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SARS-CoV-2 vaccine-triggered autoimmunity: Molecular mimicry and/or bystander activation of the immune system

Azam Safary[1,2#], Mostafa Akbarzadeh-Khiavi[3#], Jaleh Barar[4], Yadollah Omidi[2*]

[1]Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Research Center for Pharmaceutical Nanotechnology, Biomedicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Department of Pharmaceutical Sciences, Barry and Judy Silverman College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL 33328, USA

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Summary

Induced autoimmunity or autoinflammatory-like conditions as a rare vaccine-related adverse event have been reported following COVID-19 vaccination. Such inadvertent adverse reactions have raised somewhat concerns about the long-term safety of the developed vaccines. Such multifactorial phenomena may be related to the cross-reactivity between the viral-specific antigens with the host self-proteins through molecular mimicry mechanism and/or nonspecific bystander activation of the non-target antigen-independent immunity by the entities of the vaccine products. However, due to the low incidence of the reported/identified individuals and insufficient evidence, autoimmunity following the COVID-19 vaccination has not been approved. Thereby, it seems that further designated studies might warrant post-monitoring of the inevitable adverse immunologic reactions in the vaccinated individuals, especially among hypersensitive cases, to address possible immunological mechanisms induced by the viral vaccines, incorporated adjuvants, and even vaccine delivery systems.

Authors' Biosketch

Azam Safary is an Assistant Professor of medical biotechnology at the Connective Tissue Diseases Research Center (CTDRC) and Research Center for Pharmaceutical Nanotechnology (RCPN) at Tabriz University of Medical Sciences, working on the cellular and molecular mechanisms of immune-mediated inflammatory diseases, new strategies for the detection and prevention of them, nano-formulated therapeutic enzymes, and biotechnological aspects of recombinant proteins.

Mostafa Akbarzadeh-Khiavi is an Assistant Professor of molecular medicine at the Liver and Gastrointestinal Diseases Research Center (LGDRC) and RCPN at Tabriz University of Medical Sciences, working on the development of advanced nano-formulated enzymes/antibodies used for the targeted drug delivery. Currently, he is involved in a project on cellular and molecular mechanisms of chronic disease and new strategies for diagnosing and treating them.

Professor Jaleh Barar has a Ph.D. degree in Pharmaceutical Sciences (2004, Cardiff University, UK) and Pharm.D. degree from Tabriz University of Medical Sciences. She is currently working as a full professor at Barry and Judy Silverman College of Pharmacy, Nova Southeastern University (Florida, USA). Prof. Barar's research in pharmaceutical sciences have resulted in over 200 published papers in international journals, 20 book chapters, and a few patents. Her H-index is 51 and he has consecutively been listed among top 1% highly cited scientists worldwide by WoS-ESI.

Professor Yadollah Omidi has a Ph.D. degree in Pharmaceutical Sciences (2003, Cardiff University, UK) and completed a postdoctoral program (2004) at Cardiff University. He is currently working as a full professor at Nova Southeastern University College of Pharmacy, Florida. Prof. Omidi's research in advanced targeted diagnosis and therapy of diseases have resulted in over 300 published papers in international journals, 27 book chapters, and a few patents. His H-index is 61 and i10-index is 238. He has consecutively been listed among top 1% highly cited scientists worldwide by WoS-ESI.

# These authors contributed equally to this study as the joint first authors.
***Corresponding author:** Yadollah Omidi, Email: yomidi@nova.edu

A more recent pandemic of COVID-19 caused by the SARS-CoV-2 is one of the most devastating global problems, seriously threatening public health worldwide.[1,2] Despite the incredible effectiveness of the vaccines against COVID-19 in controlling pandemic and significantly reducing mortality, their biological impacts (e.g., long-term safety, adverse effects [AEs], and long-term efficacy) should be carefully clarified, especially among those who have chronic immune system-related disorders. The viral vaccination may be associated with mild to severe levels of AEs which are usually tolerable and harmless. However, individuals with a history of allergic reactions with possible IgE-mediated responses might severely respond to the vaccination and generate severe immunologic reactions.[3]

It has been shown that viral vaccination may induce autoimmunity, as a rare vaccine-related AEs.[4] Accordingly, several studies have shown autoimmune reactions after anti-infectious vaccination against tetanus, rubella, hepatitis B, and influenza.[5] Following the universal vaccination of COVID-19, some concerns about vaccine-triggered autoimmunity or autoinflammatory-like conditions as multifactorial phenomena have been raised. Such AEs may be caused by the overstimulation of the immune system through different immunological mechanisms, including (i) antigen-specific reactions related to the epitope-based vaccines, and (ii) antigen-independent activation of $CD8^+$/$CD4^+$ T or B-cells, which can be mainly addressed in the vaccines developed using conventional methods.[6,7]

Molecular mimicry (MM), an antigen-specific immune response, seems to be a possible mechanism in acquired autoimmunity post-COVID-19 vaccination. Accordingly, it has been suggested that the potential cross-reactivity of the nucleoprotein/spike protein of SARS-CoV-2 with human tissue due to the viral antigenic mimicry may be connected to an increase in autoimmune diseases.[8] In the occurrence of such autoimmune reactions, the cross-reaction phenomena must take place at "disease-related" epitopes. Perhaps, such phenomena might occur through peptides of self-antigens that are presented by major histocompatibility complex II (MHC class II) on antigen-presenting cells (APCs) to auto-reactive $CD4^+$ T-cells.[9] Regarding the MM hypothesis, there are concerns about using entire SARS-CoV-2 antigens in vaccine development and it seems that considering only specific and unique peptides would be the most effective strategy against such AEs.[10] In addition to the MM mechanism(s), mRNA vaccines before the translation might activate several pro-inflammatory cascades and lead to aberrant responses of innate and acquired immune systems, which are the basis of numerous immune-mediated diseases. Due to the higher immune system activity against viral antigens in people under 55 years, such abnormalities may occur providing great protection against viral antigens and also making them predisposed to a higher burden of immunological AEs.[11]

In addition to the specific viral antigens, the components classified as non-target antigens of a vaccine product may occasionally induce an undesired immune response in a small part of the population. Most non-target antigens can be derived from (i) the cell culture medium supplements, (ii) proteins shed from the mammalian cells into the culture medium, and (iii) adjuvants/stabilizers used for vaccine development. Bystander activation is a non-specific stimulation of auto-reactive $CD8^+$ T cells (even $CD4^+$ T cells/B cells), which can be initiated following antigen-specific responses against the viral vaccines. The proliferation of $CD8^+$ T cells can be mediated by IL-15 association with its specific receptor-α (IL-15R-α) on the surface of the APC, which can trigger the bystander stimulation of memory-phenotype $CD8^+$ T cells. In this pathway, the production of IL-15 can be provoked by increasing the interferons (INFs) α/β, γ, and INF-inducer cytokines such as IL-12 and IL-18. Added to the auto-reactive $CD8^+$ T cells, the $CD4^+$ T cells may be stimulated through IL-2 cytokine and affected the immune responses, even though the involvement of this pathway in bystander activation is less well-known.[12] It has been also suggested that vaccine adjuvants may contribute to autoimmunity by stimulating bystander activation of irrelevant T cells.[13] The exact mechanism of such a process is yet to be fully clarified, for which specific studies are further needed to address such outstanding issues.

Intriguingly, it has been also proposed that autoimmunity post-vaccination may be related to specific genetic patterns, such as human leukocyte antigen in the case of multiple sclerosis following the hepatitis B vaccine.[4,14] Thereby, personalized approaches such as genetic risk factors for autoimmunity must also be considered in the development of new vaccines.[15] Recently, different case reports or observational studies have published autoimmune diseases post-vaccination with different types of COVID-19 vaccines (Table 1). Overall, immunological side effects may be connected to several factors such as vaccine type, vaccine dose, age, gender, specific genetic patterns, and history of immune-mediated diseases. However, the clinical trials related to the approved vaccines by the World Health Organization (WHO) did not show serious safety concerns during observation,[16-19] extensive follow-up evaluations are needed to consider long-term safety and autoimmunity issues of new vaccines for public administration.

As a perspective, some vaccinologists have recently focused on the next generation of epitope-based vaccines, which are designed based on the immunodominant/safe regions of one or more protective antigen(s).[34-36] To avoid any possible undesired autoimmune reactions, amino acid residues that may show homology with vaccine recipients' proteome are predicted. In this line, sequence- and structure-based computational methods (e.g., local alignment algorithms and molecular docking/dynamics

Table 1. Some autoimmune-mediated diseases following COVID-19 vaccines

Vaccine Type*	Autoimmune disease	Age	Gender	References
ChAdOx1 nCoV-19	Immune thrombocytopenia	50	Female	17
mRNA-BNT162B2	Arthritis flare	55	Male	20
mRNA-1273	Autoimmune hepatitis	76	Female	21
mRNA-BNT162B2		35	Female	22
ChAdOx1 nCov-19		36	Male	23
mRNA-BNT162B2	Symmetric polyarthritis	49	Male	24
	Exacerbation of Behçet's disease	28	Male	
	Pericarditis	37	Male	
	Temporal arteritis-like disease	60	Male	
	Oligoarthritis	37	Female	
	Myocarditis	22	Male	
mRNA-BNT162B2	Guillain-Barre Syndrome	82	Female	25
ChAdOx1 nCov-19		48	Male	26
mRNA-BNT162B2	Graves' disease	34	Female	27
ChAdOx1 nCov-19	Granulomatous vasculitis	77	Male	28
mRNA-BNT162B2	ANCA-associated vasculitis	78	Female	29
ChAdOx1 nCov-19		63	Male	30
ChAdOx1 nCov-19	Systemic lupus erythematosus	22	Female	31
mRNA-1273	Vasculitis	39	Male	32
		81	Male	
BBIBP-CorV	Rheumatoid arthritis	85	Female	33
	Palindromic rheumatism	39	Female	
	Adult-onset Still's disease	39	Male	
	Systemic lupus erythematosus	71	Female	
		46	Female	
	Peripheral seronegative spondyloarthritis	61	Female	

* ChAdOx1 nCoV-19, AstraZeneca; mRNA-1273, Moderna; BNT162b2, BioNTech-Pfizer; BBIBP-CorV, Sinopharm.

simulations, respectively) are used and the possible flaws are excluded from the vaccine construct.[37,38] Such an approach seems to be a time and cost-effective strategy to improve the vaccine safety in terms of potential tissue cross-reactive epitope(s).

In conclusion, autoinflammatory and autoimmune conditions may be associated with the cross-reactivity between SARS-CoV-2 viral peptides and self-antigens; thus, avoiding the stimulation of autoreactive T-cells should be considered one of the most crucial safety issues in constructing new vaccines. So far, the autoimmunity phenomenon following COVID-19 vaccination has not been approved due to the low incidence of the identified individuals and lack of sufficient evidence. Therefore, deep insight into the subject's incidental and idiopathic conditions is needed to develop this hypothesis. Moreover, further studies are warranted to monitor possible predisposed individuals and clarify immunological mechanisms induced by viral vaccines and adjuvants. Collectively, it should be emphasized that the vaccination modality is the best medical practice in controlling most infectious diseases even though autoimmunity might occur with low and mild clinical symptoms compared to those associated with the incidence of severe COVID-19 infection. Nonetheless, such symptoms could become much more severe in the cases of autoimmune diseases, in which precise care might be very helpful. Collectively, similar to other types of vaccines, SARS-CoV-2 vaccine-induced autoimmunity is a complex and dynamic area of research, characterized by molecular mimicry and immune system activation. Doubtlessly, COVID-19 vaccines have been crucial in mitigating the global impact of the pandemic. However, it is important to recognize that rare cases of autoimmune reactions might occur. These reactions may arise due to interactions between vaccine components, immune system activation, and underlying genetic predispositions. By implementing rigorous monitoring, timely reporting, and further research, we can enhance vaccine safety through quality-by-design approaches to ensure that the benefits of vaccination continue to outweigh potential risks in the battle against any emerging/re-emerging infections and future pandemics.

Authors' Contribution

Conceptualization: Azam Safary, Mostafa Akbarzadeh-Khiavi, Jaleh

Barar, Yadollah Omidi.
Data curation: Azam Safary, Mostafa Akbarzadeh-Khiavi, Jaleh Barar, Yadollah Omidi.
Investigation: Azam Safary, Mostafa Akbarzadeh-Khiavi.
Project administration: Yadollah Omidi.
Supervision: Yadollah Omidi.
Validation: Jaleh Barar.
Visualization: Azam Safary, Yadollah Omidi.
Writing–original draft: Azam Safary, Mostafa Akbarzadeh-Khiavi.
Writing–review editing: Azam Safary, Jaleh Barar, Yadollah Omidi.

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