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Different stages of pluripotency determine distinct patterns of proliferation, metabolism, and lineage commitment of embryonic stem cells under hypoxia

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Abstract:

Oxygen tension is an important component of the stem cell microenvironment. Herein, we have studied the effect of low oxygen levels (2 % O₂), or hypoxia, in the expansion of mouse embryonic stem (ES) cells. In the presence of leukemia inhibitory factor (LIF), cell proliferation was reduced under hypoxia and a simultaneous reduction in cell viability was also observed. Morphological changes and different cell cycle patterns were observed, suggesting some early differentiation under hypoxic conditions. However, when cells were maintained in a ground state of pluripotency, by inhibition of autocrine FGF4/ERK and GSK3 signaling, hypoxia did not affect cell proliferation, and did not induce early differentiation. As expected, there was an increase in lactate-specific production rate and a significant increase in the glucose consumption under hypoxic conditions. Nevertheless, during neural commitment, low oxygen tension exerted a positive effect on early differentiation of ground-state ES cells, resulting in a faster commitment toward neural progenitors. Overall our results demonstrate the need to specifically regulate the oxygen content, especially hypoxia, along with other culture conditions, when developing new strategies for ES cell expansion and / or controlled differentiation.

Key-words: pluripotency, embryonic stem cells, hypoxia, neural progenitors, oxygen tension