IGF-1 / IGF-1R 訊息傳遞在小鼠精原幹細胞之多功能性及腫瘤生成所扮演的角色

Role of IGF-1 / IGF-1R Signaling in Mouse Germline Stem Cells' Pluripotency and Tumorigenesis

中文摘要

已知幹細胞之微環境對幹細胞命運，特別是自我更新或分化的調控，具有重要的影響。精原幹細胞具有自我更新及分化能力，可分化爲成熟精子並具多功能性。近期癌症相關的研究顯示，在腫瘤中存在有癌幹細胞，然而對於癌幹細胞之起源卻仍不清楚。在神經及大腸癌等研究中已知癌幹細胞可能源於其組織幹細胞，但調控精原幹細胞轉型成爲癌幹細胞的機制仍未清楚。微環境壓力 (如發炎)，已知提供幹細胞轉型爲癌幹細胞的外在訊號。我們在人類睪丸生殖細胞腫瘤組織中發現存在有發炎相關之巨噬細胞及趨化因子 MCP-1，同時也大量表現有 IGF-1 及 IGF-1R。這些發現可能暗示發炎與 IGF-1/IGF-1R 的訊號之間的交互作用可能是影響精原幹細胞轉型爲癌幹細胞的重要因子。爲了要證實這個假設，我們已建立一無血清睪丸細胞共同培養系統，並且可成功培養出具多功能性的 AP+ GSCs，我們並證明 IGF-1/IGF-1R 的訊息傳遞可調控精原幹細胞的多功能性。進一步利用體外模擬發炎反應之細胞模式，我們發現 AP+ GSCs 在發炎條件下有細胞增生現象、並同時高度表現鹼性磷酸酶活性以及與多功能性相關之基因 (Oct-4、Nanog) 。此外利用 slot blot 的方式，我們可以偵測到培養液之 IGF-1 表現量明顯增加，同時也證實此 IGF-1 乃由 Leydig cells 及 myoid cells 所分泌。綜合上述結果，我們利用已建立之無血清睪丸細胞共同培養系統證實 IGF-1/IGF-1R 相關的訊息傳遞重要地調控精原幹細胞的多功能性；同時也是參與由發炎所誘導之多功能性腫瘤生成的重要分子機制。調控癌幹細胞形成之分子機制的發現對於臨床上人類睪丸生殖細胞腫瘤的癌症治療有很大的助益。

英文摘要

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.