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The effect of different oxygen tensions on modulating the early differentiation potentials of human induced pluripotent stem cells

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Early development of mammalian embryos occurs in a relatively low oxygen microenvironment in the reproductive tract (1.5-5.3% O2). Yet, embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are routinely cultured in atmospheric conditions. In this study, our aim was to investigate the effect of different oxygen tensions on the short-term culture of human iPSCs and on stem cell-fate determination during early differentiation. We performed gene-profiling analysis of human iPSCs maintained under normoxic (20% O2) and a range of hypoxic (0%, 2%, 5%, 8% and 12% O2) conditions. The expression of genes associated with pluripotency, embryonic germ layers and hypoxia were studied using qualitative RT- PCR, immunostaining and flow cytometry. Preliminary results revealed that after four days of culturing human iPSCs at different hypoxic levels, morphological changes were observed. Additionally, hypoxia down-regulated the expression of pluripotency markers. Hypoxic conditions also promoted the expression of genes associated with the three germ layers and genes that are involved in the hypoxia-signalling pathway. Interestingly, mild hypoxia (8% O2) increased the number of cells expressing Brachyury (Mesodermal marker), while acute hypoxia (2% O2) caused 95% of human iPSCs to differentiate into ectodermal lineage indicated by Nestin up-regulation. Thus, our results suggest that hypoxia is an important component of *in vitro* differentiation for the generation of clinically relevant progenitors.

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Characterization of microRNA expression in precursor lesions and ovarian cancer stem cells

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Ovarian cancer accounts for majority of deaths seen among gynecological cancers. The advanced stage of disease at diagnosis is the primary factor underlying the increased rate of mortality. Lack of both specific symptoms and effective detection strategies make early diagnosis challenge. Therefore development of improved diagnostic methods is required to reduce disease mortality. One of the molecular changes that occur during cancer progression includes alterations in the expression patterns of microRNAs (miRNA). miRNAs belong to the class of small noncoding RNAs that are involved in gene regulation. miRNAs have emerged as promising targets for early detection owing to their stability in serum and plasma samples. Recent studies have demonstrated that a large proportion of ovarian cancers belonging to the common high-grade serous subtype may emanate from the distal fallopian tube rather than the ovarian surface epithelial cells as previously thought. We utilized a murine model of BRCA-mutated ovarian cancer originating in the fallopian tube epithelial cells that accurately recapitulates the histopathology of precursor serous tubal intraepithelial carcinoma (STIC) lesions, genomic landscape and clinical behavior of human disease to systematically identify miRNAs that are associated with ovarian cancer progression. Further, cancer stem-like cells isolated from cell lines established from these murine models were analyzed for miRNA expression. We identified miRNAs that were expressed in precursor lesions that showed a correlated expression in both cancer stem-like cells and serum samples. These microRNAs offer a new avenue towards developing strategies for early diagnosis of ovarian cancer.

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