. Pathogenic mechanisms associated with the development of autoimmune disease are numerous and depend on many different factors which can be either genetic or environmental. Autoantibodies represent an attractive target for the diagnosis and, ideally, therapy of autoimmune disorders. They can either directly interfere with the biological activity of the target molecule or can bind the antigen, thus promoting its uptake by antigen presenting cells, inflammation and tissue damage. With respect to the study by Lakota et al. [8], anti-Ku autoantibodies can be present in a wide variety of diseases. Polymyositis/dermatomyositis associated with anti-Ku antibodies is usually more severe and resistant to therapy as compared to other patients with myositis [8]. Anti-Ku autoantibodies mostly recur in patients with mixed connective tissue disease and in a minority of patients with primary Sjögren's syndrome or primary systemic sclerosis [9]. Recently, p70 and p80 anti-Ku autoantibodies have been demonstrated to correlate with specific clinical manifestations in SLE [10].

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Overview of Anti-Ku Antibodies

Anti-Ku antibodies are a unique class of anti-nuclear antibodies that primarily target the Ku protein, p70 and p80, which are a heterodimeric structure belonging to the DNA dependent protein kinase complex [11]. The first publication reporting about anti-Ku antibodies was originally published in 1985, in a group of patients with SLE [12]. Soon, it was recognized that anti-Ku antibodies have been associated with a wide variety of connective tissue diseases, including SLE, scleroderma, dermatomyositis, and mixed connective tissue disease [13]. Although this association has been studied in various populations and different parts of the world, most of this published data is limited to non-AIS populations. According to the present understanding, anti-Ku antibodies are not linked with any specific organ involvement and therefore the association of anti-Ku antibodies with other definitions of autoimmune diseases is still unclear. In comparison to other fully characterized autoantibodies, much remains unknown about the precise mechanisms by which anti-Ku autoantibodies induce autoimmunity. In addition to autoimmune diseases like CTD, it has been suggested that anti-Ku may also be associated with conditions like infectious diseases or donor-specific autoimmunity. Intensive interdisciplinary research over the last two decades has resulted in increase in published data regarding the clinical association of anti-Ku antibodies in AIS. However, despite this growing database, the association between the presence of anti-Ku antibodies in AIS and its relevance in further characterization of the disease population remains unexplored. In an excellent study conducted over an international cohort of 73 anti-Ku-positive patients, it was shown that p70/p80 anti-Ku antibodies are associated with joint/bone features. Further establishing and expanding these findings with the aforementioned cohort may prove to be useful in further understanding the association of anti-Ku antibodies with autoimmune disorders [14].

Pathophysiology of Autoimmune Disorders

Autoimmune disorders involve an immune response that is inappropriately directed against self-proteins. Autoimmunity is characterized by proliferation of autoreactive T and B cells, production of circulating autoantibodies and immune complexes, as well as the presence of immune effector cells and mediators in affected tissues. It is now clear that autoimmunity is a complex polygenic disease that involves genetic susceptibility, environmental triggers, and the presence of effector mechanisms that actually initiate and maintain autoimmune injury. Several autoantigens have been identified which serve as diagnostic and/or prognostic markers, reveal defects in immune regulation, or allow investigation of the pathogenetic mechanisms in animal models of autoimmunity [15]. Directly or indirectly, various receptors purposed to scan nucleic acids could perceive a neuroendocrine tone originating from cell-free DNA or RNA of non-cellular sources, some of which carried by exosomal vesicles. Cytokines initiated nuclear-translatable genes, while hundred more genes behave as "long-term memory" intervals controlled by epigenome masculinization. Genetic studies over the past 20 years also identified numerous new disease-associated regions for most of the common disorders, some of which are now used in risk-stratification approaches [16]. A leading hypothesis is that the glutamatergic system is dysregulated in MDD, with excessive glutamate-induced toxicity induced by chronic stress [17]. T cells and glia release glutamate, leading to increased levels of extracellular glutamate as evidenced by imaging studies in psychiatric disease. Glutamate acts on frontal cortex and hippocampus driving apoptosis and cognitive impairment while blood concentrations of the NMDA receptor antagonist kynurenic acid (KYNA) rise. The NURR1/NUC1 receptor regulates midbrain dopamine neuron development and DA synthesis via dopamine transporter expression. Glutamate induces an upregulation in the NURR1 receptor that causes a toxic downregulation of the catecholamine genes TH and VMAT2 coupled to uncoupled ATP recycling in neurons. Given a neuroanatomically-conserved basal release of glutamate afforded by unassisted vesicular exocytosis independent of transmitter impulse-stimulated vesicular release, it seems likely that a basal activation of purinergic receptors involves ATP stimulation of the cAMP/protein kinase A system. Direct stimulation of the cAMP system is neurotoxic via phosphorylated kinases that dissociate the sodium-potassium ATPase embedding depolarized cation-induced intracellular calcium/calmodulin/Ryk kinase-induced a caspase-9 death pathway. Kynurenines derived from excess glutamate and the purinergic system receptor activation can induce neurotoxicity in a pathway involving the NURR1 receptor snRNP3 repressor [18].

Immune System Dysregulation

The immune system is a network of cells, tissues, and organs that work together to defend the body against attacks by "foreign" invaders. Relevant components of the immune system include white blood cells, such as phagocytes and lymphocytes, and complementary organs like the spleen and thymus. The immune response is driven through an intense network of interactions between various immune cells. It initiates with the recognition of immunogenic antigens and lead to the generation of effector mechanisms leading to the destruction of target cells and the development of memory. Autoimmune disorders are characterized by hypersensitivity reactions resulting from immune system dysregulation against self-antigens. The awareness of autoimmunity and related diseases has significantly expanded in the last decades. There has been accumulating evidence based on

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genetic, demographic, epidemiological, and environmental studies that autoimmunity can be induced by infections, environmental antigens, hormones, and stress factors, leading to autoimmune disease development. Autoimmunity is currently fully-fledged with a new understanding of the initiation of immune responses, tissue infiltration, and target disruption. It seems that the role of innate immune cells like dendritic cells, mast cells, and macrophages has broadened, thus regulating aspects of adaptive immune responses, local tissue microenvironments, and damage.

Genetic Predispositions

In different populations and using as a reference the most frequently employed American or European diagnostic criteria, anti-Ku antibodies have been detected in various undifferentiated autoimmune diseases (UADs) such as undifferentiated connective tissue disease (UCTD), undifferentiated inflammatory myositis, and undifferentiated systemic sclerosis (SSc) or diffuse scleroderma according to the prevalence of anti-Ku antibodies. Although the population was not completely representative of the disease populations from the point of view of disease duration, treatment status, or factors considered in the PCA stratifications, anti-Ku antibodies had been detected predominantly in UCTD and SSc contexts, such as in the most numerous and some less frequent disease populations. The latter is in accordance with earlier studies that reported higher frequencies of anti-Ku antibodies in polymyositis/dermatomyositis and scleroderma. Although the latest cohort with UAD had not included patients with primary myositis, there is a possibility that they were not the first antibody to be detected, or that other factors had pushed patients toward classification. Therefore, further studies are necessary to elucidate the implications of distinctive (and similar) features between closely related diseases and to increase the awareness of anti-Ku in countries where these antibodies have yet to be detected. In studies performed in Japan, the group of UAD patients was smaller than in other countries; nevertheless, the discrimination of the disease populations was confirmed here as well. It is possible that the differences in the clinical presentation might increase the suspicion of specific autoimmune disease during the observation time, resulting in the eventual certainty of diagnosis. The unexpected separation of UCTD from SLE is another area justifiable of study. A majority of the UCTD patients in the present study had some clinical SLE-like symptoms, but the two groups of UCTD and SLE patients were nevertheless clearly distinguished. SLE patients were described to have some specific demographic and clinical presentation characteristics, suggesting that as in the situation with UCTD, other clinical features or laboratory tests might increase the suspicion of ASLE and APSLE earlier than other types of SLE.

Role of Anti-Ku in Muscular Disorders

In terms of muscular disorder, anti-Ku is associated with polymyositis (PM). PM is an autoimmune disorder characterized by symmetric proximal muscle weakness [19]. It can affect the skeletal muscles, heart muscles, or other smooth muscles, resulting in mucosal disease, bowel motility dysfunction, and respiratory failure. Autoantibodies are among the tools for the diagnosis of PM. In a very rare case reported, a 45-year-old woman who was a long-term smoker complained of chest pain. A cardiac CT scan suggested effusion and a large mass that made the pericardium thick and irregular. The woman was diagnosed with anti-Ku-positive PM. Signs of PM such as proximal muscle weakness and difficulty in activities of daily living, complete blood counts revealed no abnormalities, and strict anti-inflammatory medicine was prescribed. Notably, anti-Ku, anti-155/140, and anti-5-HT3R were recorded in the past [20]. In addition, the patient was started on 20 mg methotrexate, and later ceasing ribavirin and starting azathioprine was proposed. PM has been rarely reported in an anti-Ku-positive individual. To the best of the authors' knowledge, this is the first report of an anti-Ku-positive case with cardiac involvement presenting as pericarditis-like chest pain [21].

Myositis and Anti-Ku

Myositis is a rare group of muscle diseases characterized by chronic muscle inflammation. Idiopathic inflammatory myopathies (IIMs) include dermatomyositis (DM), polymyositis (PM), and immune-mediated necrotizing myopathy (IMNM). Myositis causes muscle weakness, with the proximal muscles being the most affected. Autoantibodies to myositis-specific (MAAs) and myositis-associated (MAAs) antigens are present in over 60% of IIM patients, and several autoantibodies have been found to be associated with certain phenotype. Among autoantibodies that belong to the MAA family, anti-Ku is a rare antibody that can be positive in some rheumatic diseases. SLE patients who are anti-Ku positive exhibit a high frequency of lung and joint involvement, but rare ocular and hematological involvement, and this antibody might be related to cardiac involvement [24]. Myositis patients who test positive for anti-Ku antibodies have a higher frequency of SOJ and LCS phenotype compared with the other antibodies. Anti-Ku autoantibodies are most frequently associated with overlapping autoimmune connective tissue diseases (CTD), and a subset of systemic sclerosis but not of systemic lupus erythematosus is defined by isolated anti-Ku autoantibodies. Patients with inflammatory myopathies with anti-Ku antibodies have poor prognosis, and survival is dependent on the presence of associated lung disease. Suspected patients with esophageal dysmotility should undergo upper endoscopy with manometry for early diagnosis. The clinical significance

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of determinants of autoantibody specificity is highlighted, as the presence of isolated SSc-associated autoantibodies is less frequent and does not preclude an unequivocal diagnosis at a later time point. The production of autoantibodies is under the control of the immune system, and genetic determinants, while selected to ultimately target autoantigens, can affect autoantibody specificity. The apparently agonistic epitope spreading and the relatively high frequency of cross-reactivity with other ribonucleoproteins in the Ro family may account for the earlier age at onset of SLE in some anti-Ro52 positive patients.

Clinical Implications

The expanding role of anti-Ku antibodies in autoimmune disorders (ADs) reflects a new direction for research on complex and, in some cases, rare autoimmune conditions. Attention to anti-Ku antibodies will enhance understanding of SLE, SRNS, overlap syndromes, scleroderma, myositis syndromes, and also cross-reactions and reactivity with environmental antigens, especially viruses. The use of solid-phase assays will catalyze further discoveries. Assays distinguishing p70/p80 isoforms of anti-Ku can provide clearer focus on specific diseases. Other solid-phase assays for related antibodies, such as anti-U1 and anti-aggregating proteins, such as La, topoisomerase I, etc., will permit expansive exploration of these lesser-known pathways. Assays for neutralizing anti-Ku antibodies can add a novel and important dynamic to better understand the sometimes-pernicious onset and rapid progression of these poorly understood ADs. Collaboration among laboratories sharing automated solid-phase technology and relevant clinical expertise might be proposed to achieve long-term discovery goals. Translational studies on the biology of Ku autoantigen, including its chromatin binding activity, accessory protein association, diketone and microscopy, stem cell expression and regenerative responsiveness, etc., are timely and important. Ku autoantigen is a dimer composed of p70/p80 subunits, required for all aspects of DNA repair. Ku scatters throughout the nucleus; at sites of damage, introduction of excess Ku increases the number of foci. p70 and p80 subunits transcriptionally control genes. Regulatory pathways will be explored. Autoantibodies to Ku hinder interaction with Ag-loaded MHC, reduce CD4+ T cell interaction, alter migration in vivo, decrease typical CD4+ and CD8+ signal recipient interaction, or influence the early cell cycle. Ku autoantigen was inattentive to transitioning from chromatin binding to AG formation and secreting antibodies. Then an endogenous DNA:AG genome was disclosed–material resulting from chronic lesions or activity of active DNA viruses. Only Ku autoantigen was identified, other autoantigens remained cryptic, e.g. those revealed by genome-wide intensity distribution analysis and, in comparison with conventional assays, with a power fivefold lower.

Anti-Ku and Skin Manifestations

Compared to other anti-nuclear antibodies, the skin manifestations accompanying anti-Ku-positive autoimmune disorders are not widely reported. A few cases of anti-Ku-positive patients with dermatomyositis have been noted. Ku antibodies were measured in serum samples from 82 adult patients with dermatomyositis or the clinically amyopathic variant of dermatomyositis. Ku autoantibodies were noted in sera from 7 of 82 patients (8.5%; 4 with dermatomyositis and 3 with clinically amyopathic dermatomyositis). Anti-Ku-positive clinically amyopathic dermatomyositis was older at disease onset than every other group. Skin lesions did not differ in the positive and negative groups, but no anti-Jo1-positive patients had clinically amyopathic dermatomyositis [22]. All anti-Ku-positive patients were free of cancer. Anti-Ku may be implicated in dermatomyositis or clinically amyopathic dermatomyositis, but whether this is distinct from other skins remains uncertain. Anti-Ku antibody positivity may be associated with some skin manifestations of systemic sclerosis, but more cases and clinical studies would be needed for characterization [23].

An atypical case of acral ischemia following anti-Ku-positive systemic sclerosis was reported. A 50-year-old woman with a subsiding fever and anuric acute kidney injury was admitted. Two months later, necrotizing vasculitis of the fingers gave rise to the development of acral ischemia that led to auto-amputation of the toes and three fingers. The majority of cases were anti-centromere negative, and one was positive for both anti-centromere and anti-Ku antibodies. Anti-Ku antibodies are associated with systemic sclerosis and other autoimmune disorders with predominantly myositis. However, there are also cases in which anti-Ku positivity is associated with a predominantly Sjögren's syndrome-like picture. The goal is to characterize the skin manifestations of anti-Ku-positive patients with systemic connective tissue disease or idiopathic inflammatory myopathy. Clinical data and serum were collected from anti-Ku-positive patients with systemic connective tissue disease or idiopathic inflammatory myopathy. The sera of patients were analyzed for various antibodies. The skin lesions were grouped into four major categories based on cases. The clinical manifestations and relevant serological data of 28 anti-Ku-positive patients were collected. The results of this study may clarify the significance of anti-Ku in skin diseases and may further expand the cognition of the roles of anti-Ku antibodies in systemic autoimmune disorders [24].

Cutaneous Lupus Erythematosus

With cutaneous manifestations being the most common presenting feature of lupus, dermatologists are often the first to encounter these cases. Lupus nonspecific lesions are usually non-specific inflammatory conditions, including, but

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not limited to, alopecia areata, Lichenoids drug eruptions, and urticaria. Each has its own unique challenges in making a diagnosis and management. The dermatoscopic features can be invaluable in differentiating them and thus assist practitioners to begin appropriate management. 15 report the case of an 18-year-old woman highlighting one such condition: urticaria on her temporal region and face-a rare presenting manifestation of systemic lupus erythematosus. Acute cutaneous lupus erythematosus (ACLE) is a dermal condition that could be identified by the apparition of a butterfly rush design. 90% of the ACLE cases are observed in females, and it frequently appears associated with UV exposition. The ACLE lesions are generally visible on the anterior cheek, nose, temples, and forehead. During ACLE development, a discrete or small erythematous macules, papules, and plaques can be observed on the face, which can coalesce for the formation of larger lesions (e.g., elevated plaques or edematous lesions). Other close regions such as the scalp, neck, and earlobes can be affected by the ACLE lesion appearance showing signs of erosions, crusting, and scaling. ACLE patients exhibit a high association with systemic disease since up to 52% of SLE patients display ACLE. In addition, a high proportion of ACLE patients are positive for antinuclear antibodies and display other autoantibodies against dsDNA and Sm (anti-Smith). Due to the involvement of the sun on the pathogenesis of ACLE, the lesions are commonly observed in summer. In addition to direct examination of ACLE lesions by immunofluorescence, a recent study indicates that patients can be distinguished from other types of CLE as they exhibit reduced numbers of CD4+ tissue-resident memory T cells.

Dermatomyositis

The dermatomyositis (DM) is a rare connective tissue disorder characterized by symmetrical proximal muscle weakness and rash on skin, primarily affecting the eyelids, knuckles, and forearm. In DM, autoantibodies to several myositis-specific autoantigens (MSA) have been demonstrated in accordance with the phenotype of DM skin and muscle lesions 17. Of these, antibodies to the Mi-2, which are directed against the chromatin remodeling enzyme, are highly specific for the classic DM phenotype, while such patients have relatively mild muscle involvement. In recent years, anti-NXP-2 antibody, which is directed against a nuclear protein implicated in the transcriptional regulation and chromatin remodeling, has been detected in various autoimmune diseases, including DM. In contrast to anti-Mi-2, patients with anti-NXP-2 exhibit a more severe form of myopathy with a higher frequency of myositis-associated interstitial lung diseases or malignancies. An increasing number of studies have provided evidence that MDA5 antibodies, originally discovered as a cause of the dermatomyositis phenotype associated with necrotizing myositis, are also detected in juvenile dermatomyositis. Patients with these antibodies may have a higher incidence of myositis-associated interstitial lung diseases and a poor prognosis, and their immunopathological findings are different from those of anti-Mi-2-positive and anti-NXP-2-positive DM. In this article, the authors report a case of an anti-Mi-2 and anti-NXP2 double-positive DM patient who exhibited distinct clinical features and was further complicated by anti-MDA5 positivity with an aggressive disease course. A 58-year-old woman with a history of breast cancer treated with modified radical mastectomy, chemotherapy with carboplatin and docetaxel, and radiotherapy was referred to Dermatology for evaluation of skin rash. One month prior to her visit, the patient developed an erythematous rash around the eyes and cheeks, along with a dry cough. A branch of the superficial temporal artery was resected, and a skin biopsy was obtained from the eyelid for histopathological analysis, confirming the diagnosis of interface dermatitis compatible with dermatitis herpetiformis. After several weeks, she developed proximal muscle weakness accompanied by collar and thigh girdle myoplegia. An extensive work-up revealed proximal muscle involvement and an anti-Mi-2 antibody, confirming Dx of DM.

Lung Involvement in Autoimmune Disorders

Pulmonary involvement with interstitial lung disease (ILD) and pulmonary hypertension (PH) is an important feature of autoimmune disorders, including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and mixed connective tissue disease (MCTD). The specific groups of anti-NR/RNP, anti-mRNA, and anti-Ku antibodies, respectively, seem to be more closely related to lung involvement than other specific antibodies, including anti-SS-A/Ro. By focusing on anti-Ku antibodies, commonly found in early or over-diagnosed so-called undifferentiated cases, and the expanding role of anti-Ku in lung involvement, it could be clarified how lung autoimmunity interacts with different underlying mechanisms of autoimmunity. It was observed that distinct localization into nucleolar caps and nuclear speckles, respectively, might explain how anti-Ku interferes with collagen modulation of RNA polymerase II [25]. On the other hand, distinguishing patients of various underlying diseases carrying anti-Ku in a clinically relevant manner could be sought because this provided better understanding and treatment response for patients. SLE is a prototypic autoimmune disease defined by the presence of autoantibodies and an array of systemic symptoms, but the precise mechanisms leading to disease onset and progression remain unknown. Hybridization of RNA isolated from kidneys of an animal model of SLE with a high-density cDNA microarray has shown extensive interstitial over-expression of numerous genes, including transcription factors, chemokines and their receptors, cytokines and membrane-

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bound signalling molecules, pro-inflammatory enzymes, matrix metalloproteinases (MMPs), and their inhibitors, which likely contribute to the complex renal lesions. MMPs and tissue inhibitors of matrix metalloproteinases have been shown to be markedly over-expressed around renal tubules and glomeruli in both active human lupus nephritis and different animal models of severe lupus nephritis. By taking advantage of a spontaneous laps-derived SLE-prone animal model, it has been possible to compare different stages of disease development. MMP-2 and MMP-9 pre-mRNA splicing and matrix deposition have been studied. An integrated view of lupus nephrites pathogenesis was obtained, thereby improving understanding of lupus kidney disease progression.

Pulmonary Fibrosis

Pulmonary fibrosis (PF) can be idiopathic but is often a consequence of other underlying conditions, including autoimmune rheumatic diseases (ARDs) affecting the lungs. Among the ARDs capable of PF, systemic sclerosis (SSc) and idiopathic inflammatory myopathy (IIM) represent two sclerosis phenotype ARD, while Sjägern's syndrome (SS) is associated with honeycomb lung pathology of interstitial lung disease (ILD). Polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) are the three major subtypes of IIMs. The latter two phenotypes (DM and IBM) appear prone to cancer and are called anti-melanoma differentiation-associated gene 5 (MDA5) positive DM and anti-cytosolic 5'-tri-phosphate-receptor (CTPR) positive IBM, respectively. These phenotypes are grouped as overlap syndromes (with concomitant other ARDs) and exhibit a particular immune response profile characterized by more anti-Ku positiveities. It is increasingly recognized that pulmonary fibrosis associated with ARDs is a distinct disease entity with different underlying pathogenic mechanisms, leading to the discovery of biomarkers such as anti-Ku antibodies (Ku) for the identification of patients who are prone to PF. Ku antibody recognition is widespread, with the majority recognizing Ku 70 kD polypeptide followed by Ku 86 kD polypeptide being largely T cell mediated because T cell lines from a Ku antibody positive patient can induce strong proliferation of autologous PBMCs that is abrogated by CDR mediated depletion of CD4 or CD8 T cell [26].

Interstitial Lung Disease

Interstitial Lung Disease (ILD) is the most serious complication of anti-Ku antibodies. Ku antigens are components of a protein complex involved in DNA repair and V(D)J recombination, including Ku70, Ku80, and the Ku70/80 complex. Anti-Ku is the second most frequent nucleic acid antibody found in patients with Idiopathic Inflammatory Myopathies (IIM), along with anti-Jo1. It is a specific antibody and has been associated with different clinical manifestations of myositis. A subset of anti-Ku-positive patients were identified who presented with ILD that was more extensive and behaved more aggressively than in anti-Jo1-positive patients. Anti-Ku has been previously described in association with ILD and in a cohort of patients with anti-ARS antibodies. Ku68, Ku80, and Ku90 were used as autoantigens in a protein array to identify anti-Ku antibodies. Similar to previously reported findings, among anti-Ku-positive patients, anti-Ku80 antibodies were more prevalent than anti-Ku68 antibodies. Only three patients had the isolate anti-Ku, the remaining patients had anti-ARS and/or anti-Ku. Anti-Ku was the second most frequent autoantibody detected in patients with inflammatory IM-ILD, while it was rarer in patients with myositis-limited IIM. The coexistence of anti-Ku with anti-ARS autoantibodies defines a subset of patients with frequent ILD and relapsing myositis. In the study of ILD-positive anti-Ku patients, anti-Ku was always associated with either anti-ARS or anti-PM/Scl. In the study of the entire population of anti-Ku patients, anti-ARS antibodies were more prevalent in patients with ILD than in patients without (94% vs 6%). The study used an antigen-based immunoprecipitation technique to examine the presence of anti-Ku antibodies in two patients with anti-ARS and ILD. One patient had anti-Ku80, while the other had anti-Ku68 antibodies. Anti-Ku is found in a minority of patients with IIM, especially in patients with anti-ARS and ILD [27].

Diagnostic Approaches for Anti-Ku

Anti-Ku has been detected using various laboratory methods, including dot blot, immunoblotting, immunoprecipitation, enzyme-linked immunosorbent assay, and Western blotting [28]. Apart from methods previously used in laboratory diagnosis, immunofluorescent automated systems have also been developed, which have successfully detected anti-Ku in various connective tissues and diseases. Anti-Ku positivity demonstrates baseline clinical compatibility with Systemic lupus erythematosus and mixed connective tissue disease if associated with anti-U1RNP. When anti-Ku has been detected in focus sclerosis, proposals for screening and laboratory investigations in similar cases needed to follow-up on possible development of connective males' disease are justified. New laboratory techniques of anti-Ku labeling continue to emerge, with autoantibodies to heteronuclear ribonucleoproteins being detected using the cell ELISA technique. This emphasizes the importance of narrowband reporting of anti-Ku subtypes in association with clinical disease, as awareness of Ku subtypes using different approaches is limited, including the screening of breast cancer in the presence of systemic lupus erythematosus or mixed connective tissue disease. However, this emphasizes the need to experimentally induce 20 antigen targets for reconciling and reporting of anti-Ku typing based on abuse in clinical settings. At the same time, basic regulatory

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systems of available common methodologies and approaches represent qualitative bases in the diagnosis of connective tissue diseases and shouldn't be neglected. Additionally, further extensive longitudinal and cross-sectional studies are needed for observational implementation using studio-like designs and questionnaires addressing anti-Ku target testing for both allergenic aspects and profession-related exposures. The reported results shed light on local aspects of anti-Ku in health and disease and can guide international joint research efforts to reach a broader perspective on anti-Ku in health and disease. Autoantibodies against Ku were detected in 9% of the positive SLE patients on a screening with 153 antigens. The antibodies were detected by indirect immunofluorescence on fixed HEp-2 cell line, showing a granular pattern of staining in the nucleoli. Antigenic specificity of the autoantibodies was determined by an ELISA using full-length recombinant Ku70 and Ku80 proteins. Sera from 90 patients were screened against Ku70/ Ku80, 75 of them showing one of the several autoantibody specificities recognized by the two antigens under study. The autoantibodies against Ku70 and Ku80 showed good agreement with the percentage of patients having them detected by immunodiffusion. Cohorts of 292 patients with clinically well-defined rheumatic diseases and 14 different Western blotting systems were used to clarify the relationship of autoantibodies to four of the diseases (rheumatoid arthritis, primary Sjögren's syndrome, systemic lupus erythematosus, and scleroderma). Ku-positivity was found in 9.5% of the patients, being most prevalent among those with SLE, whereas patients with scleroderma did not have any Ku-positivity. The European Autoantibody Standardisation Initiative endorsed an international study with the aim to establish optimal conditions for autoantibody detection towards 19 antigens, including Ku70/80. Best performance, in relation to sensitivity, specificity, and need for excessive procedural modifications was achieved by line immunoassays and ELISA techniques. Ku70/80 activity, detectability, and sensitivity were greatly dependent on the standardisation of antigen purity. The expansion of the recognition of Ku-autoantibodies from classical rheumatic diseases to other autoimmune diseases and to chronic inflammatory disorders, accompanied by recognition of various novel antigenic targets, visualised by the coordinated use of different animal and human transgenic protein expression systems in immunoblotting experiments, emphasizes the relevance of this research [29].

Therapeutic Options for Anti-Ku Positive Patients

Because of the relative rarity of the autoantibody and the heterogeneity of the cohort, very little has been published concerning treatment in anti-Ku-positive patients [30]. As with the rest of the wider group of systemic autoimmune diseases, treatment is focused on the disease rather than the specific autoantibody. However, the experience of treating individual patients at various centers is informative. One common feature of the majority of patients with an anti-Ku positive result was high disease activity associated with skin and/or joint involvements at presentation. In almost half of the cases, disease evolvement was severe or rapidly progressive. Unfortunate fatalities did occur. Because the treatment response in some patients seemed inadequate, a more aggressive approach was taken. On the other hand, some patients reported that the organ involvement, which was more pronounced at first presentation, either remained stable or even resolved [22]. In general, it seems that the autoantibody positivity is not better oriented than other biomarkers in assessing prognosis and thus response to treatment at the individual level. It might offer a more profound basis for targeted therapy on a larger scale. Traditional treatment options are available. Non-steroidal anti-inflammatory drugs can be used for arthralgia or arthritis. For MCTD-like manifestations, low and moderate doses of steroid and other immune suppressants can reduce the inflammatory component. This approach often has a high success rate in reducing the outer stiffness and enlargement of the synovium, quietening the inflammatory component. However, it does not affect the disease at the molecular level. Very slowly progressive cases don't seem to require any active intervention. It is symptomatic and needs caution not to over-intervene on the poorly functioning function, which might lead to other compensatory imbalances and aggravation. Regardless of treatment, at a time point, it might need to go on with aggressive treatment for repairing the accumulated damage caused by the unresolved metabolic imbalance. Some patients successfully received recurrent sessions, which resulted in a stable and good recovery both functionally and structurally. This probably reflects some recognition by residual autoantibodies or otherwise either in the autoimmune or inflammatory patterns and opens up a large prospect for exploring the mechanisms behind targeted therapy and personalized treatment approaches. Biologics targeting IL-1β and TNF have a proven record in BS. Autoantibodies against microbial antigens, which are also present in disease tissues and secretion, could trigger rheumatoid arthritis. Some patients with an anti-microbial profilome and suffer intestinal injury and/or joint damage could respond to tailored approaches targeting the microbiome. T and B cell activation could be triggered by tissue damage. Autoantibodies against damage-associated molecular patterns could target TLRs and activate the NF-κB, canonical and non-canonical pathways, leading to production and secretion of pro-inflammatory cytokines and chemokines. Inhibitors against either the receptor or the kinases might dampen off the inflammatory cycle and reverse damage. Anti-Ku positive patients who cannot tolerate treatment with dmards are often referred to biologics. Traditional retinoids

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are another option. A biomarker, created simply by assessing the standard clinical features of dermatomyositis, could target the relevant treatments [25].

Immunosuppressive Therapies

Autoimmune diseases (AD) represent a group of diseases caused by aberrant immune responses directed against self-antigens leading to substantial morbidity and in some cases mortality. The investigation of these diseases started in the late 19th century and although significant advances have been achieved, biobanks are still being established. As the knowledge of the precise mechanisms underlying autoimmune conditions grows, novel and excellent treatment options are being developed and tested. Immunosuppressive therapies are widely used for the treatment of ADs, particularly in their severe, debilitating forms. Broad-spectrum immunosuppressive therapy options include glucocorticoids, calcinerin inhibitors, alkylating agents, inhibitors of purine, or pyrimidine synthesis, and biologic drugs. Mycophenolate mofetil and its active form, mycophenolic acid, is a non-selective inhibitor of inosine monophosphate dehydrogenase and has become the standard immunosuppressive therapy of lupus nephritis, often in combination with glucocorticoids. Targeting downstream mediators such as transcription factors or autophagy-related systems shows promise in SLE-related animal models. mTOR inhibitors that target growth factor-mediated pathways are promising candidates for systemic and organ-specific ADs. Spleen tyrosine kinase (SYK), Bruton's tyrosine kinase (BTK) in the B-cell receptor signaling pathway, phosphoinositide 3-kinase α inhibitors, TLR9, and IL-6 blockade are also promising immunosuppressive and anti-inflammatory therapies, particularly in severe, resistant cases of ADs. Glucocorticoids have been used for many decades and are still first-line potent anti-inflammatory and immunosuppressive drugs that are relatively inexpensive and widely available. Historically, due to their safety profile, attribution of toxicity to other treatments was common. As a result, their safety was unduly downplayed. Nevertheless, real-life experiences confirm that glucocorticoids are associated with significant long-term toxicity: cardiovascular disease, metabolic and endocrine effects, bone, joint, muscle, and cutaneous disorders, neuropsychiatric disease, and overall increased mortality. Disease-modifying biotherapies are relatively novel treatment modalities for severe and drug-resistant ADs. Global experience has confirmed their potent clinical efficacy, and their safety profile seems to be reassuring. Additionally, the agent and route of administration can induce different pharmacokinetics and safety profiles as well. Consequently, in toxin-opposing, severe, and drug-resistant ADs, utilizing a sequential treatment strategy warrants the careful evaluation of biotherapies.

Biologic Agents

The recent introduction of biologic anti-inflammatory agents has transformed the treatment of numerous rheumatological conditions and other autoimmune disorders. These biologic agents are mostly monoclonal antibodies designed to specifically inhibit mediators implicated in the underlying pathophysiology of these conditions. Biologics have significantly improved clinical outcomes and quality of life for many patients. However, these biologic agents may be associated with adverse effects involving multiple systems, including the respiratory tract. There is increasing evidence that these biologics may paradoxically induce an autoimmune process as part of systemic processes and organ-specific autoimmune processes. Such adverse effects related to the respiratory system have not been extensively studied. The wider use of biological agents requires constant awareness of the risks associated with these agents by treating physicians. Lung involvement in patients with rheumatological disorders is common, and a wide spectrum of abnormalities may occur. Several diseases, including SLE, RA, and other spondyloarthropathies, are associated with pulmonary involvement. Lung pathology in SLE is diverse, ranging from acute events such as pleurisy, pneumonitis, pulmonary hemorrhage, or pulmonary emboli to chronic changes such as pulmonary hypertension, non-specific interstitial pneumonitis, or air trapping in the absence of parenchyma or pleura involvement. Pleuritis is a common manifestation of SLE with a benign prognosis; however, pulmonary hemorrhage, often associated with glomerulonephritis, has a poorer prognosis due to high mortality associated with it. Alveolar infiltrates in SLE may also be an indication of infection, and findings on imaging studies may not always indicate disease activity 25. Expansion of the application of anti-Ku has been observed in several disorders such as MS, ulcerative colitis, Crohn’s disease, and RA. However, the safety and effectiveness of this, as with all new, off-label applications, should be addressed through methodologically rigorous clinical trials. Progress on major fronts such as antigen identification, antibody testing and alignment of assays based on antibody specificity are presented. Antigen-mediated B cell depletion and reprogramming may be used as basis for treatment of RA targeting specific disease-associated autoreactivities.

Future Directions in Research

The rapidly developing field of inflammatory and systemic autoimmune diseases has shown a remarkable growing interest in autoantibodies against unknown antigens, especially exogenous stimulus factors and protein nucleic acid-complexes capable of activating innate immunity. In this novel paradigm, detailed research was devoted to better characterize nucleosome-associated autoantibodies such

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as anti-histones and anti-DNA antibodies, which are well-established biomarkers of systemic lupus erythematosus (SLE). During the last few years, studies on nuclear and cytoplasmic proteins in several autoimmune conditions have focused on the properties of these autoantibodies as potential biomarkers and/or their role in auto-immunogenicity. Antinuclear antibodies (ANAs) are the best investigated and characterized autoantibodies in autoimmune diseases. In addition to well-defined nuclear antigens, numerous cytoplasmic autoantibodies against non-RNP protein complexes were identified in distinct autoimmune disorders. The interest on ANAs and non-RNP autoantibodies was boosted by the opening of new frontiers in the understanding of their role in auto-immunity [12]. Two important areas have been explored in this regard: isotype specificity of anti-double-stranded DNA and details on the identity of cytoplasmic autoantigens. Evidence has accumulated that anti native and denatured DNA autoantibodies are produced in different contexts, being polyclonal and polyreactive antibodies generated early in disease induced by environmental stimuli falling into those of danger signals, and IgG isotype switched and more specific monoclonal anti-ssDNA antibodies associated with renal pathology that appear later during disease progression. Understanding the delicate balance of exogenous and endogenous stimuli providing the trigger, the epitope spreading that accompanies the evolution of autoantibody reactivity, the adaptation of the immune response as the disease progresses and subsequently the eventual attenuation of immunity may uncover new preventive therapeutic strategies [30].

Potential Biomarkers

A variety of autoantibodies can be detected in patients with autoimmune disease, and not all of these autoABS are directly pathogenetic. The identification of biomarker autoABS, with a focus on those that represent novel specificities, is therefore emphasized in the initial research described. Utilizing high-throughput and high-resolution protein arrays, novel biomarker autoABS have been identified in several autoimmune diseases, including systemic sclerosis, juvenile dermatomyositis, Sjogren's syndrome, autoimmune bullous diseases, and Takayasu arteritis. With a focus on the diseases themselves and the approaches used to identify the novel biomarker autoABS, initial results and avenues for future research in serological biomarker identification for other autoimmune diseases should be presented. Autoimmune diseases include many types, with a specific autoimmune disease for nearly every organ, from the skin to the brain. Tennis star Jim D. has revealed that he suffers from alopecia areata, an autoimmune disease that leads to hair loss, and American actor-turned-director Selma B. is battling multiple sclerosis. Autoantibodies (auto-Abs) to many self-antigens are found in patients with autoimmune diseases. Auto-Abs are produced by auto-reactive B cells, and some of these auto-Abs may directly or indirectly mediate target tissue injury via various immune mechanisms. Many studies have focused on finding specific biomarkers for single autoimmune diseases. However, there are currently no universal biomarkers for detecting almost all autoimmune diseases. The miRNA profile in the serum is quite stable. In order to determine whether serum miRNAs serve as universal biomarkers for diagnosing autoimmune diseases, serum miRNAs from patients with various autoimmune diseases should be profiled using a high-throughput qPCR array-based system. It may be feasible to search for specific biomarkers for almost all known autoimmune diseases.

Novel Therapeutic Strategies

Despite major advances in the understanding of autoimmunity and the development of novel therapeutic options, there are still enormous unmet needs. Since scalable identification of patients with specific autoAbs will increasingly facilitate selective, personalized therapy in the future, it is thought to be critical to employ the full potential of the available drugs to identify new therapeutic options. The purpose of this chapter is to propose to the clinicians' novel therapeutic strategies, both expressly designed agnostic of autoAb specificities as well as to target specifically anti-Ku. The most potent systemic autoimmune diseases-modifying interventions with the most encouraging preclinical data hence the highest translational potential (the "active" intervention) and candidates with efficacy primarily inferred from anecdotal human studies (the "passive" intervention) are summarized. The former includes the powerful anti-inflammatory and immune-modulating drug daratumumab, monoclonal anti-C4d Ab and the masticatory herb unani medicinal Nigella sativa/excipient thymoquinone in modified delivery methods. Well-established drugs already in clinical use to target the specific elaboration immune pathway of anti-Ku, thereby eliminating a specific disease initiation mechanism in SSc, siRNA to KU and oncolytic virotherapy with human reovirus are proposed as newly introduced therapies to combat pSS. Furthermore, efforts are being made to devise combinations of these modalities, which for many were never considered before. Lastly, mechanistic initiatives to improve current treatments of SLE and sJIA are suggested, the latter due to the burgeoning availability of new related drugs but still a clinically unresolved area. Meanwhile, newly introduced add-on therapeutics such as JAK-inhibitors, Sirdalud, canakinumab and evobrutinib are reviewed as valuable additions with unique working principles to existing therapeutics such as azathioprine through divergent mechanisms. In autoimmune orchitis, future research should evaluate the role of NT-IgD+ B cells, cofactor in autoimmune development and treatments selectively targeting these cells to re-establish tolerance. Metabolomics should be harnessed

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to assess disease activity and new pharmacological agents carefully chosen to not interfere with protective immune responses should be tested.

Conclusion

Autoantibodies against the Ku complex have been described in several autoimmune diseases. Their presence was associated with different clinical manifestations, including myositis, systemic sclerosis, mixed connective tissue disease, and undifferentiated connective tissue disease. However, knowledge regarding the presence of anti-Ku antibodies across a wider spectrum of diseases, including idiopathic inflammatory myopathy, chronic inflammatory demyelinating polyneuropathy, primary systemic vasculitis and its variants, autoimmune cerebellar degeneration, systemic lupus erythematosus and its variants, Sjögren's Syndrome, autoimmune liver disease, and antiphospholipid syndrome, is limited. The aim of this project is to gather a cohort of anti-Ku-positive patients with a wide spectrum of autoimmune disorders and investigate the associations with their disease. In addition to investigating the association of the anti-Ku antibody with distinct clinical manifestations, principal-components analysis was used to visualize the similarities of the phenotypes among the diseases. This novel analysis permitted comparing and illustrating potential transition states on the continuum from systemic lupus erythematosus and Sjögren's Syndrome all the way to autoimmune liver disease and systemic sclerosis [14]. The cohort of 73 anti-Ku-positive patients described by Lacota et al was added to the already collected samples. In addition to investigating the association of the anti-Ku antibody with distinct clinical manifestations, PCA was used to visualize the similarities of the phenotypes among the diseases. This novel analysis permitted comparing and illustrating potential transition states on the continuum from systemic lupus erythematosus and Sjögren's Syndrome all the way to autoimmune liver disease and systemic sclerosis. 73 new patients with anti-Ku antibodies were added to the already collected samples. The analyses extended the investigation of the distinct clinical manifestations of anti-Ku antibodies across a wider spectrum of autoimmune disorders. A significant association was demonstrated for the presence of anti-Ku antibodies and clinically episodic disease course outside the currently considered association with behave or cerebellar symptoms. The PCA visualized the similarities of the diseases based on patients' clinical manifestations. It showed a clear separation of anti-Ku-positive systemic lupus erythematosus and Sjögren's Syndrome patients from autoimmune liver disease and systemic sclerosis, with anti-Ku-positive mixed connective tissue disease and undifferentiated connective tissue disease samples positioned in between [5].

Highlights

- **Anti-Ku antibodies are strongly associated with overlap autoimmune syndromes**, especially involving myositis, systemic sclerosis, and interstitial lung disease.
- **Emerging evidence links anti-Ku positivity to disease severity and therapy resistance**, particularly in polymyositis and ILD.
- **Diagnostic and prognostic utility of anti-Ku is expanding**, but standardized detection and therapeutic implications remain under development.

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