Is Tolerance Broken in Autoimmunity?

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AIMS AND SCOPE

Autoimmune diseases are classified into about 80 different types based on their specificity related to system, organ and/or tissue. About 5% of the western population is affected by this anomaly, but its worldwide incidence is unknown. Autoimmune diseases are heterogeneous in nature and clinical manifestations range from benign disorders to life-threatening conditions. Autoimmunity strikes at any stage of life, but age and/or gender also play role in onset of some of these anomalies. The autoimmune pathogenesis is initiated by the origination of autoantigens, which leads to the development of autoantibodies followed by auto-immunogenicity and the ultimate onset of autoimmunity. There is a lack of suitable therapies to treat autoimmune diseases, because mechanisms involved in the onset of these anomalies were poorly understood. Present therapies are limited to symptomatic treatment and come with severe side effects. Here, I described the molecular mechanisms and cellular events involved in the initiation of autoimmunity and proposed better strategies to modulate such molecular and cellular anomalies, which will help in preventing and/or controlling autoimmune pathogenesis and ultimately aid in enhancing the quality of life.

KEYWORDS: tolerance, autoimmunity, gene editing, RNA editing, protein editing, gene mutations, transcript mutations, autoantigens, autoantibodies

About 80 different types of autoimmune diseases were identified, depending on their effect on the specific system, organ, and/or tissue. We do not have an exact worldwide incidence of these diseases, but around 5% of the Western population is affected.[1] Autoimmune diseases are heterogeneous in nature and range from mild to life-threatening conditions.[1] The onset of autoimmunity occurs at all stages of life, and some of them arise with age and/or gender bias. The presence of antibodies against self-DNA, RNA, and protein molecules is the hallmark of these diseases.[1] In this Editorial, I made an attempt to decipher molecular mechanism(s) involved in the process of origination of autoantigens (auAgs), which leads to the generation of autoantibodies (auAbs) followed by autoimmunogenicity and the ultimate onset of an autoimmune pathogenesis.

Somatic hypermutations in DNA molecules give rise to the formation of anti-DNA antibodies during the transition between mature naïve and IgG+ memory B cells, which are eliminated before maturation into memory B cells.[2] The occurrence of low-affinity auAbs in healthy individuals has been well documented, which may be necessary for T-cell and B-cell survival in the peripheral immune system.[3] DNA molecules containing structural alterations are recognized as foreign molecules by T cells and initiate autoimmune response and produce autoAbs.[4] Such autoimmunity is further boosted by stimulation of helper T-cell responses.[5] So, what are the risk factors involved in the causation of structural alterations in DNA molecules? As indicated above, somatic hypermutations are implicated in causing structural alterations in DNA molecules. In addition to the occurrence of somatic hypermutations, large-scale DNA editing of retrotransposons of the human genome has been well documented.[6] Exposure to DNA-damaging agents, such as chemicals, UV radiation, and free radicals also contributes to the occurrence of somatic mutations in DNA. All these events raise the possibility for the development of anti-DNA antibodies in humans. This concept is strengthened by the development of antibodies against such mutated DNA molecules and the presence of anti–single-stranded DNA (anti-ssDNA) and anti–double-stranded DNA (anti-dsDNA) antibodies under normal and pathological conditions.[7–11]

Similar to modulations in DNA, alterations in RNA molecules, which are independent of DNA mutations, were also identified. One major source for such alterations is RNA editing. RNA editing–mediated changes in gene transcripts translate into self-antigens with mutations.[12] About hundred million adenosine deaminases that act on RNA (ADAR) enzyme–mediated adenosine (A) to inosine (I) editing sites were identified in human transcriptome, which results in adenosine to guanosine (G) mutations.[13] Most of these editing-induced mutations are catalyzed by constitutively expressing 110-kDa ADAR1 and ADAR2 enzymes and may be tolarized by central tolerance. In a recent study, the occurrence of high frequency of A-to-I and cytidine (C) to uridine (U) RNA editing in the medullary thymic epithelial cells has been demonstrated,[14] which may play an important role in training immature T lymphocytes in the thymus to become immunocompetent and in developing tolerance to the body's own altered gene products. The type I interferon (IFN)–mediated induction of 150-kDa ADAR1 randomly edits adenosines, which are not normally edited by constitutively expressing 110-kDa ADAR1 and ADAR2 enzymes, and creates novel mutations in gene transcripts.[15,16] The 150-kDa ADAR1 is expressed during embryogenesis by unknown mechanisms.[17] Such 150-kDa ADAR1 enzyme expression may facilitate to edit new sites, which are not edited by constitutively expressed 110-kDa ADAR1 and ADAR2 enzymes, to train the immune system to recognize such edited RNA molecules and their products as self. During infection, the 150-kDa ADAR1 enzyme is upregulated and edits self-double-stranded RNA molecules to prevent the immune response to endogenous gene

transcripts,[18] which also give rise to mutated self-RNA molecules.[15,16] The upregulated 150-kDa ADAR1 enzyme edits adenosines heterogeneously.[19] This may be because of the different double-stranded structures attained by the transcript at different time points.[20] Moreover, such editing frequency is very low.[15,16,19] Therefore, expression of 150-kDa ADAR1 during embryogenesis may not edit all possible editing sites to develop tolerance to such edited RNA molecules and their products. During infection, its presence will enhance the frequency of mutated RNA and protein products. The net result will be the creation of altered self-RNA and protein molecules, which may enhance the generation of auAbs against self-RNA and its products. In addition to ADAR enzyme–mediated A to G editing, apolipoprotein B–editing enzyme, catalytic polypeptide 1 (APOBEC1)–catalyzed C to U mutations were identified in human transcriptome.[21] Some APOBEC genes are regulated by type I IFNs.[22] A low frequency of U to C and G to A transcript mutations induced by unknown mechanisms was also observed in human transcriptome.[16] The following molecular mechanisms may account for such changes: (a) amination of uracil, (b) a base modification that results in a base that mimics as another base during reverse transcription, (c) transglycosylation, and (d) nucleotide exchange.[16] At present, we do not have any data related to (a) the total number of such modulation sites, (b) how many are constitutively occurring, and (c) how many are regulated by external stimuli. Mutant protein molecules generated from edited transcripts have been identified in normal human B lymphocytes.[12] Therefore, there is a lot of chance for the occurrence of novel editing and mutation induction during lifetime compared with embryogenesis and fetal development at RNA level, which may ultimately escape the process of tolerance and manifest as foreign RNA and/or protein molecules and pave the way for the development of auAbs to such mutant RNAs and their products. The occurrence of auAbs to RNA molecules under normal and pathological conditions supports this notion.[7,23,24]

The occurrence of structural alterations in protein molecules, which are independent of DNA-specific and RNA-specific mutations, was also identified. Such modifications result mainly from the process of citrullination. Inflammation-regulated peptidylarginine deiminases (PADs) edit protein molecules by deiminating peptidylarginine to citrulline.[25] The auAbs generated against PADs activate PAD enzymes and enhance the production of citrullinated auAgs in rheumatoid arthritis (RA) pathogenesis.[25] Mutations and citrullination in vimentin create novel auAgs followed by induction of anticitrulline antibodies in patients with RA.[26] Such anticitrulline antibodies were also identified in systemic lupus erythematosus, patients with primary Sjögren syndrome, and in a small percent of healthy controls in addition to patients with RA.[26] All these studies indicate that there is a lot of chance for such alterations induced by mutations and/or editing in DNA, RNA, and protein molecules to be recognized as foreign by the immune system.[2,4,7–11,23–27] Therefore, such modulations at

DNA, RNA, and protein level are the root cause of the generation of auAgs.

Based on this information, I assume that autoimmunity is analogous to attack on a cancer cell by the immune system. In the process of attaining autoimmunity, the immune system recognizes the altered own DNA, RNA, and protein molecules as foreign because such molecules escape tolerance and cause an immune response. Some of such responses may not have any impact, whereas others may lead to specific pathological conditions depending on which system, tissue, and/or organ is targeted by such altered immune response, which is similar to presence of majority of harmless somatic mutations in human genome and occurrence of rare mutations in cancer-driving genes and induction of cancer pathogenesis.[28] This concept is justified by the presence of auAbs and/or immune complexes in normal healthy individuals.[7,24,29,30] The pathogenic impact of the auAbs depends on their affinity to bind to normal counterparts apart from binding to altered molecules and their availability. The nature of somatic mutations may contribute to auAb specificity and intensity of reactivity. Therefore, normal subjects carrying pathogenic auAbs without any pathological impact indicate their lack of and/or inefficient autoimmunogenicity.[31] The best example of such phenomenon is the occurrence of auAbs against Fc portion of IgG in healthy individuals and autoimmune patients, which are also called as rheumatoid factors (RFs). The RFs are generated against different parts of the IgG-Fc. The RF and IgG form immune complexes which contribute to RA pathogenesis. Infection is the main cause for RF generation in healthy controls.[32,33] The RFs present in healthy controls are mainly of IgM class and of low affinity.[33] The RFs identified in patients with RA belong to all classes and are structurally and genetically different from those found in control subjects.[34] The RFs analyzed from normal individuals contain silent immunoglobulin mutations, but the RFs identified in patients with RA are derived from a wide range of immunoglobulin germline genes and contain a high frequency of substitution mutations.[34] These studies demonstrate that the nature and the frequency of mutations in auAgs, which are responsible for RFs generation, play a major role in antigen recognition by RF and in determining the autoimmunogenic potential of RFs in RA pathogenesis compared with normal subjects. The innocuous autoimmune response for auAbs in healthy controls may also be due to the lack of repeated production of autoAbs to specific edited and/or mutated DNA, RNA, and protein molecules, which is necessary to boost immune response, such as repeated booster administration of vaccines to attain good immune response to pathogens.[35]

In most of the autoimmune diseases, auAbs are produced against specific molecules. For example, in multiple sclerosis (MS), auAbs are generated against oligodendrocyte glycoprotein (MOG) and anti-myelin basic protein (MBP). Moreover, they are specific to different epitopes of MOG and MBP proteins.[36] Disease status, stage, character, and intensity are associated with the specificity of auAbs.[36] This information suggests

that alterations and/or mutations in different epitopes make them mimic as different foreign molecules, and auAbs generated against each epitope have selective and/or different effects in binding with MBP and/or different intensities in destroying MBP. The destruction of the target molecule occurs due to the binding of auAb because the binding of the auAbs damages their target auAg through complement-mediated lysis or by causing hydrogen peroxide production.[37,38] Such information helps to hypothesize that auAbs present in the normal population may be less potential in binding and/or in the destruction of a target tissue or they may be less efficient in entering the cell, if they are targeting intracellular proteins. If immune tolerance is broken in autoimmunity, the presence of auAbs should be exclusive in autoimmune diseases and the nature of auAbs production should be homogeneous with reference to the gene(s) and/or gene product(s). Moreover, such auAbs should be absent in normal population, but the occurrence of auAbs has been observed in normal healthy individuals.[7,24,29] In addition, manifestation of auAbs in autoimmune patients is heterogeneous in nature and varies from patient to patient. In MS, auAbs are generated specifically against MBP, but the auAbs are structurally different and developed against multiple epitopes.[36] The MS disease status will depend on epitope-specific auAb presence.[36] Some normal people harbor pathogenic auAbs without any autoimmune diseases and the frequency of nonpathogenic auAbs increases with age in healthy individuals.[31,39] All these studies indicate that alterations in the gene(s) and/or gene product(s) cause an autoimmune response. In addition, the effect of immune response to self-molecules is similar to the impact of somatic mutations in DNA; some are harmless, whereas others induce, drive, and/or promote pathogenesis depending on the role of the affected molecule in the cellular process.[28]

Several studies have demonstrated a strong association between viral infection and induction and/or acceleration of autoimmunity. The best example to support this assumption is Coxsackie B4 (CVB4) viral infection and the development of insulin-dependent diabetes mellitus (IDDM).[40] Epitopes on nonstructural protein 2C of CVB4 virus share sequence similarity with the islet auAg glutamic acid decarboxylase (GAD65). The GAD65 epitopes (IDDM-E1 and E2) are the targets for auAb binding and result in beta-cell destruction.[41] Immune response to GAD and CVB4 viral products was observed in newly diagnosed patients with IDDM and control subjects, who are not harboring the nonstructural protein 2C.[40] These results indicate that immune response generated against nonstructural protein 2C epitopes of CBV4 is not initiating and/or generating the autoimmune response and/or cross-reacting with GAD epitopes, but conversely, autoimmune response caused against GAD epitopes is responsible for cross-reaction with CBV4 viral products. These outcomes indicate that autoimmune response is generated against altered GAD epitopes in patients with IDDM. Based on these results, it is also surmised that CBV4 infection–mediated induction of inflammation and tissue damage will enable the release of autoimmunogenic GAD epitopes. In addition, structural similarities between GAD epitopes and nonstructural protein 2C epitopes of a CBV4 virus accelerate such autoimmune response. The net result will be the production of GAD epitope-specific auAb production, T-cell activation, destruction of beta cells, and ultimately the onset of IDDM.[42] In summary, these studies indicate that viral infection aids in the initiation of autoimmune response and accelerates the propagation of autoimmune pathogenesis but does not cause the disease.

It has been well documented that patients with most of the autoimmune diseases exhibit increased serum levels of type I IFN and immune complexes (ICs) containing nucleic acids.[43] Long-term type I IFN treatment increased production of auAbs and onset autoimmune diseases.[43,44] Patients possessing auAbs before interferon alfa therapy were more vulnerable to the onset of autoimmunity.[43] Systemic sclerosis patients treated with interferon alfa exhibited aggravation of the disease.[45] All these studies demonstrate a strong association between type I IFNs and autoimmunity. The following molecular mechanisms demonstrate the role played by type I IFNs in the induction of autoimmunity. The occurrence of apoptosis, pyroptosis, and/or necrosis followed by reduced clearance of such dead cells by nucleases and proteases generates nucleic acid–containing auAgs in the interferogenic ICs.[43,46] Such ICs activate plasmacytoid dendritic cell (pDC) by the process of internalization via the FcγRIIa expressed on pDCs and reach the endosome, which in turn stimulate the relevant toll-like receptor and transcription factors and result in endogenous interferon alfa production.[43] Constant expression of type I IFNs and IFN-inducible genes during repeated viral infections promotes the production of auAgs. Moreover, upregulated type I IFNs will activate human endogenous retroviruses to produce superantigens (SAgs), which cause massive polyclonal T-cell activation and survival.[47] All these events help in the production of auAbs via B-cell stimulation. The net result of these anomalies will be the generation of auAbs and formation of ICs.[43] Such ICs play an important role in the continuous production of endogenous type I IFNs by natural interferon alfa–producing cells (NIPCs) and the onset of autoimmunity.[48] These studies indicate that type I IFNs are not directly involved in the induction of autoimmunity but indirectly aid in the onset and propagation of autoimmunity.

In summary, auAb production occurs against some altered, edited, and/or mutated DNA, RNA, and protein molecules, which are recognized as foreign by the immune system.[2,4,7–9,23–27,29–31] Our immune system tries to train T cells to recognize altered molecules as self during the process of tolerance induction, but there is a lot of chance for the emergence of such altered own molecules to skip this process and present as nonself (auAgs) and generate auAbs and autoimmunogenicity. Depending on the concentration, availability, and their specificity to cellular components, tissue, and organs, they may initiate pathogenicity or remain dormant. Moreover, pathogenic auAbs are present in some normal people without any pathological impact; this may be due to the low concentration of

such auAbs or they may not reach target antigens and/or may not bind efficiently. All this information suggests that the process of autoimmunity is not an uncommon occurrence because the immune system mounts immunity when it recognizes altered own molecules. T-cell activation will enhance the chance for altered antigens to be presented to the immune system, which eventually leads to the generation of auAbs and autoimmune response. There is 19% chance for attaining autoimmunity during long-term IFN treatment in patients with cancer.[44] We do not have such data for childbearing years in women, UV exposure, and constant infections, which are susceptible conditions for induction of autoimmune response, but in general, the prevalence of autoimmune diseases in Western population is about 5%.[1] We can minimize such autoimmune disease frequency by (a) regulating the occurrence of DNA mutations induced by various mechanisms, such as chemical exposure, UV exposure and DNA editing; (b) minimizing the frequency of free radicals and DNA-damaging agents to prevent somatic mutations; (c) regulating inducible RNA editing gene expressions such as 150-kDa ADAR1 and APOBEC1 to prevent novel editing in gene transcripts; (d) inhibiting inflammation-mediated PAD expression, which induces anticitrulline antibodies; (e) inhibiting apoptosis, necroptosis, and pyroptosis, which will prevent mutated and/or edited molecules to be presented as auAgs; (f) upregulating nucleases and proteases to clear the presence of altered and/or mutated DNA, RNA, and protein molecules; and (g) controlling constant T-cell activation during initiation and/or onset of autoimmunity-susceptible stages such as childbearing years, cancer treatment, UV exposure, and recurring infections because all these events are involved in the initiation and/or induction of autoimmunity.

Author Contributions

Conceived the concept: DL. Analyzed the data: DL. Wrote the first draft of the manuscript and made critical revisions: DL. Author reviewed and approved of the final manuscript.

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