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Research Article

Human ES Cell Culture Conditions Fail to Preserve the Mouse Epiblast State

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Mouse embryonic stem cells (mESCs) and mouse epiblast stem cells (mEpiSCs) are the pluripotent stem cells (PSCs), derived from the inner cell mass (ICM) of preimplantation embryos at embryonic day 3.5 (E3.5) and postimplantation embryos at E5.5-E7.5, respectively. Depending on their environment, PSCs can exist in the so-called naïve (ESCs) or primed (EpiSCs) states. Exposure to EpiSC or human ESC (hESC) culture condition can convert mESCs towards an EpiSC-like state. Here, we show that the undifferentiated epiblast state is however not stabilized in a sustained manner when exposing mESCs to hESC or EpiSC culture condition. Rather, prolonged exposure to EpiSC condition promotes a transition to a primitive streak- (PS-) like state via an unbiased epiblast-like intermediate. We show that the Brachyury-positive PS-like state is likely promoted by endogenous WNT signaling, highlighting a possible species difference between mouse epiblast-like stem cells and human Embryonic Stem Cells.

1. Introduction

Pluripotency is the intrinsic, unrestricted, flexible developmental potential of the embryonic cells in a developing embryo, to give rise to the three embryonic germ layers, ultimately forming all the cells in an adult organism. This can be captured *in vitro*, by deriving pluripotent stem cells (PSCs) from various developmental stages. The PSCs, derived from the epiblast of preimplantation mouse embryos (E3.75-E4.5) are called embryonic stem cells (ESCs) [1–3]. The mESCs can be brought to a so-called ground/naïve state of pluripotency, using leukaemia inhibitory factor (LIF) that sustains self-renewal [4, 5], in conjunction with the inhibition of ERK [2] and GSK3 [6] that simultaneously suppress differentiation (LIF/2i medium) [7]. The PSCs that are derived from the postimplantation embryos (E5.5-E7.5) are called the epiblast stem cells (EpiSCs), which are in a primed state of pluripotency [1, 8]. The mouse EpiSCs and human ESCs (hESCs) are conventionally cultured in Activin A and FGF2 (AA/F2). When the mESCs are exposed to the hESC/EpiSC condition (AA/F2), they transition to an EpiSC-like primed state [1, 8–11].

During gastrulation, the pluripotent epiblast cells in the developing mouse embryo undergo epithelial-mesenchymal transition (EMT) and migrate through the primitive streak (PS), forming mesendoderm cells, the common precursors of mesoderm and endoderm [12]. The epiblast cells that do not migrate through the PS form the neuroectoderm. Several signaling pathways play crucial roles in this rearrangement process, such as TGFβ/activin/nodal, WNT/β-catenin, and