IJHS

Editorial

Oxidative biomolecular damage: A possible mechanism for systemic autoimmunity

Naila Rasheed, Zafar Rasheed

Department of Medical Biochemistry, College of Medicine, Qassim University, Buraidah, Saudi Arabia

Address for correspondence:
Dr. Zafar Rasheed, Department of Medical Biochemistry,
College of Medicine, Qassim University,
P.O. Box 6655, Buraidah-51452, KSA.
E-mail: zafarrasheed@qumed.edu.sa

WEBSITE: ijhs.org.sa
ISSN: 1658-3639
PUBLISHER: Qassim University

In systemic autoimmune disorders, autoantibodies develop either directly or indirectly against a variety of cellular components. It is notable that specific autoantibodies are associated with each disorder. Hence, the autoantibodies profiles are important for diagnostic applications. Some of these autoantibodies' specificities show a unique disease restriction, while others show a broader association with several disorders.[1] As anti-Sm autoantibodies are found exclusively in sera of patients with systemic lupus erythematosus (SLE), whereas anti-U1 ribonucleoprotein (RNP) antibodies found solely in patients with mixed connective tissue disease (MCTD).[1,2] However, low-titer anti-Sm antibodies are also reported in patients with MCTD, and anti-U1-RNP antibodies are in SLE patients.[1,2] Anti-Sjogren's syndrome-related antigen A (SSA/Ro) autoantibodies are not only found in Sjogren's syndrome but also in patients with SLE, whereas autoantibodies against histone are exclusively found in drug-induced lupus erythematosus.[2] This clinical and serological heterogeneity seems to be complex but clearly associated with specific autoantibodies. It is also established that immune response against self antigen(s) could result as a consequence of several factors such as cross reactions between self-antigens and foreign antigens, dysfunctionality in random B-cell activity or possibly due to genetic predisposition.[3,4]

In recent years, reactive oxygen species (ROS) or reactive nitrogen species (RNS) have gained substantial attention as plausible causative agents that directly or indirectly play their pathogenic role in several human disorders.[5,6] In chronic inflammatory conditions, free radicals such as hydroxyl radicals, superoxide, singlet oxygen, nitric oxide, and peroxynitrite are formed in considerably higher amounts due to oxidative stress.[5,7] Peroxynitrite is an oxidant and nitrating species and is well known for its ability to damage a variety of molecules in cells.[8,9] In our previous studies, we found high-titer autoantibodies specific for peroxynitrite-damaged thymidine-monophosphate in sera of patients with SLE and showed a positive association with SLE disease activity index.[10,11] In another study, we showed for the first time that mitochondrial DNA after modification with peroxynitrite becomes immunogenic and was found to be a potential immunogen for the production of antibodies in SLE patients.[12] Furthermore, we also reported that oxidized forms of chromatin were well recognized by SLE autoantibodies.[13] Not only have these, we also demonstrated that SLE autoantibodies also recognize 4-hydroxy-2-nonenal-damaged histone H2A.[14] Hydroxyl radicals are now considered as one of the most powerful reactive species and very well known for their biomolecular damage in various pathological conditions.[15-18] In one of our previous studies, we demonstrated that antibodies against hydroxyl radicals modified human serum albumin (HSA) resembled the diverse antigen(s) binding characteristics of SLE autoantibodies.[19] This notable feature was later on confirmed by direct screening of circulating SLE autoantibodies toward hydroxyl radical-modified HSA[20] By applying various immunological assays, our data demonstrated high degree of anti-hydroxyl-modified HSA antibodies in SLE patients.[20] Furthermore, we also demonstrated that prime antioxidant enzymes, superoxide dismutase and catalase, themselves oxidized by hydroxyl radicals and their oxidized forms were well recognized by circulating antibodies of SLE patients.[21,22] Not only in SLE, we also screened sera of patients with rheumatoid arthritis (RA) and found elevated levels of autoantibodies against hydroxyl radical-damaged immunoglobulin G,[23] suggesting a similar mechanism of oxidative damage in RA. 8-Hydroxydeoxyguanosine (8-oxodG) is a well-known biomarker of oxidative DNA damage.[2] Studies have shown that isolated lymphocytes from RA or SLE patients contain abnormally higher levels of 8-oxodG,[2] indicating oxidative DNA damage in these patients and also provide further support for the onset of a free radical-mediated systemic autoimmunity.

Excess generation of oxygen/nitrogen free radicals has also been implicated in the induction of cancer via oxidative damage of cellular components at the biomolecular level.[24,25]

Not only in cancer, these radicals are also known as causative agents for several other human disorders including Parkinson's disease, multiple sclerosis, vitiligo, and alopecia areata.[2,7,26,27] In systemic autoimmune diseases such as SLE or RA, anti-DNA autoantibodies and DNA-anti-DNA antibody immune complexes are known to deposit in the joints and promote inflammation.[28] Due to inflammation, the phagocytic cells become active and induce the release of free radicals. However, when their levels exceed the normal range, these reactive species start to penetrate inside the cellular membrane and induce nuclear DNA damage, which further possibly induce the onset of systemic autoimmunity against nucleic acid antigens.[1,2,28] Native DNA is no longer regarded as an initiating immunogen for systemic autoimmunity because immunization with native DNA does not produce RA/SLE-like symptoms.[2] The most eligible candidates could be denatured/modified DNA or RNA or their polynucleotides.[9-12] It is now well-documented that anti-DNA autoantibodies found characteristically in patients with SLE and most importantly have a strong binding ability to free radical-damaged nucleic acid samples.[2,9-12] Therefore, it is assumed that oxygen/nitrogen reactive radicals formed *in-vivo* can induce nucleic acid damage, thus altering their structure/immunogenicity, resulting antibodies possibly cross-react with native DNA. The detection of 8-oxodG in the immune complexes derived from SLE or RA patients[29] provides further evidence for the involvement of biomolecular damage in systemic autoimmunity.

In short, the mechanism(s) involved in the generation of autoantibodies for systemic autoimmunity has not yet been completely defined. The initial antigen(s) against which autoantibodies are generated remains in debate and seems to be highly controversial and needs to be further explored. In systemic autoimmune disorders, it is postulated that oxygen/nitrogen free radicals generated by phagocytes cause direct oxidative biomolecular damage and make them antigenic for the generation of autoantibodies. Alternatively, a flaw in the apoptotic control or delayed in the elimination of apoptotic cells provides persistent interaction between oxygen/nitrogen reactive radicals and apoptotic cellular macromolecules including the components of nucleic acids or proteins, resulting the generating neo-epitopes for the onset of systemic autoimmunity.

References

1. Shi G, Zhang J, Zhang ZJ, Zhang X. Systemic autoimmune diseases 2014. J Immunol Res 2015;2015:183591.
2. Ahsan H, Ali A, Ali R. Oxygen free radicals and systemic autoimmunity. Clin Exp Immunol 2003;131:398-404.
3. Catrina AI, Svensson CI, Malmström V, Schett G, Klareskog L. Mechanisms leading from systemic autoimmunity to joint-specific disease in rheumatoid arthritis. Nat Rev Rheumatol 2017;13:79-86.
4. Alghasham A, Rasheed Z. Therapeutic targets for rheumatoid arthritis: Progress and promises. Autoimmunity 2014;47:77-94.
5. Closa D, Folch-Puy E. Oxygen free radicals and the systemic inflammatory response. IUBMB Life 2004;56:185-91.
6. Al-Shobaili HA, Ahmed AA, Rasheed Z. Recognition of oxidized albumin and thyroid antigens by psoriasis autoantibodies. A possible role of reactive-oxygen-species induced epitopes in chronic plaque psoriasis. Saudi Med J 2015;36:1408-19.
7. Al-Shobaili HA, Rasheed Z. Mitochondrial DNA acquires immunogenicity on exposure to nitrosative stress in patients with vitiligo. Hum Immunol 2014;75:1053-61.
8. Ahmad R, Rasheed Z, Ahsan H. Biochemical and cellular toxicology of peroxynitrite: Implications in cell death and autoimmune phenomenon. Immunopharmacol Immunotoxicol 2009;31:388-96.
9. Ahmad R, Rasheed Z, Kaushal E, Singh D, Ahsan H. Biochemical evaluation of human DNA-lysine photoadduct treated with peroxynitrite. Toxicol Mech Methods 2008;18:589-95.
10. Rasheed Z, Al-Shobaili HA, Al Robaee AA, Alzolibani AA, Wadi WI, Khan MI, *et al.* Preferential recognition of peroxynitrite damaged thymidine-monophosphate by anti-DNA autoantibodies in systemic lupus erythematosus. Nucleosides Nucleotides Nucleic Acids 2012;31:736-51.
11. Alghasham A, Al Salloom AA, Alghamadi AS, Rasheed Z. Impact of anti-peroxynitrite-damaged-thymidine-monophosphate antibodies on disease activity in patients with systemic lupus erythematosus. Nucleosides Nucleotides Nucleic Acids 2015;34:56-68.
12. Al-Shobaili HA, Rasheed Z. Physicochemical and immunological studies on mitochondrial DNA modified by peroxynitrite: Implications of neo-epitopes of mitochondrial DNA in the etiopathogenesis of systemic lupus erythematosus. Lupus 2013;22:1024-37.
13. Al-Shobaili HA, Al Robaee AA, Alzolibani AA, Rasheed Z. Antibodies against 4-hydroxy-2-nonenal modified epitopes recognized chromatin and its oxidized forms: Role of chromatin, oxidized forms of chromatin and 4-hydroxy-2-nonenal modified epitopes in the etiopathogenesis of SLE. Dis Markers 2012;33:19-34.
14. Alzolibani AA, Al Robaee AA, Al-Shobaili HA, Rasheed Z 4-hydroxy-2-nonenal modified histone-H2A: A possible antigenic stimulus for systemic lupus erythematosus autoantibodies. Cell Immunol 2013;284:154-62.
15. Tripathi T, Rasheed Z. The oxidative by-product, hydroxyl radical, damaged immunoglobulin-G in patients with non-insulin dependent diabetes mellitus. Bratisl Lek Listy 2010;111:477-84.
16. Al-Shobaili HA, Al Robaee AA, Alzolibani A, Khan MI, Rasheed Z. Hydroxyl radical modification of immunoglobulin g generated cross-reactive antibodies: Its potential role in systemic lupus erythematosus. Clin Med Insights Arthritis Musculoskelet Disord 2011;4:11-9.
17. Rasheed Z, Ali R. Reactive oxygen species damaged human serum albumin in patients with type 1 diabetes mellitus: Biochemical and immunological studies. Life Sci 2006;79:2320-8.
18. Rasheed Z, Al-Shobaili HA, Alzolibani AA, Khan MI, Ayub MT, Khan MI, *et al.* Immunological functions of oxidized human immunoglobulin G in type 1diabetes mellitus: Its potential role in diabetic smokers as a biomarker of elevated oxidative stress. Dis Markers 2011;31:47-54.
19. Rasheed Z, Khan MW, Ali R. Hydroxyl radical modification of human serum albumin generated cross reactive antibodies. Autoimmunity 2006;39:479-88.
20. Rasheed Z, Ahmad R, Rasheed N, Ali R. Enhanced recognition of reactive oxygen species damaged human serum albumin by circulating systemic lupus erythematosus autoantibodies. Autoimmunity 2007;40:512-20.
21. Al-Shobaili HA, Al Robaee AA, Alzolibani AA, Rasheed Z. Immunological studies of reactive oxygen species damaged catalase in patients with systemic lupus erythematosus: Correlation with disease activity index. Immunol Invest 2013;42:191-203.
22. Al-Shobaili HA, Rasheed Z. Immunological studies of oxidized superoxide dismutase in patients with systemic lupus erythematosus.

Correlation with disease induction and progression. Saudi Med J 2012;33:1177-84.

23. Rasheed Z. Hydroxyl radical damaged immunoglobulin G in patients with rheumatoid arthritis: Biochemical and immunological studies. Clin Biochem 2008;41:663-9.
24. Rasheed Z, Ahmad R, Rasheed N, Ali R. Reactive oxygen species damaged human serum albumin in patients with hepatocellular carcinoma. J Exp Clin Cancer Res 2007;26:395-404.
25. Rasheed Z, Ahmad R, Ali R. Structure and immunological function of oxidised albumin in lung cancer: Its potential role as a biomarker of elevated oxidative stress. Br J Biomed Sci 2009;66:67-73.
26. Rasheed Z, Alzolibani AA, Al-Shobaili HA, Saif GB, Al Robaee AA. Biochemical and immunological studies on erythrocytes superoxide dismutase modified by nitric oxide in patients with alopecia areata: Implications in alopecia patchy persistent and alopecia universalis. Immunol Lett 2014;160:50-7.
27. Alzolibani AA, Rasheed Z, Al Robaee AA. Acquired immunogenicity of DNA after modification with malondialdehyde in patients with alopecia areata. Scand J Clin Lab Invest 2014;74:312-21.
28. Naparstek Y, Madaio MP. Are DNA antibodies actually pathogenic? Lupus 1997;6:307-9.
29. Lunec J, Herbert K, Blount S, Griffiths HR, Emery P 8-hydroxydeoxyguanosine. A marker of oxidative DNA damage in systemic lupus erythematosus. FEBS Lett 1994;348:131-8.