Researchers overcome major obstacle for stem cell therapies and research

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Stem cells show great potential to enable treatments for conditions such as spinal injuries or Lou Gehrig's disease, and also as research tools. One of the greatest problems slowing such work is that researchers have found major complications in purifying cell mixtures, for instance to remove stem cells that can cause tumors from cells developed for use in medical treatments. But a group of Scripps Research scientists, working with colleagues in Japan, have developed a clever solution to this purification problem that should prove more reliable than other methods, safer, and perhaps 100 times cheaper.

The work appears in the current edition of the journal *Cell Research.*

Effective tricks for separating stem cells from other types are essential for many emerging medical treatments. These techniques begin with researchers inducing stem cells to take specific forms, or differentiate, for instance into nerve cells. These differentiated cells might then be used to repair a spinal cord injury. Other cells might enable a diabetic's body to produce adequate insulin.

A key problem is that in the differentiation process, at least some stem cells inevitably remain in their undifferentiated, or pluripotent, state. These cells can grow to form tumors in patients if injected along with differentiated cells, a concern that has already led the US Food and Drug Administration (FDA) to delay clinical trials for promising stem cell-based therapies.

A New Approach

To date, almost all attempts at purification have focused on developing antibodies—immune system attack cells—that can remove or destroy stem cells in mixtures. But this approach has had shortcomings. Effective antibodies are difficult and expensive to develop, and their use in medical therapies raises safety issues because they are produced in animals.

The Scripps Research team, led by Professor of Developmental Neurobiology Jeanne Loring, was looking for a new route to solve the purification and safety problems. The group recently began experimenting with chip-based tools known as lectin arrays. At various points on these devices, plant-produced proteins called lectins are attached. These lectins bind with specific sugars including some found on the surface of cells.

Working in the lab with cellular components, rather than whole cells, the Loring team first found that specific combinations of sugars and proteins known as glycoproteins on stem cells reliably bind to certain lectins. They were then able to exploit this connection to purify cell mixtures.

"When we discovered there was a specific binding pattern, we decided we should just go for it and see whether we could use the lectins to purify cells," said Yu-Chieh Wang, the first author of the research article. "We tested the idea and it works very well, and lectins are readily available and inexpensive."

After identifying the lectin that bound best with stem cells, the group took the work to the next level to show that they could actually separate out stem cells. To accomplish this, they first attached the lectin to tiny beads. Then they exposed these beads to mixtures of stem cells along with non-stem cells.

The researchers used a range of different types of both embryonic stem cells and induced pluripotent cells, which are embryonic stem cell-like cells that are produced by inserting certain genes into skin cells. They included cell lines from both Scripps Research and the labs of their collaborators in Japan and the United States.

In every case, the team found that the stem cells bound remarkably well to the beads, while the cells that washed past were almost all non-stem cells; this meant that both cell types could be collected separately for use in research or in treatments.

Purity's Potential

Possible uses for the new technique are essentially as numerous as those for stem cells themselves. Lectin purification could be used with any of a huge range of therapies currently in development. In addition to low cost and reliability, the lectins used are plant products, so they do not introduce the type of safety concerns that could arise from using antibodies that are produced by animal cells.

Even in more basic research, effective studies using stem or differentiated cells generally requires purification so that effects can be identified and tracked without introducing complications from impurities in a group of cells.

Loring's group, for instance, is studying the production of nerve cells that might be used to treat a specific type of autism caused by a known genetic mutation. Producing the nerve cells needed is a laborious process that will be more efficient with better purification.

The Loring team is also working to identify different binding patterns that would allow them to similarly purify mixtures of specific types of non-stem cells. "In theory, this should allow us to pull any cell type out

of any mixture," she said of the basic lectin technique.

At the more basic research level, because all the different stem cell lines from both humans and animals seem to produce similar glycoproteins binding to the lectins, it is possible these glycoproteins infer some basic qualities fundamental to the pluripotent state. Loring and her colleagues are exploring this possibility in hopes of better understanding stem cells' still mysterious abilities to transform into any type of cell. "We may have uncovered something really fundamental about pluripotency," said Loring.

More information: "Specific lectin biomarkers for isolation of human pluripotent stem cells identified through array-based glycomic analysis," www.cell-research.com/AOP/September-6-4.htm

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