Researchers rejuvenate mouse organs through cellular reprogramming

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Scientists have observed signs of rejuvenation in the pancreas, liver, spleen, and blood of mice after applying one cycle of cell reprogramming. To achieve this, the researchers have characterized rejuvenation by studying molecular marks in the DNA, gene expression, and cell metabolism.

Many diseases, including cancer, are associated with ageing and they are becoming more prevalent as life expectancy increases. Therefore, studying and understanding these processes is crucial if we are to deal with these conditions and also promote healthier ageing.

One of the fields within research into ageing addresses rejuvenation, that is, the restoration of the characteristics of younger cells in aged cells or tissues.

Headed by ICREA researcher Dr. Manuel Serrano, scientists from the Cellular Plasticity and Disease lab at IRB Barcelona have managed to rejuvenate some mouse organs and tissues via cell reprogramming. Specifically, the scientists have observed significant changes in the pancreas, liver, spleen, and blood of the animals.

"This work sought to identify the initial processes of *in vivo* reprogramming and cell rejuvenation and pinpoint those that can be modified in future studies, whether by drugs or at a nutritional level," explains Dr. Serrano.

The Yamanaka factors and cell reprogramming

All tissues in our bodies are characterised by having highly specialised cells, such as neurons or muscle cells, among many others. The identity of these cells was considered fixed and inflexible until the Japanese researcher Shinya Yamanaka found a way to alter their identity (that is to say, "reprogram them") by introducing high levels of four proteins, called the "Yamanaka factors" (OCT4, SOX2, KLF4 and MYC), into them. Although these proteins can be found in some of our cells, it is the simultaneous presence of high levels of all four that can alter cell identity.

This rejuvenation technique allows something previously unimaginable, namely taking cells that are easy to obtain from a patient (such as skin cells) and converting them into others that are difficult or impossible to collect, for example, heart cells or neurons, which can then be used for cell therapy applications.

Thanks to these advances, Dr. Yamanaka was awarded the Nobel Prize in Medicine in 2012, only six years after his discovery.

A study led by Dr. María Abad and Dr. Serrano in 2013 reported on successful cell reprogramming inside experimental animals, that is to say, without needing to extract the initial cells, reprogram them *in vitro*, and implant them. However, it is important to note that changing the identity of the cells in a living organism causes considerable imbalances in tissues, which lose their function and end up causing a type of tumour called a teratoma, typical of the embryonic state. Despite this, these findings paved the way to studying reprogramming directly in animals.

The milestone of organ rejuvenation

Three years later, Dr. Juan Carlos Izpisúa-Belmonte's laboratory, in La Jolla (California), observed that when reprogramming was started in animals and interrupted halfway through, the cells returned to their initial identity, thus preventing cell imbalances and teratomas.

To their surprise, Dr. Izpisúa-Belmonte´s team observed that when this partial and reversible reprogramming process was repeated over multiple cycles, it resulted in the cellular rejuvenation of the whole organism, making the mice healthier and better protected to a variety of diseases.

Thus, in 2016, this method of cellular rejuvenation -- which is still not fully understood and is the research focus of numerous laboratories -- stirred enormous interest.

Another step towards understanding ageing

In this latest study, published in the journal *Aging Cell,* the researchers have examined the effects of a single cycle of Yamanaka factor stimulation in order to better define the mechanisms involved. To this end, they have probed the changes in metabolism, gene expression and cellular DNA status that occur during ageing and how these changes are partially reversed by reprogramming.

"We wanted to study the initial effects of the rejuvenation process, and it was a pleasant surprise to see such evident improvements at the molecular level, above all in the pancreas," says Dr. Dafni Chondronasiou, first author of the article.

This work has been carried out in collaboration with about 20 international institutions. Of note is the contribution of the groups headed by Dr. María Abad at the Vall d´Hebron Institute of Oncology in Barcelona, Dr. Mario Fraga at the Spanish National Research Council (CINN-CSIC), the University of Oviedo (IUOPA) and the Institute of Medical Research of Asturias (ISPA); Dr. Guido Kroemer at the Institut Gustave Roussy in Paris, and Dr. Wolf Reikat the Babraham Institute in Cambridge (UK), recently appointed Director of the Altos Labs Cambridge Institute.

Story Source:

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Journal Reference:

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