Antibody Dependent Disease Enhancement and the Covid-19 Vaccine: A Word of Caution

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Key points:

- ***Antibody-Dependent Enhancement (ADE), refers to a counter-intuitive and potentially dangerous situation when the presence of antibodies, which are supposed to vanquish disease, worsens rather than quells an infection.***
- ***In ADE, instead of neutralizing the virus, host antibodies, designated as non-neutralizing antibodies, facilitate its infectivity.***
- ***Both Intrinsic and Extrinsic ADE work in tandem to enhance viral disease by increasing the number of cells getting infected and decreasing the innate response of body against that infection.***
- ***It is important for scientists to consider ADE before progressing to clinical trials***

The year is 2020, a single strand of RNA surrounded by protein has spread throughout the world like wildfire. Humanity is under siege and everyone is forced into lock-down, quarantine and social distancing. This is the state of the world no one could have predicted. Amongst this health crisis, all the hopes of mankind are poised on one breakthrough: VACCINE. Right now, nearly 180 vaccines are in various stages of trial with the end goal of a safe and effective vaccine. But a shadow loom over the global race to develop a pandemic vaccine: a little-known phenomenon called Antibody-Dependent Enhancement (ADE), also known as Disease Enhancement or Immune Enhancement. It refers to a counter-intuitive and potentially dangerous situation when the presence of antibodies, which are supposed to vanquish disease, worsens rather than quells an infection[1]. This phenomenon has been historically reported in both viral diseases and their vaccines, particularly dengue and flaviviruses[2,3]. The novel coronavirus (nCOV-2019) belongs to a family of viruses which caused health scares in the form of SARS (Severe Acute Respiratory Syndrome) in 2002 and MERS (Middle Eastern Respiratory Syndrome) in 2012. Attempts to produce vaccine against these syndromes haven't come to fruition due to the ADE[4]. The race towards the development of a vaccine against SARS-COV-2 may very well be threatened by the occurrence of ADE.

Antibody Mediated Disease Enhancement is a mechanism through which non-neutralizing antibodies produced by previous exposure of virus or through vaccine result in exacerbation of disease symptoms[5]. This was first described in 1964 by R.A. Hawkes in the flavivirus family. Hawkes was able to increase the yield of virus within chick embryo cells by exposing them to antibodies[6]. This aberrant response of the immune system was not probed further until it was demonstrated by Scot Halstread in Severe Dengue Fever patients in 1977. This study showed that dengue virus type-2 entry into peripheral β-lymphocytes taken from a sero-negative person was enhanced when they were treated with non-neutralizing antibodies[7].

In addition to controlled laboratory conditions, the phenomenon was also observed in community settings. In 2016, Philippines vaccinated one million children against Dengue virus through a commercially developed vaccine called DENGVAXIA but the program was put to end after reports of children developing severe complications of disease surfaced[8]. Investigations indicated that vaccine made sero-negative children more susceptible to subsequent infection which resulted in more hospitalizations as compared to non-vaccinated children. Several other viral families have also shown ADE, for instance Influenza virus, HIV-1, Hantavirus, Ebola virus,

Respiratory Syncytial virus, Yellow Fever Virus and Zika virus[9].

To understand how ADE can be implicated in the vaccine development of SARS-COV-2, it is pertinent to understand the mechanism of this phenomenon first. Normally, a virus enters into the body and infects cells by the interaction of viral proteins called antigens which bind to the receptors of target cells. This step is inhibited by host antibodies which prevent this by flagging it to Fc receptor bearing cells like macrophages[10]. After binding with the Fc receptor, virus-antibody complex induces the production of superoxide and interferon while mobilizing cytotoxic cells, thus rendering the virus ineffective. In the case of ADE however, instead of neutralizing the virus, host antibodies, hereby designated as non-neutralizing antibodies, facilitate its infectivity (Figure 1.1). This step is termed as Extrinsic ADE which is followed by Intrinsic ADE (elaborated in detail later). In addition to FcR-antibody mediated ADE described above, the other major receptors involved in the progress of ADE are Complement receptors (Cr). In this process, the Fc region of the virus-antibody complex binds with Cq1, a component of the complement system, hence causing infection. The latter process is especially prevalent in HIV and Ebola virus[11].

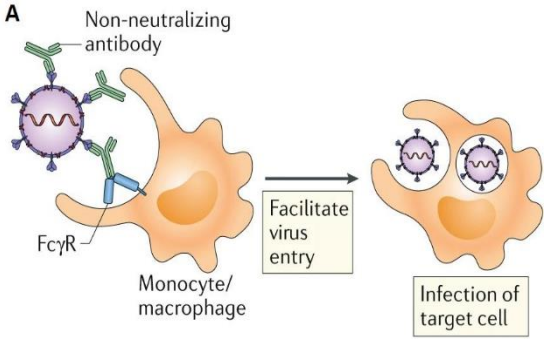

Figure 1.1. Graphical depiction of the Extrinsic ADE process[12]

Once the virus internalizes, the step of Intrinsic ADE starts in which the antiviral mechanism of cell is modulated. This is done by increasing the production of Interleukin-10 and supressing the activity of T-helper cells-1 (Th-1) while promoting the activity of T-helper cells-2 (Th-2), thus crippling the cells' defence system against a viral attack[11]. Both Intrinsic and Extrinsic ADE work in tandem to enhance viral disease by increasing the number of cells getting infected and decreasing the innate response of body against that infection[12]

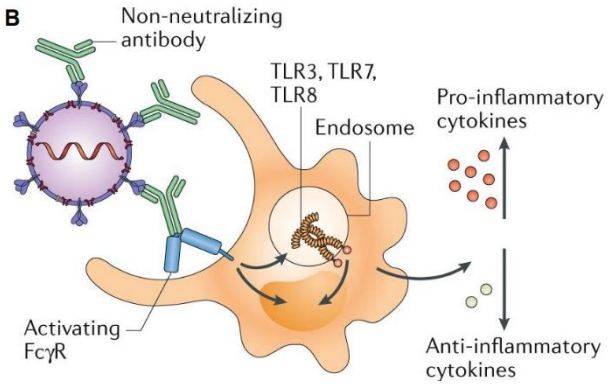

Figure 1.2. Graphical depiction of both extrinsic and intrinsic ADE[12]

Research conducted in 2014 in Taiwan showed that SARS-CoV requires the Angiotensin Converting Enzyme-2 (ACE-2) receptor to bind with pro-monocytes[4]. The anti-spike antibodies produced against the viral envelope spike protein increased the infectivity of cells, which showed enhanced cytopathic effects and the release of pro-inflammatory cytokines like TNF-α, IL-4 and and IL-6 (Figure 1.2). SARS-CoV-2 and SARS-CoV are 79.6% similar in RNA-sequence and utilize the same ACE-2 receptor for entry. If the results of the 2014 Taiwanese study are to be considered, then ADE can occur in SARS-CoV-2 as well. This poses a potent threat against vaccine development strategies against COVID-19.

Due to the severity of the pandemic, processes that take years are being done in months which is a cause of concern whether all possibilities are being considered or not. Therefore, during the ongoing vaccine development against COVID-19, it is important for scientists to consider ADE before progressing to clinical trials. Moreover, monoclonal antibodies can also be engineered since they offer much more precision than vaccine-mediated antibodies. This will ensure that the antibodies developed are safe, effective and neutralizing.

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