Terminology and definition of 'antinuclear antibodies': history and current debate

Recently, a series of letters has been published in the *Annals of the Rheumatic Diseases*^{1–10} in response to an article by Pisetsky *et al* on the variability of indirect immunofluorescence (IIF) assays for testing for antinuclear antibodies (ANAs) in systemic lupus erythematosus (SLE).¹¹ This discussion has focused on the merits and shortcomings of different assays used in the detection of ANA. Only one of the contributions briefly addresses one of the key questions: 'What is an ANA?'.³ Because the term ANA itself has been judged anachronistic and misleading by many,¹² with efforts to replace it under way,^{13 14} this is not a trivial question to answer. Since the terminology around ANA has developed historically, it is useful to explore the contexts in which these terms originated in order to understand their original definition and the changes therein over time.

From the late 1940s onwards research into the serology of SLE gradually led to the discovery that autoantibodies against components of the cells' nucleus could be found in sera of SLE patients.^{13–21} Because the exact target antigens remained largely unknown at first (except for dsDNA and histone) Holman *et al* coined the term 'antinuclear antibody' or ANA for them.^{22 23} With the advent of IIF testing on HEp-2-cells as standard method for the detection of ANA, it was possible to detect autoantibodies against a range of different target antigens; including antigens of the cytoplasm, the nuclear envelope and the mitotic spindle apparatus. Since these autoantibodies were detected in the context of ANA diagnostics, the term ANA was soon applied to them as well.¹³ This led to a gradual expansion of what was commonly understood to constitute an ANA, without any official consensus on the definition of the term itself, causing many to view it as anachronistic and misleading.

Several proposals have been made on how to improve the situation, perhaps most prominently by the International Consensus on ANA Patterns (ICAP) group, who have suggested the name 'anticellular antibodies'^{12 13} in order to broaden the definition to include cytoplasmic and mitotic antigens as well. There have, however, been other proposals as well, such as 'antibodies to intracellular antigens'.¹⁴ Since the widely shared opinion is that the term 'ANA' is too well known and too embedded in guidelines, classifications and even legislation to be replaced abruptly, other possible solutions include adding a clarifying subtitle to the term ANA (eg, 'ANA—antibodies to intracellular autoantigens'¹⁴ or 'ANA is actually a test that detects autoantibodies to cellular antigens—thus encompassing the whole cellular anatomy and all cellular structures'¹²) when reporting ANA results, possibly leading to a transitional period after which the term ANA might be replaced altogether.^{12 14 24}

Ultimately, the debate about terminology should be a secondary one. First, a consensus should be reached on which autoantibodies are to be described by the new terminology. The US National Library of Medicine in its Medical Subject Headings descriptor 2020 currently defines ANA as 'Autoantibodies directed against various nuclear antigens including DNA, RNA, histones, acidic nuclear proteins, or complexes of these molecular elements. Antinuclear antibodies are found in systemic autoimmune diseases including systemic lupus erythematosus, Sjogren's syndrome, scleroderma, polymyositis, and mixed connective tissue disease'.²⁵ This definition, as well as others currently used, appears at the same time to be too narrow in its exclusion of autoantibodies against non-nuclear antigens, as well as too vague, not specifying whether any antibody against

a nuclear antigen qualifies as an ANA or what, if any, connection there has to be between an ANA and one of the systemic autoimmune diseases, an inexhaustive list of which is given in the definition. Good examples for this are the autoantibodies against DFS70. Since their antigen is nuclear, they are considered to be ANA even in the stricter sense, but evidence has accumulated that the detection of anti-DFS70-autoantibodies, especially when isolated, rather serves to exclude the possibility of a systemic autoimmune disease.²⁶ Therefore, their inclusion in the definition of the term ANA may be counterproductive for any classification or guideline that lists the general presence of ANA as diagnostic criterion for systemic autoimmune diseases.

Therefore, in order for any future nomenclature that is to replace the term ANA to be precise the following questions concerning its definition should be considered.

Considering a definition based on the target antigens: this is the definition with the most historical precedence, the term ANA itself being defined by the nuclear nature of the corresponding antigens. This is probably why proposed new terms such as 'anticellular antibodies' and 'antibodies to intracellular antigens' also focus on the properties of the target antigens. But is it prudent to go down the same road again when the antigens in question are so diverse? Are not the proposed terms, in their attempt to be more inclusive, too vague? What makes an antibody 'anticellular'? Are antibodies against antigens like GAD65 or Hu to be included in the definition of antibodies 'to intracellular antigens'?

Considering a definition based on detection method: since it is the current diagnostic gold standard, should only autoantibodies detectable via IIF using HEp-2-cells be considered, thus including antibodies against cytoplasmic and mitotic antigens, but excluding autoantibodies against antigens such as MDA5²⁷ and HMGR,²⁸ which are tested for via immunoblotting?

Considering a definition based on disease association: should the definition include specifications about possible disease associations, thereby excluding autoantibodies against DFS70? If yes, which diseases are to be included and which to be excluded? What about anti-Ro52, which has no specific disease?²⁹ Should all autoantibodies be included that are associated with a certain ANA-associated systemic autoimmune disease, even if some are currently not considered to be ANA (eg, autoantibodies against the angiotensin II type 1 receptor and the endothelin-1 type A receptor which are associated with systemic sclerosis³⁰)?

The replacement of the term ANA and of the network of related and similarly outdated terms by a clearly defined and widely agreed terminology is still some way off. We hope to have added to the debate some helpful impulses towards a more appropriate nomenclature of autoantibodies.

Robert Daniel Heinrich Markewitz , **Klaus-Peter Wandinger**

Institute of Clinical Chemistry, University Hospital Schleswig Holstein, Lübeck, Germany

Correspondence to Dr Robert Daniel Heinrich Markewitz, Institut für Klinische Chemie, Universitätsklinikum Schleswig-Holstein - Campus Lübeck, Lübeck 23538, Germany; robert.markewitz@uksh.de

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ORCID iD

Robert Daniel Heinrich Markewitz <http://orcid.org/0000-0003-1676-1085>

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