REPRODUCTION

REVIEW

The quest for pluripotency: a comparative analysis across mammalian species

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Abstract

Pluripotency is the developmental potential of a cell to give rise to all the cells in the three embryonic germ layers, including germline cells. Pluripotent stem cells (PSCs) can be embryonic, germ cell or somatic cell in origin and can adopt alternative states of pluripotency: naïve or primed. Although several reports have described the differentiation of PSCs to extra-embryonic lineages, such as primitive endoderm and trophectoderm, this is still debated among scientists in the field. In this review, we integrate the recent findings on pluripotency among mammals, alternative states of pluripotency, signalling pathways associated with maintaining pluripotency and the nature of PSCs derived from various mammals. PSCs from humans and mouse have been the most extensively studied. In other mammalian species, more research is required for understanding the optimum *in vitro* conditions required for either achieving pluripotency or preservation of distinct pluripotent states. A comparative high-throughput analysis of PSCs of genes expressed in naïve or primed states of humans, nonhuman primates (NHP) and rodents, based on publicly available datasets revealed the probable prominence of seven signalling pathways common among these species, irrespective of the states of pluripotency. We conclude by highlighting some of the unresolved questions and future directions of research on pluripotency in mammals.

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Introduction

The zygote is a single cell, endowed with the amazing potency to develop into an entire organism that harbours extreme complexity (reviewed in Leung & Zernicka-Goetz 2015). The most important aspect is the cell fate decisions during its development to form an embryo. In terms of development, pluripotency is a transitory state exhibited by specialised cells in the blastocyst, for a very short period of time, possessing the ability to differentiate into all the cells within the three embryonic germ layers, including the germline cells (Adjaye *et al.* 2005; reviewed in Weinberger *et al.* 2016). PSCs can be derived from the pre-implantation (embryonic stem cells (ESCs)), post-implantation embryos (epiblast stem cells (EpiSCs)), primordial germ cells (PGCs) (embryonic germ cells (EGCs)) or somatic cells (somatic cell nuclear transfer (SCNT)-derived ESCs, induced PSCs (iPSCs)). Embryonic germ cells (EGCs) share similar properties with ESCs; however, they sometimes exhibit imprint erasure (reviewed in Leitch & Smith 2013).

Under *in vitro* conditions, pluripotent stem cells (PSCs) can beget all the cell types of embryonic and extra-embryonic lineages (reviewed in Beddington & Robertson 1989, Xu *et al.* 2002, Pera *et al.* 2004, Das *et al.* 2007, Niakan *et al.* 2010, Sudheer *et al.* 2012, Leitch & Smith 2013, Morgani *et al.* 2013, Roberts *et al.* 2014, Kojima *et al.* 2017). The potency of PSCs in giving rise to cells of the extra-embryonic lineage was first reported in mice, this was based on the presence of colonisation pattern of ESCs in trophectoderm (TE) of chimeras (Beddington & Robertson 1989). Later on, the competency of hPSCs to differentiate into extra-embryonic cells, such as trophoblast and primitive endoderm when exposed to BMP4 was described (Xu *et al.* 2002, Pera *et al.* 2004, Das *et al.* 2007, Sudheer *et al.* 2012, Horii *et al.* 2016, Kojima *et al.* 2017). In spite of several publications from different groups on the differentiation ability of human PSCs to extra-embryonic lineages, these protocols and concept are still debated among scientists in the field (Roberts *et al.* 2014). Our understanding of pluripotency is on a surge, as several coordinated molecular events underlying pluripotency and differentiation are being discovered, such as the role of signalling pathways, transcription factors, epigenetic factors (DNA and histone modification) and non-coding RNAs (Davidson *et al.* 2002, Babaie *et al.* 2007, Brons

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