Human-derived tissue sheds light on the origins of spinal muscular atrophy.

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What is spinal muscular atrophy?

Spinal muscular atrophy is a motor neuron disease that causes muscle wasting in infants and young children [1]. It is the second most common genetic disorder after cystic fibrosis, occurring in approximately 1 in 8000 births.

Ground-breaking research out of Germany

German scientists have discovered that this neurological condition begins earlier in human development than previously believed [2]**.** Their results suggest that diagnosing and treating this disorder might need to start in the womb.

Using two novel technologies, they studied the embryological development of spinal cord tissue from a patient with spinal muscular atrophy and compared it to its healthy counterpart.

They found that the disease, usually diagnosed in the first year or two of life, can now be detected early in the embryo's development.

Hold on, they used human embryos?

Actually, no. They used inducible pluripotent stem cells. First developed in 2006, this novel class of stem cells can be produced from fully differentiated mature cells such as skin or blood —no embryos required [3].

Better still, they can be taken directly from the person suffering from a disease to study what is happening in that particular individual—now that's personalised medicine!

What do stem cells do?

Stem cells are immature, undifferentiated cells in the embryo that transform into specialised tissue, such as heart, lung, or skin cells, during the fetus's development.

Artificially produced stem cells are similar to naturally occurring embryonic stem cells. They can be turned into almost any other cell in the human body, including spinal cord motor neurons. The researchers just add specific regulatory factors to create the particular tissue of their choosing [4].

That's where the second technique came in—organoid technology. The German team induced the stem cells to form motor neurons, the very cells that people with spinal muscular atrophy

lack. Then, they converted these developing stem cells, swimming in a Petrie dish, into a spinal cord organoid complex and studied them in their laboratory.

What on earth are organoids?

Organoids, the size of a grain of rice, were first developed in 2009 in intestinal cells [5]. Organoids are lab-grown tissues produced from stem cells. They resemble natural tissue and can help researchers study drug interactions at the tissue level. Furthermore, tissue regeneration studies show promise in areas like spinal cord repair [6].

These two new technologies allow doctors to mimic the embryological development of the spinal cord in a developing fetus.

What did they see?

To do this, blood was taken from a patient with spinal muscular atrophy. The researchers "corrected" the genetic mutation that causes the disease in the lab, creating a healthy version of the patient's cells. See this article for more information on the genetics and treatments for spinal muscular atrophy [7].

They compared the embryological development of their patient's tissue with the newly corrected version of the patient's cells.

Using a highly sensitive technique called longitudinal single-cell RNA sequencing, they showed key differences between the tissues early in embryonic development—before motor neuron cells had formed. By contrast, the patients' "corrected" tissue showed similar growth to that of healthy tissue from other donors.

Organoids from the patient's tissue had fewer motor neuron progenitor cells than the "corrected" tissue. These progenitor cells were in the process of transforming from stem cells into functional mature motor neurons. Motor neurons in the spinal cord are responsible for nerve conduction in the body and the control of muscle movement. This finding indicated that dysfunctional spinal muscular atrophy appears before the formation of motor neurons in human development.

The scientists speculated that these early abnormalities might explain why current gene therapy treatments (administered after birth) are only partially successful in treating the disease.

Could this discovery allow doctors an opportunity to provide gene therapy to the developing fetus before birth?

Shinya Yamanaka and the birth of regenerative medicine.

In 2006, Shinya Yamanaka, a cell biologist at Kyoto University in Japan, discovered how to transform adult human skin cells back into embryo-like stem cells. The inducible pluripotent stem cell (iPSC) was born. He found that just four transcription factors, now termed Yamanaka factors, needed to be supplied to the lab-grown cells to accomplish this [3]. Eighteen years later, dozens of iPSC-based therapies are in clinical trials, and Professor Yamanaka has a Nobel Prize.

A way forward …

Stem cell technology has revolutionised regenerative medicine and given hope to both young and old. However, these results are preliminary, and life-changing therapy could still be some years away.

From embryonic gene therapy to the repair of spinal cord function in people with quadriplegia, stem cells and organoid technology can potentially bring about profound and lasting change for those who need it.

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