Using proliferative properties of cancer cells to rejuvenate cardiac progenitor cells

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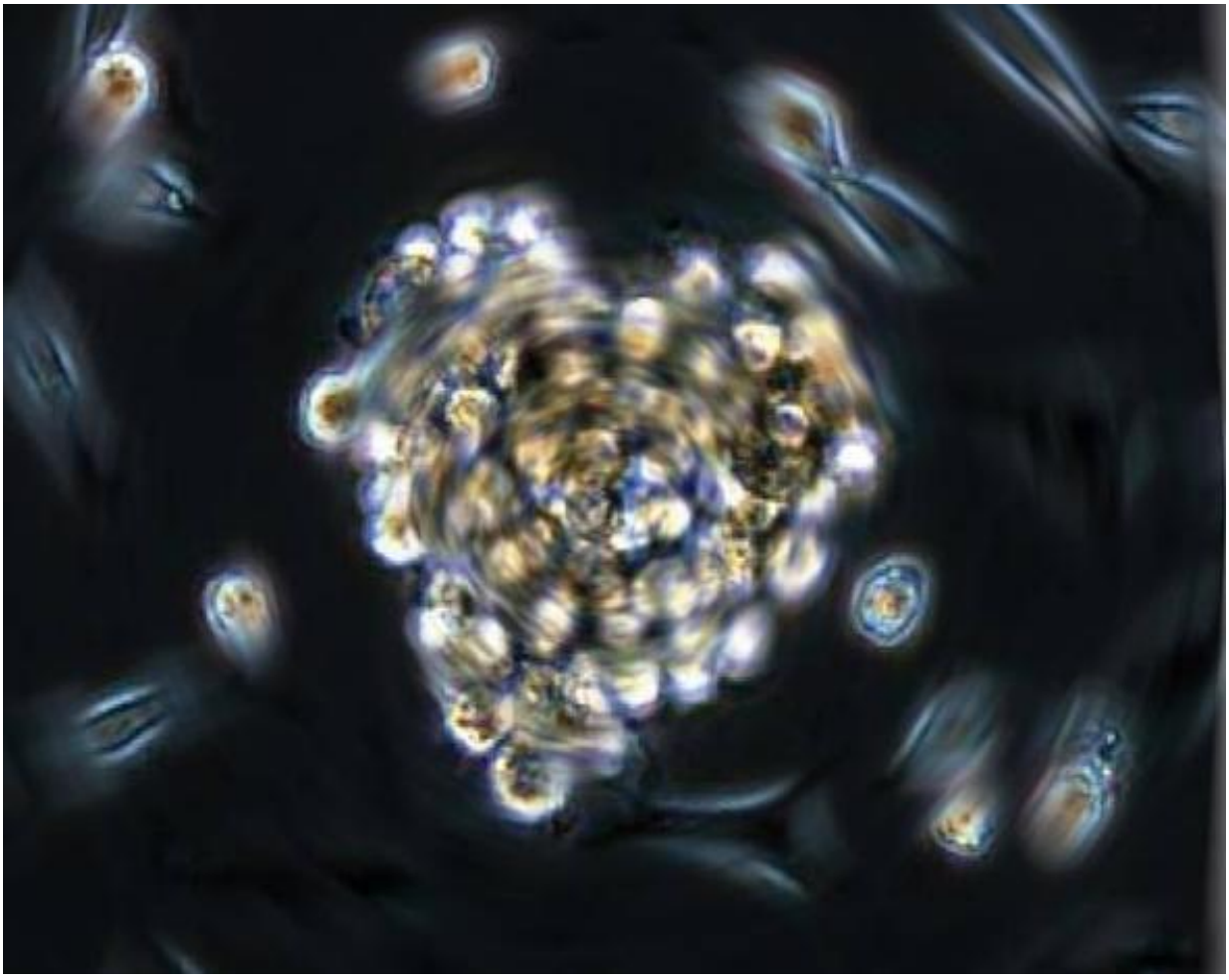

These photomicrograph cardiac stem cells isolated from mouse hearts clustered together in the shape of a heart.

In a way, trying to repair age-related heart damage and trying to fight cancer are opposite problems. Your heart cells' ability to regenerate themselves and proliferate into new, young cells degrades as you get older. They simply lose their proficiency at cell division. Cancer cells, on the other hand, are too good at proliferating. They don't know when to stop, and the overgrowth results in tumors.

This is all very simplified, of course, but it's the basic model described by Mark Sussman, chief research scientist at the San Diego State University Heart Institute, who was recently selected by the American Heart Association's Basic Cardiovascular Science division to receive this year's Distinguished Achievement Award.

The heart in particular seems to be resistant to developing cancerous cells.

"When's the last time you heard of anyone having heart cancer? It's almost unheard of," said Sussman.

That's not surprising from an evolutionary standpoint. If heart cells make a grave transcription error during cell division and your ticker ticks its last tock, there's no fixing the problem. So it makes sense that heart cells are incredibly careful when it comes to proliferating.

The razor's edge

But it's this very meticulousness that makes heart disease such an intractable problem, Sussman explained. Over time, the cells burn themselves out. Their ability to repair themselves and generate fresh replacements gets progressively worse. By the time you reach old age and start experiencing symptoms of age-related heart disease, your cardiac cells are running on fumes and aren't able to properly divide into new cells.

"There's a razor's edge balancing cellular aging and cancer risk," he said.

What if you could use biotechnology to walk that razor's edge? To use the proliferative and survival properties of cancer-prone cells to rejuvenate cardiac progenitor cells—a rare type of stem cell that replicates indefinitely into new heart cells—and get them dividing again, without forming tumors?

That's the aim of one arm of Sussman's research at SDSU. Sussman and his colleagues published a paper in the May 29 issue of the *Journal of Biological Chemistry* exploring the results of taking an enzyme, Pim, known to be associated with growth and survival of certain types of cancer cells, and causing it to be overexpressed in cardiac progenitor cells in mice.

In healthy cells, Pim helps facilitate chromosome splitting, a key part of the cellular division process.

The gene that encodes the production of this enzyme, PIM1, is what's known as a proto-oncogene. That means that by itself, the gene doesn't cause cancer. But when it teams up with another gene, Myc, tumors are likely to form.

Fortunately, the Pim/Myc combination isn't an issue in heart progenitor cells, meaning you could tweak those cells to overexpress the PIM1 gene without raising the risk of cancer.

Protecting against aging

That's exactly what Sussman's team did. They modified mouse heart progenitor cells to overexpress PIM1 in specific locations within the cell, targeting specific locations with more of the critical Pim enzyme in hopes that it would protect against aging-related heart disease.

And it worked. Compared to controls, the mice with overexpressed PIM1 lived longer and showed stronger cell proliferation. But interestingly, the way it worked was different depending on where in the cell the gene was overexpressed.

If the researchers caused PIM1 to be overexpressed in the progenitor cell's nucleus, they saw increased proliferation into new cells. If they overexpressed the gene in a different region of the cell, the mitochondria, they found that the enzyme inhibited the cell's natural self-destruct signals, causing them to live longer.

Scaling up

One technique enhanced cell division, the other warded off cell death. In humans, depending on a person's individual circumstance, either or both of these effects might help restore their cardiac cells to a younger, healthier state.

Sussman and his colleagues have replicated the results with human tissue obtained from people whose hearts have failed and who are living on a ventricular assist device that pumps their blood for them. The research team is currently trying to obtain funding to do human clinical trials wherein they obtain a patient's own cardiac progenitor cells, modify them to overexpress PIM1, then put them back into the patient's heart in hopes of rejuvenating the tissue and spurring the heart to repair itself.

"We're trying to dial back the clock to when their cells had more regenerative potential," Sussman said. "By understanding how and where Pim affects these cells, we can create specialized Pim molecules that get you all the benefits of youthfulness without the risk of cancer."

More information: "Functional Effect of Pim1 Depends upon Intracellular Localization in Human Cardiac Progenitor Cells." *J. Biol.*

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