Pathogenesis of testicular germ cell tumors a cytogenetical and pathological study
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SUMMARY

Testicular germ cell tumors of adults can be divided both clinically and morphologically in two distinct entities, seminoma and nonseminoma. In about 20% of germ cell tumors seminomas and nonseminomas coexist. Seminomas are less aggressive than nonseminomas and combined tumors. It is presently accepted that these malignancies arise from a dysplastic precursor cell via carcinoma in situ. However, it is still controversial whether seminomas and nonseminomas have a common or independent origin. One pathogenetic model suggests that seminomas and nonseminomas are independently derived from separate carcinoma in situ lesions, whereas another theory assumes that all germ cell tumors (with the possible exception of spermatocytic seminoma) have a single origin with seminoma as a stage after carcinoma in situ.

The genetic mechanisms involved in the oncogenesis and pathogenesis of testicular germ cell tumors are still poorly understood.

The characterization of the different subtypes of primary testicular germ cell tumors on the grounds of their ploidy is presented in chapter 2. Using DNA flow cytometry, a significantly different median DI was found for orchidoblastomas, seminomas, and nonseminomas, of respectively: 1.91, 1.66 and 1.43. The seminoma and nonseminoma components of combined tumors (n=16) had a significantly different median DI of 1.61 and 1.40 respectively. Three of the 10 orchidoblastomas were diploid, compared to only one of the 72 testicular tumors of adults.

The cytogenetical confirmation of these findings is shown in chapters 3 and 4. The clustering of germ cell tumors in the triploid range suggests that fusion of a post-meiotic haploid cell with a diploid cell, or tetraploidization followed by chromosomal loss are probably early events in the oncogenesis of testicular germ cell tumors of adults. However, seminomas with chromosome numbers higher than 70 are not unusual, whereas hypertriploid nonseminomas are extremely rare. As noted in chapters 3 and 4, both in seminomas and nonseminomas specific chromosomes are consistently underrepresented (e.g., #11, #13, #18, and
Y), whereas other chromosomes were consistently overrepresented (e.g., #7, #8, #12, and X). It is conceivable that the chromosomes consistently underrepresented may contain genes important for normal germ cell differentiation and/or with tumor suppressing properties. Chromosomes consistently overrepresented may contain genes responsible for a more malignant development. The average number of copies of the i(12p) is significantly lower in seminomas than in nonseminomas. Chapter 5 describes the cytogenetical findings in a combined germ cell tumor of the testis, theoretically a good model to study the possible relationship between seminomas and nonseminomas. The only structural abnormality in common between the seminoma and the nonseminoma components was the i(12p). Since this marker is found in over 80% of all testicular germ cell tumors, the presence of the i(12p) in both components does not allow per se the conclusion that they have a common origin. A simple technical approach is described, which gives the possibility of a separate cytogenetical study of the seminoma and nonseminoma components in combined tumors.

Chapter 6 describes the chromosomal changes found in a series of mature residual teratomas following chemotherapy. A cytogenetic comparison between residual teratomas and primary nonseminomas showed that residual teratomas have a lower average number of structural abnormalities (including the i(12p)), a lower number of copies of #7, #8, #12, #14, X, and Y. This finding confirms the hypothesis that residual teratomas are the result of chemotherapeutic selection of less malignant (less abnormal) clones from the primary tumor. In chapter 7 similar findings were noted in the cytogenetical comparison of the primary nonseminoma and the residual teratoma following chemotherapy in the same patient.

Chapter 8 points to the existence of i(12p) negative testicular germ cell tumors, providing some preliminary indication for a different clinical evolution and prognosis, as compared to germ cell tumors with the referred marker.

Chapter 9 presents the first chromosomal study of a case of orchidoblastoma, pointing out the similarities between infantile testicular germ cell tumors and extragonadal germ cell tumors, and the differences between the former and germ cell tumors of the adult testis.

Chapter 10 discusses the implications of the finding of an i(12p) in a Leydig/Sertoli cell tumor of the testis, which is a non-germ cell
Chapter II presents a statistical processing of all cytogenetical data obtained in primary seminomas and nonseminomas, as well as residual teratomas following chemotherapy. A striking similarity between the relative proportion of the non-acrocentric chromosomes in seminomas and primary nonseminomas was noted. This clearly points to their pathogenetic relationship, lending support to the model suggesting that seminomas and nonseminomas have a common origin. As compared to seminomas, nonseminomas show a remarkable decrease in the number of copies of #15 and #22. This finding suggests that #15 and #22 may contain genes crucial for sperm cell differentiation. The comparison between primary nonseminomas and residual teratomas shows different relative proportions of the non-acrocentric chromosomes, suggesting that the critical difference between residual teratomas and primary nonseminomas resides in changes in the balance of chromosomes favoring tumor suppression and differentiation, rather than gross chromosomal loss. The overall comparison of seminomas, primary nonseminomas, and residual teratomas shows that tumor progression of testicular germ cells of adults is accompanied by a net loss of chromosomes. Moreover, it appeared that the least aggressive tumors (seminomas and residual teratomas) have less copies of specific chromosomes, namely #7, #8, and Y, as compared to the primary nonseminomas (more aggressive).