Cardiovascular disease: Researchers pinpoint missing piece of treatment puzzle

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A healthy lifestyle is important in preventing artery clogging, but sometimes it's not enough. Credit: Unsplash

With new findings that the immune system plays a key role in conditions affecting the heart or blood vessels, options emerge for new cures.

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, responsible for 32% of all deaths. While the illness is triggered to a large extent by an unhealthy lifestyle, a flaw in the immune system has recently been found to be another important contributor.

For reasons that are only partially understood, cells from the body's inflammatory response sometimes switch from "protective" to "harmful," encouraging the build-up of fatty deposits on the inside of artery walls and putting people at risk of heart attacks and strokes.

Fat fight

Scientists are seeking a drug or vaccine, or both, to eliminate this glitch. Their work, if successful, would pave the way for a major new weapon against premature death.

It would mean that heart doctors like Dr. Dennis Wolf in Germany would no longer need to deliver the distressing news to patients—some as young perhaps as 40—that their CVD risk is high even though they eat well, exercise and avoid cigarettes and other dangerous substances.

"As a clinician, it's very challenging to explain to people that they are at high risk although they are apparently healthy and they have no sense that something is wrong," said Wolf, who is based at the University Hospital in Freiburg.

He treats patients with heart disease and studies atherosclerosis, a condition that causes a narrowing and hardening of arteries when a dangerous amount of fat builds up.

Some build-up of arterial fat is inevitable over the course of a lifetime. This becomes problematic only when the fatty layer thickens into clots that can break away and block the flow of blood.

"For many years, we didn't have a complete understanding of what drives this disease, but now it's becoming increasingly clear that high blood lipids and chronic inflammation are both key factors," Wolf said.

Beyond bad cholesterol

The main fat found in arterial plaques is low-density lipoprotein cholesterol (LDL-C)—a cholesterol sub-type often known as "bad

cholesterol." While cholesterol is needed by the body to produce cell membranes and several hormones, when there's a malfunction LDL-C accumulates in arteries.

Traditionally, atherosclerosis was seen as a "static" disease of the arterial wall. It was thought that, the more LDL-C people accumulated in their oxygen-rich blood vessels, the thicker the plaque.

The remedy seemed relatively straightforward: lower bad cholesterol and other circulating fats through lifestyle changes and take lipid-reducing drugs such as statins and good health would be restored.

But these measures work in only 30%–35% of patients—the remaining 65%–70% show little or no improvement to their condition. The reason is that the static model for the disease is flawed.

"While it's true that patients with atherosclerosis have cholesterol clogging their arteries, our research shows the condition is in fact ultra-dynamic, with chronic inflammation—and therefore the immune system—playing a central role," said Wolf.

Dual-role cells

As part of the ANIMATE project, a five-year initiative that runs through 2024, he has discovered that cells of the immune system—particularly T cells—are always found in the fatty plaque lining artery walls.

This doesn't automatically mean T cells are involved in causing the disease. What has become apparent, however, is that these cells play a double-edged role in arterial health.

When atherosclerosis is in its earliest phases, T cells are protective against further plaque formation, recognizing the excess of LDL and

fighting against it by instructing other cells of the immune system not to overreact.

But as the condition progresses, what began as a protective autoimmune response converts into a harmful one, encouraging the build-up of more plaque still. At this stage, T cells actually fuel the inflammatory reaction in arteries.

"We don't know if this switch in functionality represents a cause or a consequence of the condition," said Wolf. "But finding ways to manipulate the immune system with drugs or a vaccine is an attractive proposition."

Any future vaccine is likely to work by boosting the number of healthy T cells sending helpful messages to other immune-system cells in a person's body, thereby increasing natural protection against fatty build-up and countering the effects of T cells that have turned rogue.

"We know this works in mice—vaccinated mice develop less atherosclerosis," said Wolf. "Now we need to find a way to make this concept work in humans too."

Precise targeting

According to Professor Esther Lutgens, an expert in inflammatory and vascular diseases, any future drug would need to be highly targeted. That means it would need to be focused precisely on the cell types that are responsible for atherosclerosis-associated inflammation.

Lutgens, who is principle investigator on the CD40-INN project, says non-specific anti-inflammatory medication would be only a short-term solution for atherosclerosis.

"The problem is, this is a condition that needs lifelong treatment and you can't take strong, random anti-inflammatories—which block the immune system—forever or you'll cure your cardiovascular disease but die from an infection," she said.

CD40-INN, which will end this November after seven years, has been exploring a type of molecule that sits on the surface of macrophages—another kind of immune system cell—and influences the way these cells behave.

These molecules, known as co-stimulatory molecules, are important communicators of the immune system. When turned on, they trigger a chain of cellular commands that results in an inflammatory response; when they are turned off, inflammation is subdued.

At the project's outset, it was already known that co-stimulatory molecules nudged cells of the immune system (both T cells and macrophages) in one direction or another. Lutgens wants to untangle the precise mechanisms that lead some cells to switch from protective to harmful.

Encouraging steps

She and colleagues have identified the co-stimulatory molecule CD40 as a major driver of the inflammatory response that leads to atherosclerosis. Her hope now is to develop a drug that interferes with the actions of this molecule, with a view to preventing both the T cell switch and macrophage activation.

In animal experiments, Lutgens has already had success: mice injected with a compound that blocked CD40 developed immune cells that protected against plaque build-up.

"The compound gave proper, powerful immunity against cardiovascular disease," she said.

Unfortunately, this compound can't be tested in humans because its chemical make-up is a potential danger to them. Nonetheless, Lutgens is far from discouraged.

"We now have our proof of concept," she said. "We just need to patiently screen and eventually develop many, many compounds that might have the same impact as the one that works in mice until we find one that works in humans too but is in no way toxic or harmful."

More information:

- ANIMATE
- CD40-INN

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