Journal of Health, Medicine and Nursing
ISSN 2422-8419 An International Peer-reviewed Journal
Vol.86, 2021

Virus Vaccine Induced Immune Enhancement Mechanisms

Ibrahim M.S.Snawa
Department of Anesthesia ,Hilla University College, Rarengia .And former Professor Emeritus
Department of Biotechnology ,College of Biotechnology University of Qasim ,Qasim ,Babylon Province –IRAQ.

Abstract
In the present opinion, a go through current scientific literature have demonstrated that there are nine possible immune enhancement mechanisms [IE].IE following viral vaccine priming and exposure to live west nile, human immune-deficiency , dengue and corona virus challenges were documented. Five of which were antibody dependent[ADE]and the other four were T cell dependent .A virus vaccine may expresses more than one of the five ADE mechanisms .Sars and Mers were mediating ADE. Sars cov-2 virus induce, TH17-Treg eosinophilic IE and in an ex-vivo cell culture study has shown to induce ADE mechanism both in covid -19 patients.Sars-cov-2 DNA vaccines have shown no IE in non-human primate experiments but covid-19 vaccines are expectable to induce ADE in human vaccinee, though this wait to be elucidated.
Keywords: Antibody ,corona ,enhancement ,immune ,vaccine, virus.
DOI: 10.7176/JHMN/86-05
Publication date: February 28th 2021

1. Introduction

In general, various human vaccine strategies in post-vaccination period may leave behind some side effects among human vaccinee like; headache , fatigue and /or fever. As well as a risk of vaccine failure .One of the possible failures of the licensed human attenuated vaccines are reversion to virulent forms leading to disease(Shnawa 2019).Other vaccine failure concerning the human licensed viral vaccines are the immune enhancement[IE].IE are broadly subdivided into B and T cell dependents(Speiser &Bachmann 2020,Lee et al.2020,Wen et al.2020) Sars and Mers vaccine were mediating ADE(Wen et al.2020).So far covid-19 vaccine strategies are concerned ,two basic workers holdings are evident one holds the idea that covid-19 vaccines are far from being operative in vaccinee at post-vaccination periods(Lee et al.2020,Zellweger etal.2020,).While the other holds that IE is possible to be operable in vaccinee at post vaccination period(SPEAC.2020,Gao et al.2020).The tripartite components of the immune responses ,the innate ,cross-road as well as the adaptive types are seemingly involved in post virus vaccination IE (Speiser&Bachmann 2020,Hotez et al.2020).The cellular basis of virus vaccine induced IE are B cell,Th1,Th2,Th17,T reg.,CD8+ T cells, eosinophils and neutrophils(Wen et al.2020,Speiser & Bachmann 2020,Hotez et al.2020). The basic humeral and cellular immune mechanisms behind IE are being thoroughly expressed .

2. The General Concept Of Immuno-enhancement[IE]:

IE is the process in which a virus induces antibodies to aid infections towards more severity. Or it is the virus surface protein antigenic epitope that activate immune cells to be able to direct attack the virus pathogen with consequence of more severity of the disease due to immune tissue injury manifesting clinical disease severity. The viruses in such cases are; HIV,RSV, influenza, Dengue ,Sars, and Mers .The IE life history was starting on, when some people who received the virus vaccines were later exposed to the virus developed more severe disease than those who had not been primed with vaccine. A vaccine is designed to prime and boost our natural immune responses to an invading virus by priming it to recognize the antigenic epitopes a unique patterned molecules on the surface of the pathogenic viruses, In an ideal settings the immune system responds to the presence of these epitopes by producing special immune cells[mainly T cells] that directly attack the virus pathogen or through producing antibodies that combine to an antigen and attack immune cells that engulf and destroy the virus pathogen. The net results of these mechanisms is the dys-regulation of the immune responses(Peeples,2020).

3. Molecular Mechanisms of Immune Enhancement[IE]:

Nine molecular mechanisms are assembled under the umbrella of IE, These mechanisms are; Five were B cell Non-neutralizing anti-receptor domain antibodies and Sub-neutralizing antibodies , and four T cell dependent. (Peeples 2020,Lee et al.2020,Hotez et al.2020,Wen et al.2020).

4. B cell Antibody Dependent Immune Enhancement[ADE](Wen et al.2020):

Upon sars-cov-2 antigenic stimulations B cells produce virus neutralizing and non-neutralizing antibodies. The neutralizing type usually block the interaction of the virus with the ACE2 receptor or prevents the

conformational changes required for fusion of the virus with the cell membrane. Virus attachment to the host cells taken place through the binding with viral S protein. The non-neutralizing antibodies mediate Fc gamma receptor and facilitate viral up take leading to increasing of the infection(Hoffmann et al.2020,Lee et al.2020).

4.1 FCR mediated ADE :
The viral surface protein combine with Fc of the antibody to form virus-antibody complex. The complex strengthen the adhesion of the virus through interaction with the Fc on the antibody and the receptor on the particular cell ex. WNV,HIV and Dengue.

4.2 C3 dependent ADE:
C3 is activated through classical pathway via binding of antibody with virus surface protein following the interaction between C3 and corresponding receptor FCRII enhance virus adhesion in the form of virus-ab-C3 complex4-2; C3 dependent ADE ;

4.3 C1q dependent ADE
The virus form complex with the antibody .The complex combined with C1q promoting fusion of viral capsed and cell membrane through the deposition of the combination of C1q to its receptor. Tight binding of two or more IgG antibody to specific virus epitope allows C1q to bind to Fc portion leading to formation of virus-ab-C1q complex. The complex binds to C1q receptor on the cells initiate intracellular signaling and this promotes binding of the virus to specific receptor as well as endocytosis into the target cell.

4.4 Suppression of antiviral Genes dependent ADE:
The intracellular anti-viral genes are suppressed via the stimulation and enhancement of the target cell effect like endocytosis. In which the virus relay mainly on the Fc receptors to amplify its entry to the cells in the form of ADE, while normal entry through binding to virus receptor is decreased. This occur in the virus replication phase with in the target cells leading to suppression for the expression of the antiviral genes such as those of TNF genes and induced nitric oxide synthase ,thus helping the virus to immune escape from the functional immune cells .ex. Dengue virus.

4.5 Conformation dependent ADE
The conformational changes of the viral proteins enhances the fusion of the virus with cell membrane through its binding to antibody .Monoclonal antibodies recognize the glycoprotein gp120 on viral surface and combines with one of its sub-neutralizing concentrations. Thus then induces conformational changes in the residual sub-unites and promotes membrane fusion of the virus and the target cell via activation of the viral glycoprotein .ex. HIV.

5. T cell IE of immune activation(Speiser &Bachmann 2020,Hotez et al.2020)
Sars-cov-2 virus human infection should induce both B and T cells and both of them confer the protection so far.CD4 and CD8 T cells recognize sars-cov-2 antigens(Ahmed et al.2020).For covid-19 disease prevention ,T cell alone are probably less efficient than neutralizing antibodies(Yang et al.2004).Hence ,T cell subsets take part in vaccination immune reactions.

5.1 ADE via Th2 enhanced immune activation(Lee et al.2020) :
A TH2 subset in a faulty response triggers an allergic inflammation and poorly functional antibody that forms complexes with viral antigens. Such complexes activate complement system. The activated complement in turn induces cellular inflammatory reaction of neutrophils and eosinophils .Both of the neutrophils and eosinophils found in damaged lung tissue.TH2 allergic inflammation noticed in human vaccinee and in experimental vaccinated animals.

5.2 Th17-Treg-TH2 cells Immune enhancement(Hotez et al.2020):
Th2 is a helper T cell involved in helping B cell antibody producing immune response. Th17 is a subset of helper T cells that performed immune functions both in the innate and adaptive immune responses. Treg is a subset of T cell that have the ability to regulate immune responses(Abbas et al.2015).There is a sort of functional balance between Th17 and T reg(Hoe et al.2017).Viral vaccine may induce Th17 cell responses leading to synthesis and production of IL17 , GM-CSF and other cytokines which may lead to exacerbating immunopathogenesis through down regulating T reg cells promoting recruitment of neutrophils to the lung tissue contributing to its damage but simultaneously inducing Th2 cell responses (Ramakrishnan et al.2019,Wu &Yang 2020).

5.3 Th17-IL17(Hotez et al.2020):
IL17 can induce pulmonary eosinophilic responses disease, impart by promoting eosinophil production from the bone marrow ,recruitment and extravasation into the lungs(Murdoch et al.2012,Cheung et al.2008,ALRamili.2009).

5.4:CD8 T cell Immune Enhancement(Speiser & Bachmann 2020):
Pure CD8 T cell responses induced by vaccination may enhance potential lethal immune tissue injury leading to immunopathology.CD8 T cells can cause extended tissue damage through their direct cytotoxicity against virus infected cells which is likely increased in absence of neutralizing antibodies(Oehen et al.1991)

6. Covid-19 and IE:
Antibody dependent ADE was proved in cell culture studies for sars-cov-2 infected patients(Win et al.2020),and cell dependent IE of an allergic over-reactions in covid-19 patients(Wu and Xo 2020).Sars cov-2 inactivated vaccine prototypes was not inducing IE in non-human primate experiments (Gao et al.2020).Sars-cov-2 vaccine induced IE human vaccinee wait tobe elucidated.

7-The Features of The Immune Enhancement Mechanism:
In comparative sense ,the mechanisms of IE are characterized by the following the features and briefed in ,Table-1 ;
Covid-19 and IE:

- Vaccine induced followed by exposure to live virus challenge.
- The major cellular players of the IE are ;B cell,CD8and CD4 T cell and eosinophils
- Lung eosinophilic immune tissue injury mediate by Th2 or TH17 through immune complex formation, activation of complement, attraction and recruitment of eosinophils and neutrophils.
- The non-neutralizing with or without complement and sub-neutralizing antibodies are performing their function of IE of infection following the interrelated mechanisms
- The immune activation of IE is paired with the activation of the inflammatory responses
- The molecular mechanisms of IE is analogousd to the molecular mechanisms of eosinophilic allergic inflammation
- A virus vaccine may induce more than one of these mechanisms
- The approval sequence starts with vaccine priming ,exposure to live virus challenge ,antibody formation and activation of CD8 T cell,Th17 and eosinophils, occurrence of IE immune tissue injury increase of the disease severity.
- IE is approved in sars, and mers the pathogenic coronaviruses.

Figure 1 Sars-cov-2 vaccine induced immune enhancement mechanisms

Major cell/Mediator	Mechanism	Outcome
Non-neutralizing anti-RBD in four mechnisms	IE promotion of infection through antibody binding to virus surface with or without Complement and traffic virons to macrophage. Then internalized into it	Productive infection and severity
Sub-neutralizing anti-RBD	IE promotion of infection through antibody binding to virus surface and traffic virons to macrophage .Then internalize in to it	Productive infection and severity
Th2 cell	Poorly functional antibody combined to virus antigen forming complex the complex activate complement. The activated complement recruit neutrophil and eosinophil to lung causing damage	Allergic tissue injury leading to pathology in lung paired with severity
TH17/IL17	-Virus Th2 primed B cell produce antibody .Th17/IL17 initiate pathology through Treg promoting neutrophil migration -Th17 and IL17 recruit eosinophils from bone marrow to lung tissue	Allergic tissue injury leading to lung pathology paired with severity
CD8+ T cells	Direct cytotoxicity of the virus infected cells	Enhancement of immune activation paired with severity

8.Laboratory Biology :
Immune enhancement of infection can be detected using in-vitro assays of antibody dependent infection of the monocytes and macrophages bearing Fc-gamma-RIIa as compared to clinical severity. Immune enhancement of enhanced immune activation can be measured in-vivo by inflammatory markers ,immune- pathology and clinical

severity(Lee et al.2020)

9. Conclusion :

IE is virus vaccine induced. It is either antibody dependent or T cell dependent. The mechanisms behind which are of overlapping nature and followed by disease severity through either promotion of infection or through immune and allergic over activation.IE of infection proved by cell culture studies for covid-19(Wu et al.2020) and in covid-19 patients.IE of immune activation is still suggestive as deduced from clinical data(Lee et al.2020,Hotez et al.2020). Thus, on election of sars-co-2 vaccine health care giver should pay attention via choosing vaccine strategy that avoids non-neutralizing antibody producer and of potential polarization to Th1 response bias to reduce IE occurrence .

References

Abbas,A.K.,Lichtman,A.H.,Pillai, S.(2015).*Cellular and Molecular Immunology ,8th edition*, Chapters 10-12. Elsevier-Saunders ,Philadelphia,

Ahmad, S.F., Quadeer ,A.A .,McKay, M.R.(2020).Preliminary identification of potential vaccine targets for the Covid-19 corona virus(sars-cov-2) based on sars-cov immunological studies.*Viruses.12:254*.

AlRamili,W.A.,Prefontaine,D.,Chouiali ,F., Martin, J.G. Olivenstein ,R ., Lemiere,C.,Hamid,Q,(2009).TH17-associated cytokines(IL17A and IL17F) in severe asthma.*J.Allergy.Clin.Immunol.123(5):1185-1187.*

Gao,Q.,Bao,L.,Mao,H.et al.(2020).development of an inactivated vaccine candidate for sars-cov-2.*Science,2020.Doi.10.1126/scienceabc6284.*

Heung,P.F.,Wong,C.K.,Lam,W.K.(2008).Molecular mechanisms of cytokine and chemokine release from eosinophils activated by IL17A,IL17F and IL23:Implication for Th17 lymphocyte mediated allergic inflammation .*J . Immunol.180:5625-5635*.

Hoe,E.,Anderson,J.,Nathanielsz,J.,Toh,Z.,Marima,R.et al.(2017).The contrasting roles of Th17 immunity in human health and disease. *Microbial.Immunol.61.:45-56.*

Hotez,P.J.,Bottazzi,M.E.,Corry ,D.B.(2020).the potential role of Th17 immune responses in coronavirus in immunopathology of vaccine-induced immune enhancement.*Microbes and Infection.22:165-167*.

Lee,W,S.,WheaA.K.,Kent,S.J.,Dekosky,B.J.(2020).Antibody -dependent enhancement and sars-cov-2 vaccines and therapies.*Nat.Microbiol.5:1185-1191*.

Murdock,B.J.,Fakowski,N.R.,Shrener,A.B.,Akha,A.A.S.,McDonald,R.A.et al.(2012).Interleukine-17 derives pulmonary eosinophilia following repeated exposure to Aspergillus fumigatus conidia.*Infect.Imm.80:1424-1436*.

Oehen,S.Hengartner,H.,Zinkernagel,R.M.(1991),Vaccination for disease *Science.251:195-198*.

Peeples,L.(2020).Avoiding pitfalls in the pursuit of a covid-19 vaccine. *PANAS. 117(15:8218-8221.*

Ramakrishnanan,R.K.,ALHeialy,S.,Hamid,Q.(2019).Role of IL17 in asthma pathogenesis and implications for the clinic.*Expert Rev.Resp.Med.13:1057-1068*.

Shnawa,I.M.S.(2019).*Vaccine Technology At A Glance.Boffin Access.U.K*.

SPEAC.(2020).Consensus consideration on the assessment of the risk of disease enhancement with covid-19 vaccines. *The Task Force For the global Health .March.20.v5.1-5*.

Speiser,D.E.& Bachmann,M.E.(2020).Covid-19:Mechanisms of vaccination and immunity.*Vaccines.8(404):1-19.*

Wen,J.,Cheng,Y.,Ling,R.,dai,Y.,Huang,B.et al.(2020).Antibody dependent enhancement of coronavirus.*int.J.Infect.Dis.100:483-489*.

Wu,D. & Yang,X.O. (2020).Th17 responses in cytokine storm of covid-19:An emerging target of JACK2 inhibitor Fedratinib .*J.Micronio l. Immunol .Infect.53:368-370*.

Wu,F.,Yan,R.,Liu,Z.,Wang,Y.,Luan ,D.et al.(2020).Antibody dependent enhancement of sars-cov-2 infection in recovered Covid-19 patients :studies based on cellular and structural biology analysis. *MedRixiv .non-peer review preprint*.

Yang ,Z-Y.,Kong,W-P.,Huang,Y.,Roberts,A.,Murphy,B.R.et al.(2004).DNA vaccine induces sars coronavirus neutralization and protective immunity in mice.*Nature.428:561-564*.

Zellweger,R.M.,Wartel,A.,Marks,F.,Song,N.,Kim,J.H.(2020).Vaccination against sars-c0v-2 and disease enhancement- knowns and unknowns.*Expert Review of Vaccines.19(8):691-698.*

Bell, G.A., Cooper, M.A., Kennedy, M. & Warwick, J. (2000), "The Development of the Holon Planning and Costing Framework for Higher Education Management", Technical Report, SBU-CISM-11-00, South Bank University, 103 Borough Road, London, SE1 0AA.

Bongaerts, L. (1998), "Integration of Scheduling and Control in Holonic Manufacturing Systems", *PhD Thesis*, PMA Division, K.U.Leuven.

Deen, S.M. (1993), "Cooperation Issues in Holonic Manufacturing Systems", *Proceedings of DIISM'93 Conference*, 410-412.

Techawiboonwong, A., Yenradeea, P. & Das, S. (2006). A Master Scheduling Model with Skilled and Unskilled Temporary Workers", *Production Economics* **103**, Elsevier, 798-809.

Valckenaers, P., Van Brussel, H., Bongaerts, L. & Wyns, J. (1997), "Holonic Manufacturing Systems", *Integrated Computer Aided Engineering* **4**(3), 191-201.

Van Brussel, H., Wyns, J., Valckenaers, P., Bongaerts, L. & Peters, P. (1998), "Reference Architecture for Holonic Manufacturing Systems: PROSA", *Computers in Industry* **37**(3), 255-274.