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Drugs or Cells?

Stem Cells: Plural Paths to Harnessing Pluripotency

By Anette Breindl
Science Editor

The most obvious way to use stem cells is to differentiate them in a petri dish and transplant the resulting cells into tissues or organs that are damaged or diseased.

But there are other ways to harness stem cells. They can be activated with therapeutic proteins or small molecules – as Amgen Inc.'s Epogen (epoetin alfa), which activates hematopoietic stem cells, has shown.

A study published last week suggests that more stem cell stimulating factors remain to be found. A team from the University of Pittsburgh showed that in mice, transplanting muscle-derived stem cells could delay the symptoms of aging, even though the stem cells did not integrate into tissue and directly replace damaged cells. The authors concluded that the cells must be secreting a factor that affected nearby cells.

Corresponding author Laura Niedernhofer's team used something of a brute-force approach: they transplanted young muscle-derived stem cells into mice with two different forms of progeria, or premature aging.

Niedernhofer cautioned that the studies were done "in a model of progeria – it is not direct proof that this is going to work in normal aging." Still, she told *BioWorld Insight*, the mouse model mimics not only human progeria, but also normal human aging "very well." The mice develop symptoms like osteoporosis, disc degeneration and muscle wasting – "many of the things we fear as we age."

One model is quite extreme, with animals having a natural lifespan of only three to four weeks. In such animals, the stem cell transplants prolonged lifespan – a result that has led to much buzz about the fountain of youth. But Niedernhofer said she was more excited about the results in a second, milder, model that usually allows mice to live for seven months. In these animals, the transplanted cells "delayed the onset of 75 percent of aging symptoms."

Niedernhofer cheerfully admitted that the fact that her team's approach worked "surprised us too . . . serendipity sometimes works in your favor."

And the surprise continued with how the cells do it. They do not appear to integrate into tissue to replace damaged cells.

"We expected the cells to home towards muscle tissue," since they were muscle derived, "or at least tissue that was of the same mesodermal origin," Niedernhofer said.

Instead, the cells were widely distributed, mainly in the connective tissue next to major organs – and one place where Niedernhofer and her team specifically did not detect them was in muscle tissue.

Both the location of the cells and their numbers, which were too low to account for their effects, suggest to Niedernhofer and her colleagues that the cells must be secreting factors that benefit the progeric mice. To date, the team has not identified those factors, but they are working on doing so.

"That is really the goal," Niedernhofer said. "We're dying to know what those factors are."

Such factors could conceivably be made recombinantly and used as treatment, bringing the benefits of stem cells without the need for a transplant. And even if that turns out to be impractical, Niedernhofer and her team showed in their studies that stem cells from old animals, which are normally less sprightly than younger ones, could be rejuvenated by exposing them to the culture medium of younger stem cells – both supporting the idea that secreted factors are at work, and suggesting that if

using the factors directly as therapeutic proteins does not pan out, isolating stem cells and retransplanting them after a spa day with culture medium could allow autologous transplantation.

Companies working on activating stem cells pharmacologically include Juventas Therapeutics Inc., which is developing therapeutics to improve stem cell homing for cardiac repair, and Neuralstem Inc., which recently started a Phase Ib trial with its neural stem cell activator NSI-189 to treat major depression. The company is developing both drug treatments and cell-based treatments for nervous system disorders.

Neuralstem's chief scientific officer Karl Johe told *BioWorld Insight* that several conditions need to be met for pharmacological stimulation of stem cells to be a viable strategy. Specifically for brain disorders, "one limitation is that endogenous stem cells are limited to only one area in the brain," namely, the hippocampus. This means that activators such as NSI-189 are likely to be useful only in diseases with hippocampal involvement.

Those diseases tend to be psychiatric rather than neurological. In addition to depression, they include Alzheimer's disease, schizophrenia, post-traumatic stress, and possibly, age-related dementia. Although animal studies have also shown that stem cell numbers can increase in the injured area in some neurological diseases such as stroke, Johe said that in neurological diseases stem cell proliferation is "not a widespread phenomenon."

Another question is what sort of biological effects on the brain are necessary for a therapy to be successful. Depression, for example, is characterized by a relatively subtle imbalance of brain chemistry, and so activating endogenous stem cells has a chance of success. But in his opinion, for diseases where more extensive rewiring of neural connections is necessary – such as in spinal cord injury and Huntington's disease, both areas where Neuralstem is pursuing cell-based approaches – "a simple small molecule cannot be expected to do that kind of drastic repair." ■