

ROLE OF IGF-1 / IGF-1R SIGNALING IN MOUSE GERMLINE STEM CELLS' PLURIPOTENCY AND TUMORIGENESIS

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Stem cell niche is known to affect cell fate critically, especially for self-renewal and differentiation. Germ line stem cells (GSCs) are cells which are able to self-renew and differentiate into mature sperms and are known to be pluripotent for their in-vivo ability in teratoma formation. Recent advances in cancer research suggest that there exist cancer stem cells (CSCs) in tumors. The resources of CSCs are unclear. Originality of CSCs from its stem cells have been hypothesized (like glioma CSCs and intestine CSCs). However, mechanisms which regulated the transformation of GSCs into CSCs still remain unclear. The niche stress such as inflammation may provide external signals in stem cell transformation. Our preliminary observations in human pluripotent testicular tumors (seminomas and embryonal carcinomas) have found the high expression of inflammatory proteins (CD68 macrophage and chemokine MCP-1) as well as IGF-1/IGF-1R protein in tissues. This observation strongly highlights the cross-talking of niche inflammation and IGF-1/IGF-1R signaling in formation of germline CSCs. To address this point, in this thesis, we have successfully established a serum-free stem-niche cell co-culture system to generate pluripotent GSCs from neonatal mouse testis (AP+GSCs). Further experiments have demonstrated the role of IGF-1/IGF-1R signaling in germ cell pluripotency. Interestingly, by utilizing an in vitro inflammation model, we found the AP+GSCs showed in high proliferation rate, and expressed strong AP activity and pluripotency-associated gene (such as Oct-4 and Nanog). Moreover, by using slot blot, we also detected a significant increasing of IGF-1 level in medium which is secreted by Leydig cells and myoid cells. In summary, in this study, we presented a serum-free testicular stem-niche cell co-culture system to demonstrate the inflammation effect on AP+GSCs' pluripotency and tumorigenesis; and, such regulation mechanisms may through IGF-1/IGF-1R-mediated PI3K/Akt signaling. This finding may provide clinical values in tumor therapy of human testicular germ cell tumors.