

HYPOXIA STRESS ENHANCES THE IGF-1 SIGNALING IN PLURIPOTENT MOUSE GERMLINE STEM CELLS

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Recent advances in cancer research suggest that existence of cancer stem cells (CSCs) in tumor tissues. The origin of CSCs are still controversial; but it has been proved CSCs are possibly originated from organ stem cells (e.g. glioma CSCs and intestine CSCs). The niche stress such as hypoxia effect may provide external signals in stem cell transformation. However, the mechanism of hypoxia-induced stem cell transformation still remains unclear. Our preliminary observations in human pluripotent testicular tumors (seminomas and embryonal carcinomas) showed a high level of hypoxia-inducible protein HIF-1 α /HIF-2 α as well as IGF protein expression in tissues. This observation strongly highlights the cross-talking of niche hypoxic stress and IGF-1 signaling in transformation of germline stem cells into pluripotent cancers. To address this point, we have successfully established a serum-free stem-niche cell co-culture system to generate pluripotent germline stem cells from neonatal mouse testis (AP+GSCs), and uncovered the role of IGF-1/IGF-1R signaling in germ cell pluripotency. Interestingly, while comparing with the normoxia (21 % O₂), the AP+GSCs showed a dramatic increase of alkaline phosphatase activity (AP), cell proliferation, HIF-1 α , HIF-2 α , Oct-4 protein expression, and pluripotent gene expression (such as Oct-4, Sox2, Nanog, Klf-4, and c-Myc) under hypoxia condition (5 % O₂). Moreover, the IGF-1 and IGF-1R expression were also significantly increased under hypoxia. Further analysis by using PPP (a specific inhibitor of IGF-1R phosphorylation) and/or LY294002 (a specific PI3K inhibitor) treatment dramatically reduced the Oct-4 expression as well as HIF-1 /HIF-2 protein of AP+GSCs. These results highlight the regulation of Oct-4/HIF-2 α expression by IGF-1/IGF-1R signaling. In summary, our results demonstrated an up-stream regulation of stemness (Oct-4, Sox2, Nanog, and Klf-4) and tumor factor (c-Myc) of AP+GSCs which was cross-talking with IGF-1/IGF-1R signaling in stem cell transformation under hypoxia condition.