IJAE
Vol. 119, n. 1 (Supplement): 192, 2014
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Role of Pten deletion and BRafV600E mutation in the generation of testicular germ cell tumors

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Testicular germ cell tumors (TGCT) represent the most common solid malignancy affecting males between the ages of 15 and 35, while ovarian germ cell tumours (OGCT) are a type of ovarian neoplasm principally affecting young women. Germ cell tumors (GCTs) account for about 95 % of testicular cancer cases and for only 2-3% of ovarian cancer cases (Siegel et al., 2011). Most TGCT are potentially curable, however approximately 5% of patients with TGCT develop chemoresistance and die from the disease. PTEN deletion and mutational activation of BRAF are frequent genetic alterations found in human TGCTs, suggesting that they might be directly involved in germ cell tumorigenesis. Furthermore, BRAF mutation positively correlates with the acquisition of resistence to cisplatin, the most commonly chemotherapic agent employed for the treatment of human TGCTs. We obtained heterozygous floxed Ptenloxp/+ BRafCA Spo11Cre mice showing ovarian teratomas and testicular tumors with an incidence of about 30% at 20 days post partum (dpp) . Since Spo-11Cre is active at around 13.5 days post coitum (dpc) in female germ cells and at around 7 dpp in male germ cells (18), these results suggest that ovarian teratomas origin from early meiotic germ cells in the fetal period whereas GCT formation in males can be a postnatal event. By histological inspection, we found that cancer cells in testes showed features reminiscent of seminoma such as a diffuse, confluent multinodular pattern. However, by immunohistochemical staining, we observed that the cells within the tumor showed heterogeneous positivity for the pluripotency markers Oct4, Sox2, Nanog, Kit and Prdm14, suggesting that they can represent a mixed form of seminoma and embryonal carcinoma cells.

Our results indicate that deregulated MAP and PI3 Kinase activation can lead to postnatal male germ cells transformation.

References

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