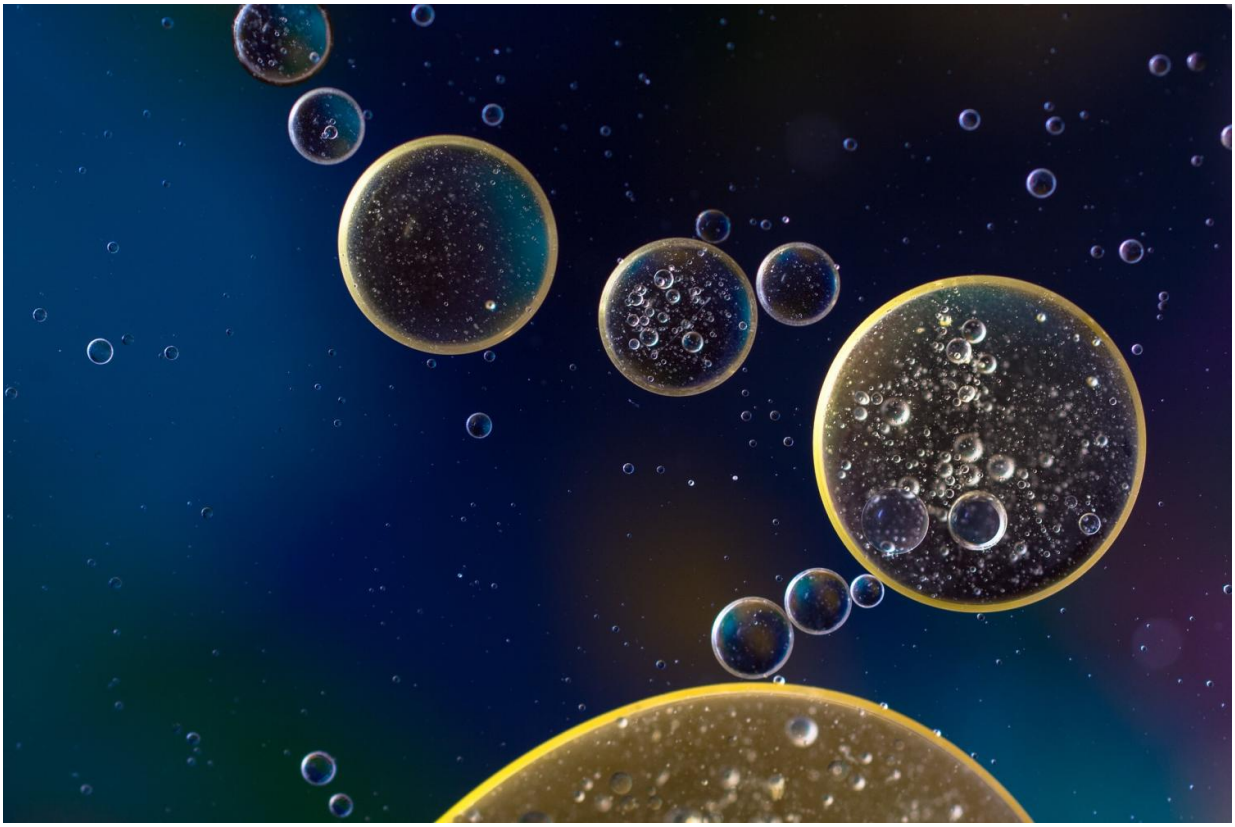
MedicalXpress

Study describes new 'molecular tool' to trigger targeted immune responses

August 9 2022



Credit: CC0 Public Domain

A research team at the University of Oklahoma published a study in the journal *Advanced Science* that presents a new approach to triggering an adaptive immune response.

The study was led by Handan Acar, Ph.D., the Peggy and Charles Stephenson Assistant Professor of Biomedical Engineering in the Gallogly College of Engineering, with collaborators in the Department of Microbiology and Immunology at the OU Health Sciences Center Mark Lang, Ph.D., and Susan Kovats, Ph.D., who is also a researcher at the Oklahoma Medical Research Foundation. Doctoral student Gokhan Gunay is the first author of the paper.

How cell death causes an immune response

It might sound violent, but cell death is an important biological process. Immunogenic cell death occurs when cells are under stress and their membranes are damaged. Besides pathogens—microscopic disease-causing organisms—innate immunity is responsive to what scientists call "Damage-Associated Molecular Patterns," or DAMPs. These so-called "danger molecules" are released from stressed or dying cells to alert the body to impending danger. When under stress, cells induce the DAMPs danger signals to alert the immune system to the location in the body where the stress is being experienced.

"Cell membrane damage can be accidental because of a physical force like a cut or burn or programmed because of a virus or bacteria, and that damage induces DAMPs release," Acar said. "For example, if there is an infection in a cell, the pathogen might use the resources in the cell and drive its stress and slow death. The stressed cells release signals to the immune system, which also triggers programmed cell death. Depending on the amount of damage and the duration of time the danger signals are being sent, the immune response increases."

There are two kinds of immune responses, innate and adaptive. Innate immunity offers initial protection to a virus or bacteria that originated outside of a body, but it is not specific. Through this DAMPs response process, the innate immune system absorbs pathogens and teaches cells

adaptive immunity. Put another way, adaptive immunity comes from the body learning over time and creating antibodies specific to those pathogens.

Acar's research team wanted to know how to make a cell stressed enough to release the damage signals that trigger the innate immunity to talk to the adaptive immune response, teaching the immune cells in a similar way to what happens when receiving a vaccine.

Developing a mechanical tool to trigger immune response

The research team applied a methodological framework presented in a previous study to create molecules that can integrate into a cell, aggregate and cause enough stress on its membrane to release the signals that recruits immune cells to its location.

By creating a molecule that can trigger immunogenic cell death intentionally and administering a small part of a pathogen, they are stimulating a process to teach the immune system how to react to a specific bacteria or pathogen, which the researchers believe could have incredible potential for therapeutic applications.

"As engineers, we provide tools for physicians and clinical scientists to create therapeutics, improve diagnostics or otherwise improve patient care," Acar said. "The peptides we are creating are a kind of mechanical tool—a molecular knife—that is not specific to a protein, so they are effective in all cells, creating this immunogenic cell death and DAMP release. These tools can be used in immunology to understand the effects of the DAMPs in innate and adaptive immunity in a more controlled way."

Acar explains that therapeutic antibodies provoke a stronger immune response by "marking" the infected cells for destruction by the powerful immune cells, whereas protective antibodies recognize the virus or pathogen, cover it and prevent it from infecting other cells.

"In general, vaccines and adjuvants produce protective antibodies, but cannot produce therapeutic antibodies," she said. "It is great to protect the body, but if we are exposed to a high amount of virus, they might not be enough. Then, we need the therapeutic antibodies."

When testing the process with a protein of the influenza virus, the researchers found that after 75 days following one injection and one booster injection, protective and therapeutic antibodies—which can tag the infected cells for immune cell clearance—increased as much as 15 times.

"Most of the adjuvants that are currently available are not able to produce this level of therapeutic antibodies," Acar said. "What is also exciting is that because the peptides are so tiny, it didn't produce any antibodies against it, so we can use this method again and again for different viruses. The peptide has a huge potential to be used in cancer immunotherapies or vaccine applications."

Now the research team is looking to better understand the applications of this process in fighting cancer cells for melanoma and pancreatic and breast cancer, hoping to simulate responses that suggest there may be multiple pathways to achieving positive results from their approach.

More information: Gokhan Gunay et al, Peptide Aggregation Induced Immunogenic Rupture (PAIIR), *Advanced Science* (2022). DOI: 10.1002/advs.202105868

Provided by University of Oklahoma