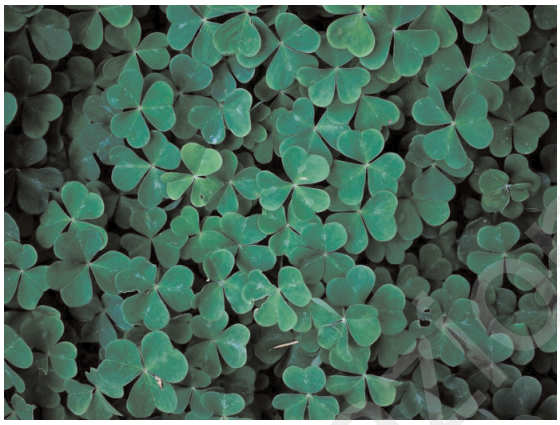
Land of hope and dreams

Selection of life science and translational medicine literature

by Marco Confalonieri



A pairs of articles recently published on Nature reported new findings about an intriguing biological phenomenon of great interest. The Authors found that just squeezing or bathing cells in acidic conditions can readily reprogram them into an embryonic state. It's enough to expose differentiated mature cells to low pH, and physical squeezing through a capillary tube to obtain totipotent stem cells. This innovative and unsophisticated method designed by a team of Harvard's researchers can provide stem cells faster and more efficiently than iPS (induced pluripotent stem cells). The simplicity of this revolutionary method seems to mimic Mother Nature's way of responding to injury. No genes, no nuclear transfer or protein reactions was used to reprogramming differentiated cells back to a pluripotent or even totipotent state, but simply by exposing the cells to extreme environmental stress, as showed by the Authors also by means of online videos. The researchers report the creation of iPS like cells via sub-lethal stress and have named the cells stimulus-trigged acquisition of pluripotency (STAP) cells. The second paper reports the astounding finding that the STAP cells are in fact not just pluripotent, but totipotent and can make extraembryonic tissues too. That seems really surprising. Both studies have practical implications for potentially simple reprogramming of cells, and also suggest some fundamental concepts about cell and organismal biology that are exciting novelties including the idea that differentiated cells can have an extreme plasticity never imagined before. Moreover, we can argue that when animals and hence their cells sustain injuries, a stem cell-like program may be induced without direct nuclear manipulation. We urge these results may be reproducible by other labs also in human adult cells before this revolutionary method may be considered a cornerstone of unique importance for biology and medicine, as it could be considered at a first look.

1) Stimulus-triggered fate conversion of somatic cells into pluripotency

Haruko Obokata, Teruhiko Wakayama, Yoshiki Sasai, Koji Kojima, Martin P. Vacanti, Hitoshi Niwa, Masayuki Yamato & Charles A. Vacanti.
Nature 2014 Jan 30;505:641-647

Abstract

Here we report a unique cellular reprogramming phenomenon, called stimulus-triggered acquisition of pluripotency (STAP), which requires neither nuclear transfer nor the introduction of transcription factors. In STAP, strong external stimuli such as a transient low-pH stressor reprogrammed mammalian somatic cells, resulting in the generation of pluripotent cells. Through real-time imaging of STAP cells derived from purified lymphocytes, as well as gene rearrangement analysis, we found that committed somatic cells give rise to STAP cells by reprogramming rather than selection. STAP cells showed a substantial decrease in DNA methylation in the regulatory regions of pluripotency marker genes. Blastocyst injection showed that STAP cells efficiently contribute to chimaeric embryos and to offspring via germline transmission. We also demonstrate the derivation of robustly expandable pluripotent cell lines from STAP cells. Thus, our findings indicate that epigenetic fate determination of mammalian cells can be markedly converted in a context-dependent manner by strong environmental cues.

2) Bidirectional developmental potential in reprogrammed cells with acquired pluripotency

Haruko Obokata, Yoshiki Sasai, Hitoshi Niwa, Mitsutaka Kadota, Munazah Andrabi, Nozomu Takata, Mikiko Tokoro, Yukari Terashita, Shigenobu Yonemura, Charles A. Vacanti & Teruhiko Wakayama
Nature 2014 Jan 30;505:676-680

Abstract

We recently discovered an unexpected phenomenon of somatic cell reprogramming into pluripotent cells by exposure to sublethal stimuli, which we call stimulus-triggered acquisition of pluripotency (STAP). This reprogramming does not require nuclear transfer or genetic manipulation. Here we report that reprogrammed STAP cells, unlike embryonic stem (ES) cells, can contribute to both embryonic and placental tissues, as seen in a blastocyst injection assay. Mouse STAP cells lose the ability to contribute to the placenta as well as trophoblast marker expression on converting into ES-like stem cells by treatment with adrenocorticotropic hormone (ACTH) and leukaemia inhibitory factor (LIF). In contrast, when cultured with Fgf4, STAP cells give rise to proliferative stem cells with enhanced trophoblastic characteristics. Notably, unlike

conventional trophoblast stem cells, the Fgf4-induced stem cells from STAP cells contribute to both embryonic and placental tissues *in vivo* and transform into ES-like cells when cultured with LIF-containing medium. Taken together, the developmental potential of STAP cells, shown by chimaera formation and *in vitro* cell conversion, indicates that they represent a unique state of pluripotency.