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## The germ cell – oncogenic and embryogenic correlates

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*Summary.* This study is based on 100 consecutive germ cell tumors of the gonads, received during a 5-year period. Benign teratomas, with totipotent differentiation are the commonest ovarian germ cell tumors, whereas the nullipotent germinomas from the bulk of the testicular tumors. Differentiation in the rapidly proliferating testicular teratomas, occurs in the form of embryoid bodies and organoid structures. From an analysis of the germ cell tumors it is evident that the ovum confers differentiating functions on the zygote, while the spermatozoon confers functions of organization and proliferation. This difference in the behavior of the 2 germ cells is due to local feedbacks within the cortical and medullary zones of the gonads.

Embryogenesis and oncogenesis have 2 important features in common. Both processes involve rapid proliferation and changing levels of differentiation, although one is well regulated and the other is erratic and uncontrolled.

The role of the gonadal germ cells in embryogenesis has been outlined in the present work by observing their behavior during oncogenesis.

*Materials and methods.* The study is based on the morphology of 100 gonadal germ cell tumors, received in the Department of Pathology, Maulana Azad Azad Medical College, New Delhi, during a 5-year period. Multiple sections have been taken from each tumor, to ensure a proper diagnosis. The tumor distribution in the 2 sexes have been compared.

*Results.* Germ cell tumors: Of the 100 tumors in both sexes, the largest number are benign teratomas (50). Germinomas form the second largest group, there being 27 in all. There are 15 malignant teratomas, while germinomas mixed with other tumor types are 5 in number. 2 are undifferentiated malignant tumors and there is 1 gonadoblastoma (table).

A comparison of the ovarian and testicular germ cell tumors: Ovarian germ cell tumors form 63% and the testicular tumors form 37% of the total.

The variant potential of the germ cells is evident from the relative frequency of the different tumor types (table). The nullipotent germinomas form the bulk of the testicular tumors (22), in contrast to the high incidence of totipotent, well differentiated benign teratomas of the ovaries (49). The testicular germinomas form 81.5% and the ovarian germinomas form 18.5%. The ovarian teratomas show differentiation into the 3 germ layers with the formation of mature but haphazard tissues. The malignant teratomas (5) arise from unipotent, committed cell lines within the ovary. Only one benign teratoma is seen in the testis, while malignant teratomas have a high incidence (10). These show an organoid differentiation, with the formation of embryoid bodies which mimic the early, 2- to 3-layered blastoderm, with little further differentiation. The anaplastic tumors have an equal distribution in the 2 gonads.

*Discussion.* The germ cells arise from the yolk sac to migrate into the cortex and medulla of the genital ridge[2]. In the ovary, the cortical germ cells remain to become the oocytes. As only 1 ovarian follicle matures at each cycle[3,4], the oocytes are very stable cells.

In the testis, it is the medullary germ cells which persist and come to line the seminiferous tubules. The spermatogonium undergoes constant mitosis and is a highly labile cell.

In both the gonads the germ cells are supported by cells from the cortex (the granulosa and Sertoli cells)[5–8], and the interstitial cells which arise from the medulla (the theca and Leydig cells)[9]. Thus the difference in the germ cell activity is due to their location within the stroma of the cortex or the medulla. The reversal of the gonadal sex by extirpation of one of these zones supports this fact[10].

It is evident that there is a distinct difference in the behavior of the germ cell present in the 2 gonads, determining the pattern of incidence and the morphogenesis of the germ cell tumors.

The occurrence of a large number of benign and well differentiated tumors reflects the totipotential nature of the ovum. Even the rarer malignant teratomas arise chiefly from fully differentiated cells. This has been a consistent observation made by many other workers also[11,13].

The pattern of testicular germ cell tumors is another well-defined feature[12,14–16]. The frequency of germinomas indicates that this germ cell maintains its nullipotency. The differentiating tumors are all malignant teratomas with organoid differentiation and the formation of embryoid bodies indicating organizational properties. As noted by other workers[17], inspite of rapid proliferation in most testicular germ cell tumors, the ovarian tumors are twice as frequent.

Comparison of ovarian and testicular germ cell tumors

| Sample No. | Tumors | Ovarian No. | Ovarian % | Testicular No. | Testicular % | Total No. |
|---|---|---|---|---|---|---|
| 1 | Benign teratoma | 49 | 77.8 | 1 | 2.7 | 50 |
| 2 | Malignant teratoma | 5 | 8.0 | 10 | 15.0 | 15 |
| 3 | Mixed tumor | 2 | 3.1 | 3 | 5.0 | 5 |
| 4 | Germinoma | 5 | 8.0 | 22 | 59.5 | 27 |
| 5 | Anaplastic tumor | 1 | 1.6 | 1 | 2.7 | 2 |
| 6 | Gonadoblastoma | 1 | 1.6 | 0 | 0 | 1 |
| | Total | 63 | 63.0 | 37 | 37.0 | 100 |

From these observations, it is evident that the oocytes have the ability to differentiate and are more prone to oncogenesis, whereas the spermatogonia tend to show rapid proliferation to give rise to nullipotent cells or organoid formations mimicking the early blastoderm, suggesting a directional differentiation. As tumor cells mimic and retain the properties of the cells of origin, it can be concluded from this study, that the ovum contributes the differentiating functions while the spermatozoon initiates organisation and proliferation in the zygote. The differing properties of the germ cells are related to their location within the genital ridge and to the local interactions and feedbacks.

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## Orange II induced cytogenetical changes in albino mice

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*Summary.* Daily feeding of the common food color Orange II to mice in doses of up to 3.0 g/kg b.wt for 180 days had deleterious effects on somatic and spermatogonial chromosomes. The chromosomal abnormalities induced were breaks, gaps, constrictions, centric fusion, fragments of unknown origin, translocation, deletion, stickiness, ring chromosomes, pyknosis and other bizarre configurations.

Food colors are used extensively in a variety of ways to make food more appealing and acceptable to the consumer. Orange II [Monoazo: C.I. Acid orange 7 (15510)] is the sodium salt of p-[(2-hydroxy-1-naphthyl) azo] benzene sulphonic acid and has been toxicologically classified under the category C II by the Joint FAO/WHO Expert Committee on Food Additives[2], indicating that virtually no information on long term toxicity of this color is available. It is most commonly used in bakery products, beverages, ice cream, soft drinks, confectionery, milk products, sausages, snack foods, pet foods, cereals and multicolored medicinal tablets.

40 male ICR/Swiss mice (average weight, 20–25 g; age, 6–8 weeks old) were used for the study. They were divided into 4 groups and each group was force-fed orally with 0.0 (control), 0.1, 0.5 and 3.0 g/kg b.wt Orange II (superior

Table 1. Effect of Orange II feeding on the bone marrow cells of male mice as shown by chromosomal abnormalities

| Sample No. | Treatments | Normal cells | Abnormal cells (=%) | Type of abnormality | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Breaks | Fragmentation | Centric-fusion | Translocation | Deletion | Ring-formation | Short, thick, stumpy |
| 1 | Control mice fed with ordinary lab chow | 98 | 2 | 1 | – | 1 | – | – | – | – |
| 2 | Mice fed with 0.1 g/kg b.wt Orange II | 99 | 1 | – | – | 1 | – | – | – | – |
| 3 | Mice fed with 0.5 g/kg b.wt Orange II | 98 | 2 | 1 | – | – | – | – | – | 1 |
| 4 | Mice fed with 3.0 g/kg b.wt Orange II | 81 | 19 | 1 | 2 | 10 | 1 | 1 | 2 | 2 |