Autoantibodies to intracellular antigens form a large family of immunoglobulins directed to a variety of ubiquitously expressed intracellular molecules, including numerous enzymes, some ribonucleoproteins and double-stranded DNA. These anti-self antibodies have been found to be selectively expressed in sera of patients with several systemic (non-organ-specific) autoimmune diseases, such as systemic sclerosis (SSc), SLE, mixed connective tissue disease, Sjögren's syndrome and idiopathic myopathies. Despite their important diagnostic and prognostic value and their utility in assessing disease activity, little is known about the molecular mechanisms involved in their generation and role in autoimmune diseases nor is it known why particular autoantibodies are preferentially expressed in certain diseases. Here, we review the different lines of research which are presently being conducted to understand how these autoantibodies are generated (e.g. through apoptotic body formation, molecular mimicry and other mechanisms) and how they encounter antigen in order to cause an autoimmune disease. The recently reported mechanism of intracellular immunity mediated by Ro52 (or tripartite motif containing 21, TRIM21) in a cellular model of adenovirus infection is opening new perspectives for studying the effects of autoantibodies once they get inside cells.
mechanisms for V region diversity include VDJ (or VJ) recombination (V1 can recombine with any of D and J), VH and VL assortment and somatic mutations. V, D and J recombination takes place in central lymphoid tissues, while somatic mutation occurs in peripheral lymphoid tissue later on during the immune response [2].

Given the high diversity in their specificity, B- and T-cell receptors can recognize 20%-50% of self proteins prior to positive and negative selection [3]. Nonetheless, only between 3% and 6% of individuals develop an autoimmune disease [4], indicating the existence of mechanisms that prevent B and T cells from attacking one’s own body tissues. These mechanisms are referred to as tolerance. Immune tolerance initially develops in the thymus (for T cells) or bone marrow (for B cells) by means of clonal deletion and RAG gene-dependent editing of B- and T-cell receptors (central tolerance mechanisms). Autoreactive B or T cells that escape these mechanisms and migrate into peripheral lymphoid sites can still be kept in an anergic state through additional mechanisms, including those involving the action of other T cells referred to as regulatory (peripheral tolerance) [5]. Indeed, the constant presence of autoreactive cells in the periphery is demonstrated by the transient appearance of autoantibodies (e.g. anti-nuclear antibodies, rheumatoid factors) following bacterial or viral activation of the immune system in otherwise healthy individuals. In this case, however, no autoimmune damage or disease develops. Even the constant serum expression of an autoantibody population is not necessarily expression of autoimmune disease. For an autoimmune disease to develop, an appropriate genetic background is required along with one or more environmental triggering events, such as infection and exposure to drugs or physical agents (e.g. UV radiation) [6].

2. Organ-specific and non-organ-specific autoimmune diseases

The hallmark of an autoimmune disease is the continuous aggression of body tissues by the immune system [7]. Tissue damage is mediated by humoral, cellular or both arms of the immune system and, in humans, three main clinical settings are observed. First, autoimmunity can be responsible for the main clinical syndrome, causing a primary autoimmune disease such as systemic lupus erythematosus (SLE) or rheumatoid arthritis. Autoimmunity can develop as a complication of an already established disease, such as lymphoproliferative disease or cancer, with the appearance of pathogenic autoantibodies (e.g. antibodies to red blood cells or to myelin basic protein); in some cases it is the first clinical manifestation of an underlying tumor [8]. A third possibility is the transient occurrence of pathogenetic autoantibodies in the context of viral infection, myocarditis or cardiomyopathy [9] or during an ischemic heart attack [10]. In this third case, the damage triggered by these pathogenic autoantibodies usually fades as soon as the primary disease is clinically controlled.

Irrespective of which arm (humoral, cellular or both) of the immune system mediates the tissue or organ damage, the outcome of an autoimmune disease is strongly influenced by the tissue distribution of the target self antigens. Thus, autoimmune diseases have long been subdivided into organ-specific and non-organ-specific subsets [7]. The former are generally characterized by an immune system aggression restricted to one organ or apparatus, as in autoimmune Hashimoto’s thyroiditis [11]. Non-organ-specific autoimmune diseases are characterized by the systemic involvement of the body as a consequence of an autoimmune reaction against different, widely distributed antigens. SLE is considered a prototype of this autoimmune disease subset [12]. Finally, a third subset includes autoimmune diseases that combine immunological and clinical features of both the first and second subsets.

3. Pathogenetic role of autoantibodies and cellular localization of antigens

Autoantibodies can be directly responsible for tissue damage, contribute to tissue lesions or just be an epiphenomenon generated by a polyclonal activation of the immune system [6]. The cellular localization of the target antigen is believed to play a critical role in the pathogenetic potential of autoantibodies [13] (Table 1). It is generally accepted that autoantibodies against integral membrane proteins, namely hormonal receptors and surface proteins expressed by red blood cells and platelets, are usually pathogenic [11,38]. Those against extracellular matrix-associated and soluble molecules might be pathogenic, while those against intracellular antigens usually have no pathogenetic role, unless the antigen can reach the cell surface [39] or can be released into the extracellular space [40].

Pathogenetic autoantibodies to membrane-associated and extracellular antigens have been clearly demonstrated in a number of autoimmune diseases in animal models and in humans, and have been the object of extensive study. The following well-known

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Table 1

<table>
<thead>
<tr>
<th>Cellular location</th>
<th>Antigen</th>
<th>Diseases</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma membrane-associated</td>
<td>Desmoglein 1 and 3</td>
<td>Pemphigus</td>
<td>[14,15]</td>
</tr>
<tr>
<td></td>
<td>Thyroid stimulating hormone receptor</td>
<td>Graves diseases</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td>Platelet-derived growth factor receptor</td>
<td>SSC</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td>Parietal cell-associated specific antigen</td>
<td>Chronic autoimmune gastritis</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td>Blood cell surface molecules (proteins, glycoproteins, polysaccharides)</td>
<td>ITP, Evans syndrome, AHA</td>
<td>[18-20]</td>
</tr>
<tr>
<td></td>
<td>Acetylcholine receptor</td>
<td>Myasthenia gravis</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>Myelin associated protein</td>
<td>Multiple sclerosis, neuropathies</td>
<td>[22]</td>
</tr>
<tr>
<td></td>
<td>Phospholipids</td>
<td>Anti-phospholipid syndrome</td>
<td>[22,24]</td>
</tr>
<tr>
<td></td>
<td>Fc region of Ig, citrullinated protein, collagen</td>
<td>Rheumatoid arthritis</td>
<td>[25,26]</td>
</tr>
<tr>
<td>Extracellular (matrix-associated or soluble)</td>
<td>Double stranded DNA</td>
<td>SLE</td>
<td>[12]</td>
</tr>
<tr>
<td></td>
<td>RNP</td>
<td>MCTD, SLE</td>
<td>[27]</td>
</tr>
<tr>
<td></td>
<td>SSA (Ro 60 and S2) and SSB (La)</td>
<td>SS, SLE, congenital heart block</td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td>Spindle kinesin-like protein</td>
<td>SLE, SS</td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td>DNA topoisomerase (Sc1-70) and centromere-associated proteins</td>
<td>SSC</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>Aminoacyl-tRNA synthetase</td>
<td>Idiopathic myositis</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Peptidyl arginine deiminase-4</td>
<td>Rheumatoid arthritis</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Myeloperoxidase (p-ANCA)</td>
<td>Vasculitides (mainly Wegener granulomatosis)</td>
<td>[34]</td>
</tr>
<tr>
<td>Intracellular</td>
<td>Proteinase 3 (c-ANCA)</td>
<td>Vasculitides (mainly Churg-Strauss, microscopic polyangiitis, necrotizing glomerulonephritis)</td>
<td>[33]</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial associated enzyme (from M1 to M9)</td>
<td>Primary biliary cirrhosis</td>
<td>[35,36]</td>
</tr>
<tr>
<td></td>
<td>Glutamic acid decarboxylase-65</td>
<td>Type 1 diabetes</td>
<td>[37]</td>
</tr>
</tbody>
</table>

ANCA: anti-neutrophil cytoplasmic antibodies; AHA: autoimmune hemolytic anemia; ITP: idiopathic thrombocytopenic purpura; MCTD: mixed connective tissue disease; RNP: ribonucleoprotein; SSC: systemic sclerosis; SS: Sjögren syndrome.
experimental criteria have been outlined as proof of their pathogenetic role [13]: a) ability to induce cellular damage in vitro; b) ability to transfer autoimmunity from mother to fetus; c) ability to passively transfer an autoimmune disease in an animal model; and d) improvement of the clinical signs of disease following autoantibody removal by plasmapheresis. It is noteworthy that when an autoantibody binds to the corresponding membrane or extracellular antigen, tissue damage can be induced by complement activation [41], opsonization [39], or antibody-dependent cell-mediated cytoxicity (ADCC) [39]. When complement is involved in either type II or type III hypersensitivity reactions, there is a well characterized hierarchy in its activation that depends on antibody isotype: IgG1 and IgM are more effective than IgG3 and IgG4 subclasses, whereas IgG2 is the least effective [42]. An additional mechanism occurs when antibodies recognize a cell surface receptor and functionally mimic its corresponding ligand, resulting in blocking or stimulating effects [16,21,43]. Despite this abundant evidence for the pathogenicity of autoantibodies to extracellular antigens, many questions remain unanswered regarding the generation and the potential pathogenic role of autoantibodies to intracellular antigens.

4. Autoantibodies to intracellular antigens: how are they generated?

Intracellular proteins are the preferential targets of autoantibodies in a number of connective tissue diseases, namely systemic sclerosis (SSc), SLE, mixed connective tissue disease, Sjögren’s syndrome and idiopathic myopathies. Although these proteins are ubiquitously expressed in tissues, specific subgroups are preferentially targeted in different autoimmune diseases. Examples include nucleosome and spliceosome (RNP and Sm)-associated proteins in SLE, centromere-associated proteins (CENPs) in Ssc, and translational machinery-associated proteins (aminocetyl-tRNA synthetase) in idiopathic myopathies.

The importance of autoantibodies to intracellular antigens in the clinical assessment of patients has been suggested by the following observations: 1) the correlation between serum titer and disease activity (for example, as seen for anti-DNA in SLE); 2) a clear association between autoantibody specificity and prognosis (e.g. as noted for anti-Scl70 and anti-CENP antibodies in SSc) [30]; and 3) an association between the presence of certain antibodies and the involvement of a particular organ, in the setting of a systemic disease (e.g. a higher incidence of renal involvement in the presence of anti-RNA polymerase I/III and anti-Sm antibodies in Ssc and SLE, respectively) [12,44]. Thus, there has been a trend to include some autoantibodies to intracellular antigens among diagnostic, classification and disease activity criteria.

Despite their clinical importance, no clear proof of their origin or pathogenicity has been obtained so far. Different lines of research have been followed in order to understand why some ubiquitous, intracellularly expressed antigens mount an immune response, why they are preferentially targeted in specific disease subsets and what is the pathogenicity of their corresponding antibodies. To understand the origin of autoantibodies to intracellular antigens, four hypotheses have been explored, namely that they arise following: a) a general dysregulation of the immune system which is at the basis of autoimmune diseases; b) apoptosis leading to exposure of intracellular antigens on the cell surface or their release into the extracellular environment; c) alternations in epigenetic modification; and d) molecular mimicry.

4.1. Dysregulation of the immune system

Two lines of evidence led to the consideration that dysregulation of the immune system could favor the development of autoantibodies. First, it is known that otherwise healthy individuals may express polyreactive natural (or naturally occurring) autoantibodies (even to intracellular antigens) [45,46], which are usually encoded by germ-line immunoglobulin V region genes [47]. Second, a general dysregulation of the immune system characterizes most autoimmune diseases [7]. Thus, it was logical to conclude that such dysregulation might conceivably lead to an uncontrolled expansion of pre-existing polyreactive natural autoantibodies. This possibility was ruled out, however, by the demonstration (with a few exceptions) that the V regions of autoantibodies to intracellular antigens are somatically hypermutated, indicating continuous contact between antigen and B cell epitope during their production in an autoimmune disease (antigen-driven immune response) [48–50].

4.2. Apoptosis and apoptotic blebs

Casciola-Rosen et al. [51] demonstrated that apoptotic cells in SLE release microbodies (apoptotic bodies or blebs) whose membranes express various intracellular antigens, the most frequently being nucleosomes and splicing ribonucleoproteins. Subsequent studies in several autoimmune diseases or disease models reported a defective clearance of these microbodies, resulting in their accumulation and activation of dendritic cells in an adjuvant-like manner [52,53], and in the generation of a potent immune response against their membrane-associated antigens (reviewed in [54]). Similar observations have been reported in autoimmune dermatopolymyositis and even in a human cancer setting. In the first case, histidyl-transfer RNA synthetase was able to activate chemokine receptors on T lymphocytes and immature dendritic cells [55,56]. In the second, B lymphocytes infiltrating human medullary breast carcinoma were found to express B cell receptors against an intracellular antigen (actin) that had translocated to the tumoral cell surface in an early apoptotic phase; the high level of somatic mutation of these receptors provided evidence for an antigen-driven immune response [40].

These data support the notion that the defective clearance of apoptotic bodies may trigger an autoimmune disorder [57] and that the particular reactivity profile of autoantibodies to intracellular antigens, detected in different clinical disorders, could be related to the expression profile of antigens on apoptotic bodies [58].

4.3. Epigenetic modification

Alterations in epigenetic modification may represent an additional mechanism for the generation of autoantibodies to intracellular antigens. Epigenetic modifications include DNA methylation (or demethylation), histone acetylation (or deacetylation) and microRNA expression. Histone acetylation and DNA hypomethylation are usually associated with an up-regulation of transcriptional activity, while deacetylation and hypermethylation have an opposite effect by silencing transcription. MicroRNA (miRNA) are single-stranded RNA of 20–25 nucleotides in length which are believed to regulate the expression of other genes; this regulation occurs by miRNA binding to one or more messenger RNA molecules, resulting in the inhibition of protein translation.

Increasing evidence suggests that epigenetic modification can contribute at several key points in B cell autoimmunity (reviewed in [59]). One of the first pieces of evidence for the role of epigenetic modification in autoantibody production to intracellular antigens came from the understanding that the SLE-like syndrome, observed in patients receiving certain drugs (e.g. hydralazine or procainamide) [60], was due to the drugs' ability to inhibit DNA methylation, as demonstrated in both human cancer cell lines [61] and a mouse model [62]. The association between epigenetic modification and autoimmunity is not limited to SLE [63]. Indeed, in patients with vasculitides caused by anti-neutrophil cytoplasmic antibodies (ANCA), a loss of epigenetic gene silencing was found to contribute to an increased intracellular expression of myeloperoxidase and proteinase-3, the main targets of the antibodies [64]. The aberrant expression of these antigens
may contribute to the development of the corresponding autoantibodies. Finally, over-expression of miRNA-17-92 in lymphocytes was shown to promote autoimmune disease and anti-nuclear antibody production in a mouse model, by interfering with the synthesis of tumor suppressor PTEN and the proapoptotic protein Bim [65].

4.4. Molecular mimicry

Another line of research has explored whether pathogenetic auto-antibodies could be generated by molecular mimicry, i.e. antigenic cross-reactivity between what is believed to be the actual target of an autoantibody and foreign or extracellular self proteins. According to this hypothesis, foreign proteins from bacteria, viruses or fungi elicit antibodies that ultimately cross-react with an intracellular antigen. One way to test this hypothesis is to determine the exact epitope of intracellular antigens targeted by autoantibodies (B cell epitopes) and search for homology with known protein sequences. In this context, several studies (reviewed in [66]) used peptide scanning (pep-scan), which involves testing biological fluids (usually sera) containing antibodies to intracellular antigens for binding specificity to a panel of synthetic peptides (overlapping by 2 to 5 amino acids), synthesized on the basis of the primary sequence of the targeted protein used as template.

Interesting results have emerged from these studies. First, for a number of intracellular antigens it has been possible to define the major antigenic epitopes (although with this method only linear, sequence-dependent epitopes are defined). Second, antigenic cross-reactivity between some of these epitopes and foreign proteins has been discovered. An example is offered by Ro60: one of its epitopes, targeted by anti-Ro60 autoantibodies and spanning amino acids 169–180 (Ro169–180), was found to be antigenically similar to a ribonucleoprotein of *Mycobacterium smegmatis* and to the amino acid stretch S8–72 of the Epstein-Barr nuclear antigen-1 (EBNA-1) latent viral protein [67]. In SSc, the anti-CENP-A-specific major motif (GA)P(RS)RR, identified by pep-scan and mutation analyses and found in three repeats on the NH2-terminus of CENP-A, was discovered to also be present in several intracellular antigens and in EBNA-I [68]. Pooled sera from SSc patients reacted with a peptide of human cytomegalovirus late protein UL94 and the corresponding (affinity-purified) antibodies induced endothelial cytotoxicity in vitro [69]. Additional studies (reviewed in [70]) have highlighted the cross-antigenicity or similarity between intracellular antigens and a number of viral proteins, namely retroviral gag polyproteins, simian virus 40 large T-antigen, HIV TAT proteins, herpes simplex virus type 1 ICP4 and influence B virus C terminal epitope.

Although these data raised interesting questions regarding the possibility that some bacteria, viruses and fungi can trigger the production of antibodies that cross-react with intracellular antigens and cause autoimmune disease, the exact relationship between these pathogens and autoimmune disease remains obscure. Moreover, two criticisms of this hypothesis should be considered. First, many of the intracellular antigen-derived epitopes identified by pep-scan are hidden epitopes [70], i.e. peptide sequences that are not exposed on the intact, folded protein, thus casting doubts on the functional significance of these epitopes in intermolecular interactions. Furthermore, although pep-scan analysis is useful for defining the molecular contact site of a given antibody population, it does not provide information on the amino acids of that epitope that effectively come in contact with the autoantibody. Identification of these critical motif amino acids is required for an accurate database search for epitope cross-reactivity. One way to obtain this information is to use a phage display peptide library (PDPL), which consists of phage clones engineered to express peptides at very high diversity. Peptides can be either linear or cysteine-constrained, thereby permitting the identification of conformational epitopes [71].

Along this line, we panned a PDPL with a subset of antibodies isolated for their specificity to the major antigenic determinant of CENP-A, the intracellular antigen targeted in SSc [72]. This peptide (amino acids 17–30) includes the previously reported motif (GA)P(RS)RR identified by pep-scan and mutation analyses. PDPL panning resulted in the identification of two new motifs, PTPXXGPXXR and P(ST)XGPS, which were quite different from the previously identified one. The first motif, PTPXXGPXXR, was found to also be present in FOXE3, a human protein never described as target of anti-CENP-antibodies. When this motif was used to query a bacterial protein database, only one protein (diacylglycerol O-acyltransferase from *Mycobacterium tuberculosis*) was retrieved, whereas no results were obtained searching a viral protein database (Perosa F. and Dammacco F., unpublished observations). The discrepancies in the results obtained by pep-scan and PDPL panning indicate how critical is the choice of methodology to unveil cross-reactivity between an autoantibody epitope and other proteins.

It should be kept in mind that either of the two analytical methods is useful for assessing the antigenicity of a peptide, i.e. the ability of the peptide (or of the protein containing it) to be recognized by the given antibody population, but neither proves that the peptide (or protein) actually induced the antibodies. In fact, when mice were immunized with peptide Ap17–30, which contains both the (GA)P(RS)RR motif found by mutation analysis [68] and the motif obtained by PDPL panning [72], we were unable to isolate antibodies able to produce the typical immunofluorescent centromere pattern as human anti-Ap17–30 antibodies do [72]. These data reinforce the hypothesis that proteins other than CENP-A might generates anti-CENP-A antibodies in humans.

5. Autoantibodies to intracellular antigens: do they have a pathogenetic role?

To explore the potential pathogenicity of autoantibodies to intracellular antigens that do not reach the plasma membrane or are not released into the extracellular space, an additional line of research has investigated the possibility of antibodies entering into cells and exerting cytopathic effects. Since the first description of anti-ribonucleoprotein antibody entrance into a subset of T lymphocytes (Ty lymphocytes) [73], several reports have shown similar findings for other autoantibodies in different systems. Examples are offered by anti-dsDNA antibodies and their nucleolar localization in living cells [74,75], anti-nuclear antibodies in the nucleolus of kidney and liver cells [76], anti-mitochondrial IgA in primary biliary cirrhosis [77] and anti-SSA and -SSB antibodies in salivary gland epithelial cells (reviewed in [78]). In the majority of these studies, apoptosis was the most commonly described mechanism to explain the final antibody-induced cytopathic effects [74,76]. Antibody penetration into cells may occur via membrane Fc receptor (FcR)-mediated intracellular uptake, but this cannot be considered the only mechanism since cells lacking FcRs also take up antibodies [79]. Additional pathways for intracellular antibody uptake include receptors other than Ig-FcR, e.g. brush border myosin I [79] and non-receptor mechanisms such as electrostatic interaction [80] or endocytosis [81].

To break the dogma that antibody-mediated effector functions occur in the extracellular compartment only, it is important to mention recent research on the intracytosolic protein SSA (Ro52) [82], one of the antigenic targets of autoantibodies detected in Sjögren’s syndrome and SLE. Also referred to as tripartite motif containing 21 (TRIM21), this cytoplasmic protein (an E3 ubiquitin ligase) has been found to be a high-affinity immunoglobulin receptor. Its immunomodulatory effects are supported by the fact that TRIM21 knock-out mice develop an SLE-like systemic autoimmunity [83], while a murine B cell line that over-expresses the protein has reduced proliferation and increased apoptosis [84]. In HeLa cells exposed to antibody-adenovirus complexes, TRIM21 rapidly bound the antibodies and targeted the complexes to proteasomes (before any virus-induced cytopathic effect was triggered), thus revealing a novel mechanism of antibody-mediated intracellular immunity [82]. Overall, these data provide a clear demonstration that antibodies bound to their antigens can penetrate cells and that
exists a TRIM21-antibody intracellular immune response. It is of interest
that, in this model, antibody entrance occurs through the formation of
membrane vesicles irrespective of the expression of membrane FcRs.
Extrapolation of these findings to autoimmune diseases, irrespective
of whether TRIM21 (SSA/Ro52) is or is not an autoantibody target, leads us
to hypothesize the existence of additional mechanisms by which
autoantibodies to intracellular antigens modulate the immune attack
once they get inside cells. It is tempting to speculate that at physiological
expression levels, TRIM21 may rapidly neutralize intracellular auto-
antibodies, but if TRIM21 expression is low, these autoantibodies may be
more pathogenetic. Therefore, investigating the mechanisms of this arm
of immunity (i.e. those related to TRIM21 expression) may reveal novel
ways to down-regulate the pathogenetic potential of these antibodies.

6. Conclusion

Elucidating the mechanisms of autoantibody generation and
pathogenesis is crucial for the study of autoimmune diseases because
this knowledge has implications for both basic research (e.g. analysis
of the B cell receptor of autoreactive B cells) and clinical practice
(diagnostic criteria, identification of disease subsets, evaluation of
disease activity and prognosis). The pathogenicity of autoantibodies is
believed to depend on the cellular location of the target self antigen.
For autoantibodies that target membrane-associated and extracellular
antigens, the molecular mechanisms leading to autoimmune diseases
have been elucidated in many cases and experimental criteria to
prove the pathogenicity of these autoantibodies have been elaborated.
Instead, the genesis and pathogenicity of autoantibodies to intracellu-
lar antigens remain one of the most intriguing issues in the field of
autoimmune research. Analysis of a possible general dysregulation
of the immune system, alterations in epigenetic modifications, molecu-
lar mimicry, and apoptotic bleb formation are the main lines of
research being carried out to understand how such antibodies are
generated. Studies on intracellular penetration and cytotoxicity have also
been performed in different models of systemic autoimmune diseases.
Interestingly, a recent report on a TRIM21-mediated mechanism of
intracellular immunity in a HeLa cell model of viral infection has
provided the first strong evidence that adaptive immunity occurs inside
the cell and suggests new lines of research to explore the pathogenicity
of autoantibodies to intracellular antigens, once they get inside cells.

Many questions about autoantibodies to intracellular antigens remain
unanswered. Progress in this field would be useful not only to define the
mechanisms that trigger autoimmune disease but also to identify key
pathogenetic steps that could be targets of therapeutic action.

Conflict of interests

The authors declare that they have no competing interests.

Take-home messages

• Autoantibodies can recognize intracellular antigens with wide
tissue distribution.
• They are selectively expressed in certain disease subsets and have
important diagnostic and prognostic value.
• Analysis of apoptotic body formation, epigenetic modification
changes and molecular mimicry are active lines of research to
understand their genesis and pathogenicity.
• TRIM21-mediated pathway of intracellular immunity may open
new perspectives for studying autoimmune disease mechanisms
and novel therapeutic approaches.

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