Muse cell offer new hope for reparative medicine

Researchers at Tohoku University in Japan have discovered the potential of Muse cells to be the new tool of reparative medicine in the 21st century

You are investigating endogenous non-tumorigenic pluripotent Muse cells, how are you building on existing stem cell research?

Up to now, embryonic (ES) and induced pluripotent stem (iPS) cells were considered the gold-standard pluripotent stem cells for regenerative medicine. These are highly pluripotent and are able to generate all kinds of cells. On the other hand, there are several problems that need to be overcome for the use of these cells in clinical applications: the risk of tumorigenesis; time and cost for the preparation and differentiation of cells prior to transplantation; ethical issues with the use of fertilised eggs in ES cells; and the necessity of surgical operations for transplantation. Since Muse cells are non-tumorigenic and are able to repair damaged tissues through an intravenous drip of donor-derived cells, they may resolve many of the current problems in regenerative medicine.

Can you explain the Reparative Medicine approach you are working on?

Muse cell treatment is performed through an intravenous drip of donor-derived Muse cells. This is innovative compared to other stem cell types in regenerative medicine because Muse cell treatment does not require a surgical approach for delivering cells to the target organ. Therefore, generalisation of regenerative medicine to general city hospitals and clinics is possible. In addition to this, Muse cells also have other strengths mentioned above. In summary, Muse cells do not require the introduction of new genes, nor differentiation prior to transplantation. Cells from the patient themselves are also not required as donors are compatible, and there are not any ethical complications. We like to call our approach ‘reparative medicine’ rather than regenerative medicine. They accumulate to damaged tissue and how we receive signals from their microenvironment.

What type of research work are you currently involved in?

We are propelling the Muse cell project in the two major streams: clinical application and basic research. The study for clinical application is conducted by Life Science Institute, Inc. (LSII) and clinical doctors. LSII succeeded in generating clinical-grade Muse cell preparation. After approval from the Japanese regulatory organisation, LSII started clinical study in acute myocardial infarction and stroke in 2018, based on the intravenous drip of donor-derived Muse cells. After evaluating safety of Muse cell, LSII will expand target diseases for clinical trial. The basic research is mainly conducted by our laboratory and other independent laboratories. In our lab, we aim to unveil the dynamics of Muse cells in vivo, both at steady and diseased states. We are also attempting to clarify the mechanism for how Muse cells accumulate to damaged tissue and how they receive signals from their microenvironment to spontaneously differentiate into tissue-compatible cells after homing.

Can you talk briefly about what you hope to learn from your work?

I would like to learn the mechanism of how our body maintains tissue homeostasis throughout our life. The concept of repair seems too ordinary and we tend to take it for granted. However, the mechanism of the innate repair system is not well known. Muse cells are one of the explanations for how we maintain our body through daily minute repairs.

Furthermore, full utilisation of the innate reparative system is safe and thus may provide medical care compatible with that of nature. Muse cells may open a door to a ‘Next-Generation Medical Care’ compatible with the body’s natural repair system, which does not rely on artificial gene introduction or manipulation. In this sense, the medical care provided by Muse cells is ‘reparative medicine’ rather than regenerative medicine.

The future of medicine in the 21st century is rooted in the development of several key tools and techniques. Acquisition and analysis of large amounts of medical data will allow healthcare providers to understand the trends and causes of disease like never before. Greater ability to analyse an individual’s health will also allow for the tailoring and personalisation of medical treatment to the individual. Finally, a key improvement in healthcare will be in regenerative medicine. The aim of such medicine is to repair the damage done by disease and accidents in such a way as to fully regenerate the area as new. Such an approach would lead to fewer complications from an injury or disease, less pain and better long-term recovery.

The torch-bearer for regenerative medicine has long been stem cell technology. Stem cells are called capable of differentiating into a wide range of different cell types. This is known as the potential of the stem cell. Professor Mari Dezawa, a researcher at Tohoku University in Japan, is an expert in this field. She explains that there are various different levels in stem cell potency, but where regenerative medicine is concerned, pluripotent stem cells capable of becoming almost any kind of cell are most desired. ‘For just over a decade, the two candidates for stem cell medicine have been embryonic stem cells (ES) and induced pluripotent stem cells (iPS).’ outlines Dezawa. ‘ES cells are derived from the fertilised embryos and are thus both extremely potent and ethically questionable. IPS cells are generated from adult cells by introducing several genes, reverted to a pluripotent state and re-differentiated before being grafted onto the site of regeneration.’ This is a lengthy and costly process that involves invasive and sometimes risky surgery, and as a result neither solution is currently ideal.

Dezawa and her team have discovered a novel stem cell type that is ideal candidate for regenerative medicine. Known as Multilineage-differentiating stress enduring cells (Muse cells), these are a type of stem cell that is essential in day-to-day repairs in the body. They reside all over the body, including in the bone marrow, peripheral blood and connective tissues. ‘The natural role of Muse cells is that they function as endogenous reparative stem cells in our body, contributing to minute reparative maintenance,’ Dezawa outlines. ‘Therefore, they are able to differentiate into the broad spectrum of cell-types that comprise our body. They accumulate to damaged tissue either through blood stream or local migrations, spontaneously differentiate into tissue-compatible cell and repair the tissue.’

A new candidate for next-door generation medical care

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REMARKABLE PROPERTIES
Since discovering the cells in 2007, Dezawa and her team have spent years honing the understanding of Muse cells. This included many of the very basics, such as the best way to consistently isolate and culture them and their basic role in nature. Once they began to understand more about the cells, their potential for use in regenerative medicine appeared clear. ‘Not only are Muse cells capable of repairing tissues all across the body, but they do so in a non-tumorigenic way,’ confirms Dezawa. ‘This is in contrast to ES and iPS cells which proliferate extremely quickly and can stray from the site of repair causing an unwanted tumour.’ She also found that Muse cells naturally migrate to the site of injury. This means that they need only be injected into the patient and they should find their own way to the site of injury.

Muse cells also have specific systems to modulate immunoreactions. For example, HLA-G is one of the factors expressed in fetal cells in placenta that strongly suppress immunological attack from maternal immune system. Thus, fetal cells are protected from maternal immunological attack. Since Muse cells also express HLA-G, allogenic Muse cells can escape from immunorejection after systemic administration to patients. Through various tests Dezawa’s team found that the allogenic Muse cells appeared to have no harmful effects and should therefore prove safe for general use. ‘As Muse cells need only be grown to create more of them, there is no need to work out how best to differentiate them in vitro,’ she points out. As a result of their huge potential, Dezawa has teamed up with Life Science Institute, Inc., a healthcare and medicine provider, to begin trials and, hopefully, distribution of the treatment.

FUTURE POTENTIAL
The future of Muse cells is extremely promising. Human trials are beginning for their use in acute myocardial infarction and stroke patients. The range of potential uses is almost limitless if these trials are successful. For Dezawa and her team this is culmination of many years of work, however, there is still much to find out. ‘Muse cells are still a very interesting target from a biological point of view,’ she confirms. ‘We are now planning to expand our study of their biology in order to compare the endogenous reparative systems of human against those of lower animals such as amphibians and fishes.’ Further foundational work such as this will continue to shed light on the clinical applications which Dezawa and her team will also remain heavily involved with.