Improving vaccines to trigger T cell as well as antibody response

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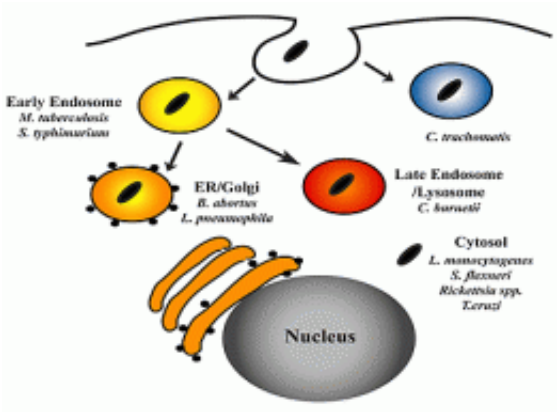

Intracellular pathogens exhibit a wide variety of behaviors that the immune system has learned to recognize, such as lurking in the endosome (salmonella), the endoplasmic reticulum and Golgi bodies (Legionella), the lysozyme (Q fever) and the cytosol (Listeria). Effective vaccines must mimic this behavior in order to stimulate a complete immune response. (Portnoy lab/UC Berkeley, Courtesy of Cell Press)

(PhysOrg.com) -- Killed or disabled viruses have proven safe and effective for vaccinating billions worldwide against smallpox, polio, measles, influenza and many other diseases.

But killed or severely "attenuated" vaccines, which are safer than "live" vaccines, have been largely unsuccessful for many non-viral diseases, including illnesses like tuberculosis and malaria.

A new study by researchers from the University of California, Berkeley, and Berkeley-based Aduro BioTech provides clues why killed and severely attenuated vaccines don't always work. It also suggests ways to engineer an attenuated vaccine to make it as potent as a live vaccine but as safe as a killed vaccine.

"It's not only that these killed or attenuated vaccines can't immunize, it's that they also suppress immunity," said co-author Daniel Portnoy, UC Berkeley professor of molecular and cell biology and of public health. "What this says is that the immune system knows the difference between a live bug that's virulent and a dead one that is harmless."

The study, which appears in the Sept. 4 online edition of the journal PLoS Pathogens, suggests that for killed or severely attenuated non-viral vaccines to work - and for viral vaccines to work better - it's necessary to make the microbes act as if they're alive.

"In general, killed vaccines have not lived up to the potency of live vaccines, and our finding might partially explain this observation," said co-author Dirk Brockstedt, director of research and development at Aduro. "The finding is really key for us to develop a strategy to select new bacterial strains that induce the right kind of immune response."

The findings support a new hypothesis about how the innate immune system distinguishes pathogenic from non-pathogenic microbes, proposed by Portnoy, UC Berkeley colleague Russell Vance, assistant professor of molecular and cell biology, and Ralph Isberg of Tufts University in the July 23 issue of the journal Cell Host & Microbe. They argue that it's not only how a pathogen looks that determines how the immune system responds, but also how it acts - where it goes in the cell, what pathways it interferes with, and how disruptive it is.

"There are a series of different things that pathogens have to do in order

to be pathogenic, so it makes sense for the immune system to try to detect these common patterns," Vance said. "We know already that there are surveillance pathways in the cytosol that seem to respond specifically to pathogens and not to non-pathogens."

The findings are most important for creating effective vaccines against pathogens - bacteria, parasites and viruses - that live and hide inside cells. While some pathogens, such as viruses, can be knocked back when they exit one cell to infect another - hence the effectiveness of some antiviral vaccines - other intracellular pathogens never completely leave the cell.

A vaccine against these intracellular pathogens would need to induce a so-called cellular or T cell response that is not effectively induced by current available vaccines, Brockstedt said.

A delicate balance

The body's immune system is a complex interplay of activation and suppression that operates to keep the body in a balanced state with no inflammation until it's needed, Portnoy said. The first line of defense against invading pathogens is the innate immune system, which deploys when the body recognizes characteristics of viruses and microbes that are common enough that they have been programmed into our genes and are with us from birth.

The more sophisticated system, however, is the acquired or adaptive immune system, which kicks in after the innate immune response. It recognizes unique aspects of pathogens - the proteins and sugars that they sport and generates antibodies to latch onto and target them for destruction. It also mobilizes T cells to attack the invaders or, more importantly, infected cells.

Listeria generates one of the strongest immune responses of any intracellular pathogen, which makes it a promising vehicle to deliver antigens that will immunize against a range of illnesses, from cancer to HIV. Portnoy has studied Listeria bacteria for 22 years to understand why it is so immunogenic, and how Listeria can be used as a vaccine without itself inflaming the immune system and causing disease.

Based on their and other experiments, Portnoy and Vance argue that the immune system looks at more than the microbe's coat, but also at how the microbe behaves. Listeria bacteria, for example, enter macrophage cells by luring these cells to engulf them. Once inside the phagosome, or stomach, of the macrophage, the bacteria secrete proteins that punch holes in the phagosome that allow the bacteria to spread throughout the guts of the cell, the cytosol.

It has been known for decades that killed Listeria vaccines don't provide protective immunity. It was believed that failure to reach the cytosol was the major reason. In earlier experiments, Portnoy and others found that mutant strains of Listeria that are not able to break out of the phagasome fail to stimulate an immune response. The current study shows why.

Killed Listeria suppress immune system

Portnoy, Brockstedt, Keith S. Bahjat of the Earle A. Chiles Research Institute in Portland, Ore., and Nicole Meyer-Morse of UC Berkeley's Department of Molecular and Cell Biology injected mice with a mixture of attenuated, but live, bacteria that stimulate a good immune response and dead bacteria that produce no response. They found that the cells' response to this mixture was less than if the researchers had injected only the effective vaccine.

"You would think, 'Why wouldn't the immunogenic strain still immunize?' But by having the non-immunogenic strain, it suppressed

immunity," Portnoy said.

The implication, the researchers argue, is that the innate immune system monitors behavior as well as the antigens on the surface of invaders to know how aggressively to respond. The initial response of the innate immune system determines the level of response of the acquired immune system.

"You need to have an innate response to get adaptive responses to occur properly," Vance said. "For example, a killed virus might stimulate certain kinds of innate signals that lead to good antibody production, but might not generate the right response to properly activate T cells."

"Potentially, if we could figure out what kinds of responses are the ones that are really best at inducing immunization, this could have a lot of importance for how we design vaccines in the future," Vance added.

New vaccines for cancer, salmonella, anthrax

Portnoy's work has already led to two promising Listeria-based vaccines. Aduro's predecessor, Anza Therapeutics, collaborated with Portnoy to produce live, attenuated Listeria vaccines against cancer and hepatitis C that have been evaluated for safety in Phase I clinical trials. Aduro is continuing this line of work but is also developing what it calls a killed, but metabolically active (KBMA), form of Listeria to serve as a vaccine vector for a range of infectious diseases.

KBMA retains the ability to break out of the cell's stomach into the cell's cytosol, just like live Listeria, but, unlike live Listeria, it is unable to grow, said Portnoy. The KBMA strategy has also been extended to salmonella bacteria and, most recently, to anthrax, as reported by Portnoy and Aduro colleagues in the April 2009 issue of the journal Infection and Immunity.

But Portnoy has hopes that Listeria can do even better. His lab is currently searching for mutant strains of Listeria that can mimic the behavior of live bacteria even when killed or attenuated.

"The field has moved so rapidly that we now have the opportunity to make designer vaccines that can be used for many different applications," Portnoy said, noting that he has engineered Listeria to express foreign genes, turn on various immune pathways, and even pop or not pop. "We can make Listeria dance the salsa."

"The whole battle with vaccines is that you want them to be completely immunogenic and completely avirulent and safe, which today is a disconnect," Portnoy said. "We would like to enable this, so that we can have a completely safe and fully immunogenic vaccine. That is what everyone wants."

Source: University of California - Berkeley (news : web)