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RESEARCH HIGHLIGHT

Bmi1 puSHHes reprogramming

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In 2006, the group of Shinya Yamanaka demonstrated that somatic cells could be reprogrammed into induced pluripotent stem cells (iPSCs) by ectopic expression of four transcription factors associated to stemness: Oct4, Sox2, Klf4 and c-Myc [1]. This groundbreaking discovery opened the possibility of generating patient-specific cells for research, drug development and regenerative medicine. Due to the tremendous potential of its clinical applications, understanding the process of reprogramming has become a priority and one of the most fascinating biomedical research topics.

In the last five years, scientists around the world are racing to solve two main issues regarding reprogramming. The first one is technical and consists in improving the efficiency of reprogramming and avoiding the necessity to integrate exogenous DNA into the reprogrammed host cells. Several advances have been made over the last years, both in replacing individual factors with chemicals, and in eliminating the need to alter the genome of the host cell [2]. However, pure chemical reprogramming has not yet been achieved despite intense efforts, and integration-free reprogramming is still poorly efficient [2]. Another major focus of research is to understand the molecular mechanisms underlying reprogramming. However, the low efficiency of the process makes this task challenging. Recently, our group reported that the *Ink4a/Arf* locus is a major barrier for reprogramming [3]. For example, complementation of the Yamanaka factors with an shRNA against the *Ink4a/Arf* locus greatly improves reprogramming efficiency [3].

Bmi1 is part of the Polycomb Repressive Complex 1 (PRC1) involved in transcriptional silencing through heterochromatinization. The *Bmi1* gene is a well-characterized oncogene that silences the *Ink4a/Arf* locus and cooperates with *c-Myc* in lymphomagenesis [4] and it is overexpressed in several human cancers [5]. In addition to this, Bmi1 has been shown over the years to be a key regulator of self-renewal in multiple adult stem cells including hematopoietic stem cells (HSCs), neural stem cells (NSCs) and, more recently, prostate stem cells (PrSCs) [5, 6]. Sonic hedgehog (Shh) signaling is a major developmental signaling pathway and Bmi1 together with N-Myc and cyclin D2 are major downstream effectors of Shh for proliferation and self-renewal of cerebellar progenitor cells [5]. Based on the impact of Bmi1 on the *Ink4a/Arf* locus and on stem cells, one might speculate what is the role of Bmi1 in reprogramming?

In a recent paper published in *Cell Research*, Moon *et al.* [7] explore the role of Bmi1 in reprogramming. When overexpressing Bmi1 in mouse embryonic fibroblasts (MEFs), the authors show a marked increase in the levels of endogenous Sox2, N-Myc and Klf4, together with drastically reduced levels of Ink4a, Arf and p53. In line with this, Moon *et al.* demonstrate that iPSCs can be generated from MEFs using a simplified reprogramming cocktail consisting only of Bmi1 and Oct4, and with comparable efficiency to the Yamanaka three-factor cocktail (Sox2, Klf4 and Oct4). This is an important and satisfying finding, however, the oncogenic activity of Bmi1 is not very appealing for future therapeutic applications. Therefore, Moon *et al.* took their findings one step further. As mentioned above, the Shh signaling pathway was known to induce Bmi1 expression in neural progenitors [5]. They treated MEFs with Shh and exposed them to NSC culture medium. Using this protocol, MEFs were transdifferentiated into NSC-like cells, a process that was also recapitulated by overexpression of Bmi1 [7]. Neural stem cells were previously known for being reprogrammed only with Oct4 due to their high endogenous levels of Sox2 and Klf4 [8]. Therefore, Moon *et al.* transduced Oct4 into the Shh-induced NSC-like cells and were able to obtain iPSCs. This takes the authors to their last *tour de force* by which they reprogram MEFs with the combination of two chemical Shh agonists (oxysterol and purmorphamine) and Oct4 [7].

The above findings illuminate the process of reprogramming and also get us closer to chemical reprogramming. The advantage of a hypothetical chemical reprogramming resides in its simplicity and safety, which are of high

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importance for future therapeutic applications. Previously, two other teams have published in *Cell Research* that combining Oct4 with either BMPs or with a combination of small molecules are sufficient to reprogram somatic cells to iPSCs [9, 10]. The new findings by Moon *et al*. [7] broaden the spectrum of molecules that could be used in combination with Oct4. So far, Oct4 is the only factor that has not been replaced by small molecules. However, based on the speed of progress in this field, it is not unrealistic to anticipate that pure chemical reprogramming will be achieved in the near future.

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