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Review

Development

# Stem cell dynamics: naïve pluripotency and reprogramming

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## Abstract

**Introduction**

Embryonic stem cells exist in inter-convertible sub-states leading to observed heterogeneity arising from seemingly homogeneous populations. Recently, it has been proposed that the stem cell compartment contains the ground state characterised by naïve pluripotency. Understanding molecular dynamics governing the transition from and towards naïve stem cell state is crucial for stem cell biology. It is important to elucidate molecular interactions that regulate lineage commitment and the reprogramming of somatic cells into naïve pluripotent cells. We review key experimental and computational studies that provide an improved understanding and characterisation of the molecular aspects underlying stem cell naïve pluripotency and their impact in the context of reprogramming.

**Conclusion**

Further computational efforts should be made for elucidating the molecular interaction dynamics governing the transitions between naïve and primed hES cells states.

## Introduction

Stem cells are a very important cell type and hold tremendous promise in developmental biology, medicine and clinical research. The most important feature of stem cells is the fact that they have the potential to differentiate, producing all types of specialised cells in the human body (pluripotency) or alternatively to divide, generating other stem cells in a potentially unlimited manner (self-renewal), thus maintaining their own population pools.

Embryonic stem cells were first derived from mouse embryos in 1981[1]. Based on the experience accumulated with mouse stem cells, human embryonic stem cell (hES) were then first derived from human embryos in 1998[2] and subsequently a large number of hES cells lines have been reported by several groups[3]. During the last decade, genes such as Oct4, Sox2, Klf4 and Nanog have been described as forming a core regulatory network that plays a fundamental role both in mouse and in human embryonic stem cell pluripotency, with commitment to differentiate and reprogramming[4,5]. In this study, experimental and computational efforts have been made to better understand molecular dynamics governing reprogramming and fluctuations between the naïve and primed stem cell states.

## Discussion

The author has referenced some of his own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

### Ground state

Maintenance of mES cells *in vitro* requires the presence of external factors, such as leukaemia inhibiting factor (LIF)[6,7] and bone morphogenetic protein (BMP4)[8]. These external factors inhibit differentiation by acting on the mES cell regulatory network, particularly the core genes described above. When mES cells are maintained in LIF plus BMP4 medium, the expression of key pluripotency transcription factors (TFs) can be heterogeneous. Heterogeneity has been observed in key stem cell TFs such as NANOG[8–11], REX1[12] and STELLA[13]. Different external stimuli, such as fibroblast growth factor (FGF) and ACTIVIN are also used to maintain hES cells *in vitro*[14,15]. Heterogeneity is also observed in the expression of core TFs in hES cultures.

Recently, it has been shown that serum/BMP4 can be replaced by small molecules, which inhibit FGFR, MEK and GSK3 (3i) or MEK and GSK3 (2i)[16]. The 2i/3i (two or three types of differentiation inhibiting molecules) medium is used successfully to maintain mouse stem cells *in vitro* in combination with or without LIF. The mES cell maintained in 2i/3i medium is in a 'ground (naïve) state', unbiased to any developmental specification. Two active female X chromosomes and homogeneous expression of pluripotent-associated transcription factors OCT4, SOX2 and NANOG demarcate the stem cells naïve pluripotency. When cultured in LIF plus BMP4, mES cells fluctuate between inter-convertible sub-states, for example, NANOG-low, NANOG–high, REX1–low, REX1–high. The fluctuations in NANOG expression correspond to mES differentiation attempts[10], with the cells in the NANOG-low state being more prone towards lineage commitment and differentiation[11]. These findings underlie the notion that NANOG is an important factor in the core ES gene regulatory network and it acts as a 'gatekeeper' of pluripotency[17]. One important question is what

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molecular dynamics within the gene regulatory network account for NANOG heterogeneity. Recently, Navarro et al.[18] showed that NANOG self-interaction is auto-repressive, OCT4/SOX2 independent and is a major regulator of Nanog transcription switching. While this might be a plausible explanation for NANOG heterogeneity, it would also be interesting to explain the molecular dynamics that lead to a homogeneous NANOG expression when mES cells are in the naïve state.

Epiblast stem (EpiS) cells were derived from the epithelial epiblast of post-implantation embryos[14,19] and more recently from the pre-implantation mouse embryos[20]. EpiS cells are characterised by self-renewal, potential to differentiate in all three germ layers and express only some of the pluripotency factors: OCT4, SOX2 and NANOG are highly expressed, while KLF4 is present only at very low levels[17,21]. The discovery of EpiS cells put forward the idea that the stem cell compartment is composed of two stable pluripotent states: naïve and primed (Figure 1). EpiS cells, even though of murine origins, are maintained in FGF and ACTIVIN. Experiments show that over-expressing NANOG[17] or KLF4[21] inside EpiSC along with changing the medium from FGF/ACTIVIN to LIF/2i lead to the appearance of iPS cells in the colonies. These findings are interesting, since only over-expression of one transcription factor or stringent maintenance of conditions are necessary for successful reversal into the naïve state.

The EpiS and hES cells are maintained in the same medium and have similar morphology. These interesting aspects suggest that these cell lines represent mouse and human orthologs of a primed pluripotent cell state[22]. De Los Angeles et al.[22] highlighted the efforts made so far in achieving naïve human pluripotency. One attempt to obtain hES cells in a naïve state was directly from

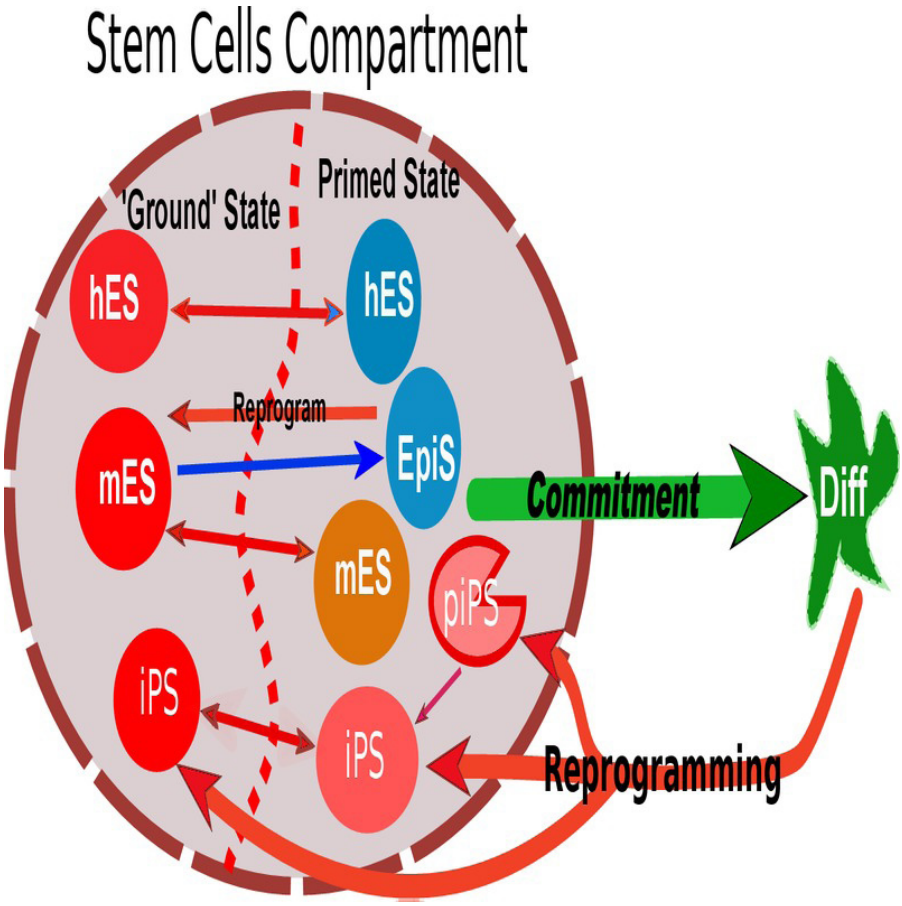


*Figure 1:* Schematic of cells states along with possible transitions.

pre-implantation embryos[23]. The resulting cells had two active X chromosomes; however, they could not be maintained in 2i medium. Efforts were also made for achieving ground state of hES cells through reversion of primed pluripotent hES cells and through reprogramming of somatic cells[24]. A combination of experimental and computational studies is still needed to validate the existence of hES cell ground state and to elucidate the molecular dynamics necessary to induce human naïve pluripotency.

**Reprogramming**

Ectopic expression of the pluripotency transcription factors OCT4, SOX2, KLF4 and c-MYC enables the transition from somatic cells to induced pluripotent stem (iPS) cells both in mouse and in human[25]. This reprogramming protocol with only these factors is inefficient, as only 1% of the reprogrammed cells become iPS cells. Over-expression of c-MYC and the use of retro-viruses or lenti-viruses increased the tumourigenicity of the cells. Hence, substantial efforts are being made to overcome these drawbacks. The vector integration methods are being replaced by the use of plasmids, protein and Sendai viruses. Several groups of stem cell researchers are trying to improve the reprogramming efficiency either by changing the list of over-expressed transcription factors[25] or by tuning the amount or changing the order of over-expressed transcription factors[26]. However, the reprogramming process remains inefficient and a more extensive understanding of the process is still needed. Two possible



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scenarios have been put forward to explain low reprogramming efficiency. The first scenario assumes the existence of different states of the cells in the initial population, where 1% of the cells have a selective advantage towards becoming iPS cells through reprogramming. The second scenario puts forward the idea that reprogramming is a highly stochastic event and iPS cells occur randomly in low percentage even from a homogeneous initial cell population[27]. Many groups favoured the second scenario and the current view is that all the fibroblast cells begin the reprogramming process, but only a small percentage of cells gets to the final stage due to stochastic events, which still need to be more clearly understood[27]. Stochastic computational models of gene regulatory networks containing factors involved in reprogramming and important players for pluripotency could shed light on the stochastic events that lead to fully reprogrammed iPS cells. It would also be interesting to investigate whether the partially reprogrammed (piPS) cells have a selective advantage over the iPS cells in the colony and whether there are means of manipulating them for improving the reprogramming efficiency.

Another interesting problem raised within the new cell-reprogramming field is that of the differences and similarities between iPS and ES cells. Some groups claim that there is a 'dark side' of iPS cells because on top of variation in gene expression, DNA methylation, and pluripotent potential, there are other potential abnormalities, for example, somatic mutations[28]. In a recent review, Shinya Yamanaka claimed that both ESCs and iPSCs are actually manmade since they require maintenance in a specific medium, and that the groups finding differences between the two types of cells considered small numbers of ES and iPS cells clones[29]. In the same study, the author highlights the importance of understanding why these two types of cells with different origins are so similar. He also suggests that efforts should be made to understand the necessary mechanisms for forming tissues, organs and model organisms from iPS cells parallel to the existent ES cells research community. A collaborative effort involving both experimental and computational methods should be further conducted for investigating the molecular dynamics at the core of the iPS and ES cells from mouse and humans both for comparison and for a better understanding of the differentiation process towards various tissues (Figure 2).

## Computational efforts

The cutting edge experimental data from life sciences have made feasible the use of mathematical and software models to understand the molecular interactions that maintain cells in a pluripotent state, leading to commitment and differentiation and allowing a return to the naïve state from a committed or a primed state[30,31]. The notion that both human and mouse ES cells occupy a multiplicity of sub-states, with stochastic transitions between them, was put forward during the last few years[12,31–33].

Deterministic studies have explored the dynamics of the OCT4-SOX2-NANOG regulatory network and its role in mES cell fate decisions[34]. A bistable switch, which arises due to multiple feedback loops in the gene network, was described to control the transitions between pluripotent and committed cell states. Stochastic implementations of the core gene network were proposed showing the role of transcription factor heterogeneity and the impact of both external noise[11,35] and noise from within the network[36] on stem cell commitment and differentiation.

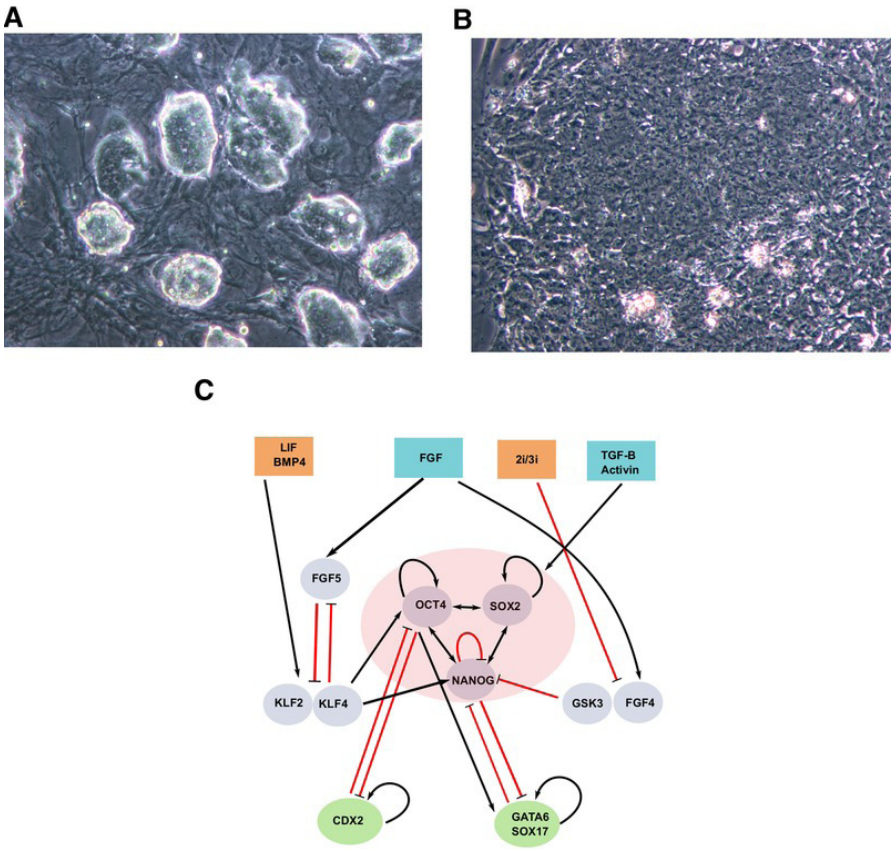


*Figure 2:* (a) Mouse embryonic stem cells in culture. (b) Human embryonic stem cells in culture. (c) General gene regulatory network for mES and hES cells based on reviewed studies.



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Nanog gene expression fluctuations were linked to attempts of ES cells to differentiate[9]. Kalmar et al.[11] propose an excitable model based on positive and negative feedback between OCT4 and NANOG, where cells fluctuate between a stable NANOG-high state and an unstable NANOG-low state. Cells expressing low levels of NANOG respond better to differentiation cues. The proposed model explains observed bimodal heterogeneity of NANOG; however, it does not rule out the possibility of noise-induced fluctuations between two stable states. Glauche et al.[35] propose two models that could explain observed NANOG heterogeneity. In the first model, NANOG induced by OCT4-SOX2 acts like a bistable switch and cycles between low and high levels. The second model consists of an activator–repressor mechanism, where NANOG can oscillate on a fixed limit cycle. Both models give a plausible explanation of how NANOG acts like a 'gatekeeper' suppressing external differentiation signals. In this study, the transitions between substates of mES cells are influenced by noise introduced through external stimuli. Chickarmane et al.[36] put forward a model, which analyses the role of NANOG fluctuations in both allowing cells to transition between ES substates and spontaneously exiting irreversibly into a differentiated state. The proposed simplified network model shows that the decision of staying in the ground state or commitment to a differentiated state is fundamentally stochastic being modulated by external factors, for example, 2i/3i plus LIF medium, which reduces fluctuations in NANOG expression. In this study, the fluctuations between stem cells sub-states are influenced by existing internal noise in the gene regulatory network. The impact of noise on decision-making from viruses to bacteria, yeast, lower metazoans and mammals has been reviewed in a study by Balazsi et al.[37].

Reprogramming through over-expression of transcription factors is one of the most promising discoveries of the last decade. However, there is a great need for improving the efficiency of the process. There are only a few computational studies applied to this important problem.

Hanna et al.[27] developed an experimental and computational study, which demonstrates that reprogramming is a stochastic process ruling out the model, where only a small percentage of cells in the initial population have reprogramming selective advantage. They over-expressed Yamanaka's factors in murine B cells and used Nanog-GFP as a reporter of pluripotency. The conducted reprogramming experiments showed that iPS cells appear in most populations given a large amount of time. The authors also combined experiments with a computational model to assess the impact of over-expressing different transcription factors on reprogramming efficiency. It was shown that p53, p21 and Lin28 increased the cell division rate, which seems to relate to the increase in the speed of reversals to the iPS state.

Artyomov et al.[38] proposed an epigenetic and genetic regulatory network, which describes transformations resulting from expression of reprogramming factors. Their computational model offers mechanistic explanations for empirical observations of transcription factor-induced reprogramming. For example, the stochastic nature of the reprogramming process and its low efficiency could be explained by the fact that the trajectories leading to successful reprogramming are realised rarely by stochastic perturbation of the epigenome by the reprogramming factors. The proposed model can be used to identify rare pathways that allow reprogramming, which can be experimentally tested.

Chickaramane et al.[36] proposed a deterministic and stochastic computational study of the mES cell gene regulatory network governing stem cell decisions. This study provides a framework for reprogramming from somatic cells, and conveys an understanding of reprogramming efficiency as a function of OCT4 over-expression[36]. The proposed model recapitulates the important experimental result that reprogramming efficiency peaks when OCT4 is over-expressed within a specific range of values[26]. Results from stochastic simulations of the model show that the stem cell medium where somatic cells are maintained after transduction also plays an important role in reprogramming efficiency. This study shows that fine-tuning the degrees of over-expression and choosing the iPS cells medium should be considered for optimising reprogramming efficiency.

## Conclusion

This study has reviewed a body of experimental and computational studies aimed at achieving a better understanding of regulatory dynamics within the stem cell compartment and its impact on reprogramming scenarios. Several experimental and computational groups have focused their efforts towards explaining mES cell naïve pluripotency. A frequent approach has been to conduct experiments for describing naïve pluripotency in human cells based on observations made in murine models. Further computational efforts should be made for elucidating the molecular interaction dynamics governing the transitions between naïve and primed hES cells states.

Substantial experimental efforts are being made for improving reprogramming efficiency and elucidate possible pathways between the differentiated and naïve state. Advances in single cell experimental technologies have the potential to provide more accurate stem cells gene regulatory networks. Mathematical models of gene networks containing the over-expressed factors along with important factors for pluripotency will be beneficial for discovering novel and improved ways to increase reprogramming efficiency. It is of major interest to better



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understand and control noise within the core gene regulatory networks of mES, EpiS, hES and iPS cells as this will lead to control of cell fate decisions at colony levels.

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## Abbreviations list

BMP4, bone morphogenetic protein; EpiS, Epiblast stem; FGF, fibroblast growth factor; hES, human embryonic stem cell; iPS, induced pluripotent stem; LIF, leukaemia inhibiting factor; TF, transcription factor.

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