BIOLOGY AND BIOCHEMISTRY

Reprogram to pluripotency: a new logic and a chemical cocktail

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Somatic cells from animals and humans can be reprogrammed into pluripotent stem cells by pluripotency factors. Hongkui Deng and colleagues discovered that pluripotency can also be induced with exogenous lineage specifiers via balancing competing differentiation forces. In a related study they achieved, for the first time, restoration of pluripotency in adult somatic cells using a chemical cocktail alone.

'Rejuvenation' or '返老还童' has been desired throughout human history. Evidence of this exists in ancient records [1] and arts (Fig. 1). Biologists have been on quest for cellular rejuvenation, highlighted by the Nobel Prize in Physiology or Medicine awarded last year jointly to Gurdon and Yamanaka '*for the discovery that mature cells can be reprogrammed to become pluripotent*', a capacity to generate all cell types in the body. A new field is emerging with goals to understand basic mechanisms underlying cellular reprogramming and to develop efficient and safe reprogramming approaches for use in regenerative medicine. Two recent studies from Deng's group at Peking University of China have provided novel insights into the mechanisms of reprogramming to pluripotency, reaching a major milestone in the field [2,3].

The method first reported by Yamanaka to reprogram somatic cells to induced pluripotent stem cells (iPSCs) by the forced expression of four transcription factors, OCT4, SOX2, KLF4 and c-MYC (now named Yamanaka factors), was based on the hypothesis that core transcription factors normally expressed by embryonic stem cells, once overexpressed in somatic cells, can suppress the original somatic cell fate and reset the transcript network to achieve a new 'ground-state' of pluripotency [4]. Since then, iPSCs have been derived from many somatic cell types from different species, including humans, using a various combinations of factors [5]. OCT4 appears to be the most critical factor for reprogramming, as all three other Yamanaka factors can be substituted and OCT4 alone is sufficient to reprogram certain cell types into iPSCs [5]. Deng's group performed large-scale expression cloning of OCT4 substitutes for reprogramming [2]. Surprisingly, multiple mesendodermal lineage specification genes, including GATA3, can replace OCT4 to reprogram mouse fibroblasts into pluripotency, together with the other three Yamanaka factors. Mechanistically, OCT4 and its substitutes attenuate the expression of several ectodermal lineage specification genes that were induced by SOX2. In contrast, ectodermal lineage specification genes, such as GMNN, can replace SOX2. Strikingly, the concurrent expression of two counteracting lineage specification genes GATA3 and GMNN is sufficient to induce pluripotency in the absence of any exogenous core pluripotency factors, normally expressed by embryonic stem cells. As opposed to the classic 'ground-state' model, these results lead to a new 'seesaw' model in which the pluripotent state can be achieved by a fine balance between competing forces that drive differentiation into mutually exclusive lineages. A recent study from an independent group showed that lineage specifiers can replace OCT4 and SOX2 to reprogram human fibroblasts to iPSCs [6], thus supporting the model in humans. Together, these findings generate a new framework for understanding pluripotency and reprogramming.

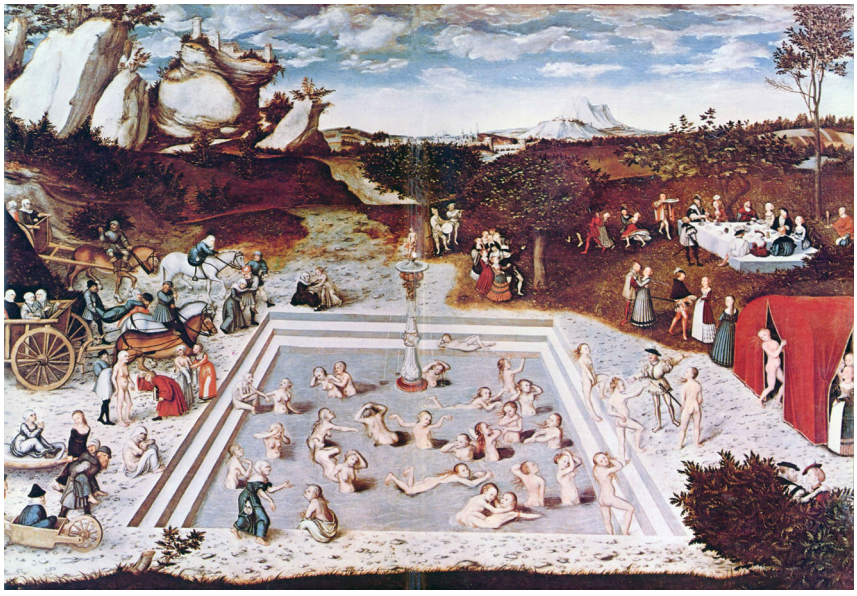

Figure 1. *The Fountain of Youth* by Lucas Cranach the Elder. This image is in the public domain.

In the second study, Deng's group started with a chemical compound screen and found OCT4 replacements in reprogramming to pluripotency [3]. Chemical reprogramming is more appealing in the context of safety for future clinical applications as it removes the need of exogenous reprogramming factors, many of which are oncogenes. Deng's group was already able to replace the other three Yamanaka factors with a chemical cocktail identified from a previous screen [7]. A combination of chemical substitutes for all four Yamanaka factors turned out to be insufficient for complete reprogramming. Moving forward, Deng's group performed a third

chemical screen and finally arrived at a cocktail of seven small molecules that effectively reprogram mouse fibroblasts into functional iPSCs that passed the most stringent functional tests. Mechanistically, the chemical combination up-regulates two pluripotency genes SOX2 and SALL4 as well as several extra-embryonic endoderm genes, including GATA4 and GATA6 [3]. This result is consistent with their first study, in which SALL4, GATA4 and GATA6 can replace OCT4 in the induction of pluripotency [2]. Together, this study not only achieved a major milestone in complete chemical reprogramming of somatic cells into a pluripotent state, but also provided new mechanistic insight underlying reprogramming. More importantly, the feasibility of chemical reprogramming of mouse cells opens doors for the future generation of safe human iPSCs for clinical applications and provides dynamic tools to demystify the black box of the reprogramming process.

In summary, focusing on genetic and chemical replacements of OCT4 in reprogramming, Deng and colleagues discovered a new logic and a chemical cocktail for reprogramming to pluripotency. Deng's group represents one of many laboratories in China that have been making major contributions to the fields of reprogramming, stem cell biology and regenerative medicine. Given the major drive in China for biomedical research, more landmark discoveries will surely be forthcoming, moving closer to the dream of eternal youth.

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MATERIALS SCIENCE

Functionalized interleaf technology in carbon-fibre-reinforced composites for aircraft applications

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At the recent 19th International Conference of Composite Materials (ICCM-19), in Montreal, Professor Xiaosu Yi from the Beijing Institute of Aeronautical Materials, Aviation Industry Corporation of China, gave a plenary lecture on 'How to Make the Structural Composites Multi-functional'. His lecture highlighted the recent developments from his research team in functionalized interleaf technology (FIT). Their work has improved both the electrical conductivity and the impact damage resistance of carbon-fibre-reinforced composites for aircraft applications.

Carbon-fibre-reinforced polymer (CFRP) and glass-fibre-reinforced polymer (GFRP) composite structures are widely used in today's aerospace, green energy, marine, sport and transportation industries. These materials provide manufacturers and builders with cost-competitive alternatives to conventional metal alloys. However, the introduction of polymer composites in mainframes of modern structures presents special challenges and issues regarding their multi-functional properties (e.g. electrical and thermal conductivities) in addition to the potential risk of incurring extension of interlaminar damage under impact and fatigue loading, due to the brittle nature of the matrix resins. For example, such composite structures are poor conductors of extreme electrical currents generated by a lightning strike. Composite materials are either not electrically conductive at all under a moisture-free condition (e.g. GFRPs with electrical conductivity in the order of 10^{-16} [S m^{-1}]) or are significantly less conductive (e.g. CFRPs with the order of 10^{0}–10^{3} [S m^{-1}]) than metals (with the order of 10^{6}–10^{7} [S m^{-1}]).

Two approaches of FIT were detailed in Professor Yi's lecture. The first approach is associated with the use of perforated amorphous phenolphthalein poly-ether-ketone (PEK-C) films as interleaves [1,2]. When an interleaved composite laminate with a thermosetting matrix (e.g. bismaleimide) is cured, highly toughened thin interlaminar regions are established with phase inversion and phase separation. The key advantage of such a technique is