Developing vaccines that train our innate immune system to be stronger

After I received a vaccine as a child, my mom would take me to get ice cream. While I inhaled my vanilla twist, my body was mounting a response to the inactive virus or bacteria injected into my left arm.

In an orchestral sequence of events, the body processes antigens, substances that provoke an immune reaction, in the vaccine and produces antibodies to defend itself. In vaccines, these antigens are commonly live, weakened, parts of, or dead pathogens. When we encounter these invaders in the future, antibodies identify the antigen, call in backup, and the threat is eliminated. This specific reaction is known as the adaptive immune response, one of two pillars that make up our immune system.

This symphony is wildly successful in many cases – the vaccine is the most important invention in medicine. Hundreds of millions of people saved, millions of disease cases and deaths prevented, billions of dollars saved in healthcare. Take polio, for example: an injection of inactivated poliovirus has nearly wiped it from existence.

However, in some of the biggest threats in our generation, current attempts to produce a vaccine for HIV, malaria, RSV-F, and Tuberculosis are struggling. To be clear, the reasons behind these failures are complex and could range from how the clinical trial was conducted to the design of the vaccine. But new studies suggest that the innate response has immense potential to help fix these failures. It's time to design therapies aimed at both pillars of the immune system, not just the adaptive response.

Before the doctor injected that vaccine into my arm all those years ago, the other pillar, termed the innate immune system, was prepared to respond to invaders. This response is the natural, front-line defense we are born with. If the adaptive immune response is the SWAT backup, then our innate response consists of the physical barriers, alarm systems, and first responders. These two systems work hand in hand against enemies of our cells. All walks of life have innate immune systems, from plants to fungi to our multicellular ancestors.

Recent evidence suggests that innate immunity can be trained to respond more effectively

Until recently, our innate immunity was thought to lack the memory that makes our adaptive response so powerful in response to specific disease-causing pathogens. This idea is now being challenged: Maziar Divangahi at McGill University and his team recently published evidence suggesting that the cells and processes that form our innate immunity can be trained to respond more effectively the second time it encounters that pathogen.

tb ward 34 2 18

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Early tuberculosis ward.

Divangahi studied this phenomenon using the most administered vaccine in the world, Bacillus Calmette-Guerin (BCG). BCG contains live Mycobacterium bovis, a non-pathogenic strain closely related to Mycobacterium tuberculosis.

The BCG vaccine does a good job at preventing childhood tuberculous meningitis, but its performance for other Mycobacterium tuberculosis-caused diseases is debated and unconvincing. Considering 1.7 million people die annually from tuberculosis, primarily in the lungs, this is an issue. Motivated by efforts to develop an effective tuberculosis vaccine and by growing tuberculosis (TB) antibiotic resistance, Divangahi and his team tested if administering the BCG vaccine directly into the bloodstream, rather than in the top skin layer, in mice could improve the response to Mycobacterium tuberculosis.

Intravenous, rather than localized, administration allows the vaccine to reach the bone marrow, home to hematopoietic stem cells, a self-renewing factory that produces an army of immune and blood cells. In this army of cells are those commonly responsible for our innate immune response: macrophages, natural killer cells, neutrophils, and dendritic cells.

Trained immunity

Instead of relying on the vaccine to ignite the adaptive immune response, the researchers hypothesized that they could educate the stem cells to produce better-trained innate immune cells – better first responders. And they were right. Exposure to the live, weakened bacteria from the BCG vaccine resulted in greater protection in the mice they studied. This protection was sustainable for several weeks afterward. To make their case stronger, mice without T-cells in their bone marrow were used to compare, which allowed them to confirm it was the innate system at work, not the adaptive. The changes researchers found in which genes were expressed and how they were regulated in the study suggests that how and where we administer vaccines can fundamentally alter the ability of our innate immune system to respond to disease-causing pathogens.

Despite these convincing results, this research is still in its infancy. For starters, the study was done in mice, and mice are not humans. Any vaccine design stemming from this study or others like it, like all vaccines, will face a gauntlet of excruciating safety and efficacy testing before reaching patients. Nevertheless, Divangahi and his co-authors explicitly consider the failure of T cell-targeted vaccines combined with their results as reason to revisit the design of TB vaccines.

> The vaccine created in 1921 for tuberculosis is still used for attracting and priming our immune cells – to eat cancer cells

Trained immunity may be a viable option, alone or as a supplement, to bolster our defenses. Interestingly, we may have already been doing this without fully realizing it. Numerous studies have shown that live vaccines, like BCG, provide protection beyond their intention. In fact, BCG has been used to treat bladder

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idea of trained immunity is catching on. Cancer chemotherapies are being tested in combination with tiny fragments of protein derived from the wall of Mycobacterium. A new pertussis vaccine seeks to utilize both the innate and adaptive responses. Even the widely covered cancer vaccine, from Ronald Levy at Stanford, that cured nearly 97 percent of mice of solid tumors all over their bodies, employs a similar strategy. Direct administration of immunotherapy and an innate activating chemical caused an incredibly effective response.

Two themes emerge: where and how the immune system is engaged can dramatically impact the outcome. In the case of tuberculosis vaccination, exposing the birthplace of our immune cells to bacteria trains them to be more fundamentally more effective defenders against tuberculosis and, as it turns out, many other invaders.

It's also worth mentioning the blurring of lines between what is considered innate and adaptive. And this response may not always be desired. Researchers have shown issues arising in innate immunity during vulnerable states like sepsis or chronic inflammatory conditions.

These insights about *how* and *where* we administer vaccines hold promise about new strategies to tackle diseases. Compounded with new curative, mRNA vaccines – a topic for another time – and economics in favor of widespread commercial support, I feel optimistic that the next decade will be the vaccine's time to shine.

Josh Peters is a PhD student in Biological Engineering at MIT. He looks at how both human and bacteria cells change on a genetic level in response to each other, as a member of the Blainey Lab, located in the Broad Institute, and Bryson Lab, located in the Ragon Institute and MIT. Follow him on Twitter @joshpetepeters.

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