How the Aging Immune System Exacerbates COVID-19

Interview with Arne Akbar, PhD
Professor of Immunology
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Arne Akbar is a Professor of Immunology at University College London (UCL). His research is focused on how aging impacts the function of immune cells. This summer, he published a viewpoint article in Science, along with UCL colleague Derek W. Gilroy, which discussed how the aging immune system may exacerbate COVID-19 disease. HVP Editor Kristen Jill Abboud recently discussed this topic with Akbar and asked him about how vaccine responses, including those to future COVID-19 vaccines, may also vary among older adults.

An edited version of the conversation appears below.

It appears that older adults experience increased inflammation even in the absence of viral infections. Why is that?

This has been observed for quite a long time and it is referred to as “inflammaging.” Older people have high levels of inflammatory markers. This increased inflammation is important because it’s linked to frailty. Some older people are very frail, some people are as healthy as you and I or even healthier. But if you have increased inflammation, it is usually associated with frailty. This is why people became very interested in studying inflammaging.

As to the source of the inflammation, there have been several propositions and none of these are mutually exclusive. Firstly, the barrier function in your body wears down as you get older. The gut, the skin, and the lungs are all barriers that work very well when you’re young, but each of these lines of defense might become compromised as you get older, allowing more bacteria to enter the body. That’s one source of inflammation.
Another source might be the fact that older people don’t handle damaged proteins very well. You have misfolded proteins and altered proteins floating around in your body and, normally, you have components that degrade these proteins very well. When you get older, the body doesn’t handle them as well as it used to and then you have an accumulation of debris. This debris can also cause inflammation. Increased levels of adipose tissue or fat cells also play a role in increased inflammation.

A final source of inflammation that has gotten a lot of interest recently are senescent cells that accumulate as you get older. These old cells, which come from many different tissues, are also inflammatory, so much so that a new class of drugs called senolytic drugs that are specifically designed to clear away these old cells are now being tested in Phase II and III trials.

All of these things lead to the increased inflammation that occurs as you get older.

**Are immune responses also hindered as you age?**

Immune responses are hindered, yes, and again there’s not one clear answer as to why. If you have dysregulated inflammation or too much inflammation, then you’re getting mixed signals and the immune system is not actually being activated appropriately. This is separate from increased inflammation. The increased inflammation you experience as you get older is not coming from the immune system, it’s coming from all the other phenomena I described.

**How does this affect older individuals who are infected with SARS-CoV-2?**

That’s a very interesting question and there are many different hypotheses—obviously, nobody knows the straight answer right now. Because older people are susceptible to mounting inflammatory responses anyway, they can’t control the added inflammation that occurs when they are infected with a pathogen like SARS-CoV-2, which by the very nature of what it does causes inflammation. Then, as a result, you have even more dysregulated inflammation, which exacerbates the problem.

**Can this trigger the cytokine storms that are a sometimes-deadly complication of COVID-19?**

Yes.

**Which is the greater risk in older adults: the response to the virus or the virus itself?**

It isn’t clear yet, but it could be both things. We know for a fact that the steroid dexamethasone may help improve survival, and what dexamethasone does is it blocks inflammation at the point where you have this cytokine storm already kicking off. My group has been doing research to try to understand if blocking this inflammation, even in healthy people, can make the immune system work better. We’ve shown that if you treat older individuals with an anti-inflammatory agent, we can actually boost their immune response in the skin. This says two things: firstly, yes you can block end-
stage inflammation to improve health, but you might also be able to block inflammation earlier in the response before it all kicks off to make the immune system work better.

**How does this relate to the response to vaccination in the elderly?**

It's been known for a long time that older people don't respond very well to vaccination, whether it's against influenza, pneumonia, hepatitis B, or many other vaccines. They just don't work very well in older people. It is possible that vaccination against SARS-CoV-2 might not work very well in older people either, because of their high levels of inflammation. One hypothesis for this is that their elevated inflammation at baseline may be inhibiting the responses to vaccination. This hypothesis has led us to study whether blocking inflammation temporarily before you give the vaccine could enhance the response, and there are now at least a couple of companies looking at blocking inflammation to see if it will improve vaccine responses.

**What about vaccines that are specifically for older adults, such as the shingles vaccines? Don't they work quite well?**

There are two vaccines that are being used now for shingles. One is a live-attenuated vaccine (Zostavax) that was shown to be more effective in younger people—people in their 50s—but, the older you get the less well it works. That vaccine didn't have an adjuvant. Then there is a newer vaccine called SHINGRIX that uses a very strong adjuvant. And we're not really sure why—I've spoken to the vaccine people at GSK about this and they're not absolutely sure why either—but SHINGRIX actually gives you a very good response even in older people. The conundrum is how does the adjuvant work. Some people say it's a way of creating a long-lasting antigen depot that stays in the lymph node, other people say it's there to create inflammation. So, if you were going to give an anti-inflammatory agent to enhance vaccine responses, the point at which you intervene with an anti-inflammatory agent is going to be very important.

**Could adjuvants potentially help boost immune responses to COVID-19 vaccines in older adults?**

The problem is that there is so much inflammation going on that is detrimental with COVID-19 disease, I'm not sure you would really want to give an agent that causes even more inflammation.

**How do the immune responses to the COVID-19 vaccines that are currently in clinical trials look so far in older adults or is it too soon to tell?**

We don't know yet. I think one blind spot everyone has at the moment is that the readout for assessing immunity in clinical trials of these vaccines is the antibody response. But I think everyone is becoming more aware that it's not just the
antibodies that protect you. Your T cells are also very important and the T-Cell response to the virus could be equally protective, if not more protective, than the antibody response itself. We are looking at the results in a semi-blind way; we're looking at one parameter but not the whole story of how immune a person is.

I think it's important that if people are looking at vaccine efficacy, they look at both arms of the immune system and not just in terms of antibodies. In some people who have had the disease, their antibody levels are very low.

**Is there any evidence that T-cell responses might be better in the elderly than their antibody responses?**

That research is emerging right now but there isn't a lot of consensus just yet.

Putting the emotional burden of this disease aside, it's a very interesting time for immunologists. We're learning, inadvertently, a lot about the immune system through this infection, and also the aging immune system, which is very important.

*Interview by Kristen Jill Abboud*

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**Global COVID Lab Meeting**

Join us for the next Global COVID Lab Meeting on October 29th at 10:00 am EDT with Dr. Davide Corti, Senior Vice President leading Antibody Research at Vir Biotechnology in Switzerland. Dr. Corti will present his research about antibodies against SARS-CoV-2. [Register for the webinar here.](#)
Must Read

Research on SARS-CoV-2 continues at breakneck speed. Data on COVID-19 vaccine candidates and monoclonal antibodies continues to be reported. At the same time, researchers are tracking the rapidly changing epidemiology of the disease across the globe and detailing the role of different types of immune responses in controlling the disease.

- Additional data from two trials of mRNA-based vaccine candidates were recently published. The safety and immunogenicity of mRNA-1273 in older adults was reported in *The New England Journal of Medicine*. Additional data on immune responses to mRNA BNT162b1 were reported in *Nature*.
- While COVID-19 vaccine trials are ramping up, the epidemiology of the disease is changing rapidly across the globe. Authors of *this paper in Vaccine* recommend pooling epidemiological data from different groups to enable more efficient prioritization of vaccine trial sites.
- In a commentary in *Nature*, researchers from the African Centers for Disease Control and Prevention highlight the importance of including and enabling African countries to conduct COVID-19 vaccine trials and in ensuring access to vaccines.
- An article in *Nature Reviews Immunology* outlines three broad scenarios for the roles of CD4+ T cells in COVID-19 disease.
- In a related paper in *Cell*, researchers describe the potential role of cytotoxic SARS-CoV-2-reactive CD4+ T cells in the severity of COVID-19 disease.
- A news article in *Science* summarizes early results for therapeutic use of monoclonal antibodies against SARS-CoV-2.
- Data on monoclonal antibodies with potent SARS-CoV-2 neutralizing activity, which were described by *Emanuele Andreano during the recent Global COVID Lab Meeting*, are now available in *this preprint*.
- Another group reports that similarly potent human monoclonal antibodies protected hamsters against SARS-CoV-2 challenge in *this article in Science*.
- Antiviral antibody responses across the human virome are detailed in *this recent paper in Science*.

COVID-19 in Numbers

**Vaccine Candidates in Development by Platform**

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