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Editorial

Differentiation patterns in human testicular germ cell tumours

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It has now been generally accepted that testicular germ cell tumours arise from primordial germ cells. Such an origin implies a high potential for differentiation, a potential which under normal, non-neoplastic conditions, is realized in human embryogenesis. Studies dealing with differentiation patterns in germ cell tumours are thus of great interest and constitute the subject of the present editorial.

Teilum (1965) divided human germ cell tumours into two main groups: seminomas and non-seminomatous neoplasms. The seminoma was considered to represent a committed tumour which had not acquired the potential for further differentiation, while the non-seminomatous tumours were judged to be capable of differentiation in embryonal and extra-embryonal directions.

The hypothesis that seminoma lacks differentiation potential has been challenged on the basis of pathological observations such as the frequent admixture of seminoma in non-seminomatous germ cell tumours, the presence of non-seminomatous elements in metastases from pure primary seminomas (Bredael et al. 1982) and by chromosomal investigations (Oosterhuis et al. 1989).

In recent years the intermediate filament (IF) protein profile has emerged as a useful means for the study of differentiation patterns in normal and neoplastic tissues (Franke et al. 1982). Thus, with few exceptions, cytokeratins are found in epithelial cells, vimentin in cells of mesenchymal origin, desmin is a major constituent of cells of myogenic differentiation, neurofilaments are characteristic of neuronal differentiation and glial fibrillary acidic protein occurs in astrocytes.

There have been a number of studies dealing with the IF pattern in human testicular germ cell tumours. Seminomas were either completely devoid of cytokeratins (Battifora et al. 1984) or contained predominantly vimentin with only occasionally cytokeratin positive cells (Miettinen et al. 1985; Ramaekers et al. 1985; Denk et al. 1987). Denk et al. (1987) also observed positive staining of seminoma cells with antibodies to desmoplakins. The desmosomes thus identified were associated with IF of the vimentin rather than of the cytokeratin type. Nakagawa et al. (1988) did not demonstrate cytokeratins or vimentin in gonadal seminomas but showed these IF proteins to be present in intracranially located seminomas.

In a recent study by Fogel et al. (1991) of the IF protein profile in 26 seminomas, a much larger than hitherto used battery of monoclonal antibodies was employed. In 4 of these tumours neither cytokeratins nor vimentin were detected. Three showed vimentin-positive tumour cells but no cytokeratins, while in 4 cases only cytokeratins were detected. In the remaining 15 cases both cytokeratins and vimentin were present. Although in most instances the cytokeratins were of the "simple epithelial type", namely 8 and 18 (Moll et al. 1982), in 2 instances seminoma cells also contained cytokeratins 4 and 17 normally found in stratified epithelia. In most cases cytokeratin positivity in seminomas was focal or patchy. Of particular interest was the presence in tumour cells of desmin and neurofilaments in 3 and 2 cases respectively. These results showed a varied differentiation pattern in seminomas, mainly of epithelial and mesenchymal nature, but also occasionally myogenic and neurogenic. Thus, the previously mentioned concept that seminomas are committed tumours, not capable of further differentiation, does not appear to be tenable. In view of the above a revision of the histogenesis and interrelationship of testicular germ cell tumours, as attempted by Skakkebaek and Berthelsen (1981) certainly appears to be warranted.

Studies dealing with IF patterns in non-seminomatous germ cell tumours in the past have been few and have employed a rather limited number of antibodies. Battifora et al. (1984) stressed that in contrast to seminoma, embryonal carcinoma stained positively with broad spectrum antibodies to cytokeratins. Ramaekers et al. (1985) confirmed these findings and in addition reported positive staining for cytokeratin 18 in non-seminomatous germ cell tumours. The latter were also reported to stain for cytokeratins 8, 18 and 19 (Miettinen et al. 1985). Similar results were obtained by Denk et al. (1987), who observed positive staining for low molecular

weight cytokeratins in testicular embryonal carcinoma, endodermal sinus tumour and choriocarcinoma.

The most recent study is that of Lifschitz-Mercer et al. (1991), who examined a total of 20 testicular non-seminomatous germ cell tumours. Cytokeratin 8 and 18 were identified in all these neoplasms. Cytokeratin 19 was absent to scarce in embryonal carcinoma, but was strongly expressed in endodermal sinus tumours, choriocarcinoma and teratoma. Staining of endodermal sinus tumour for cytokeratin 19 also enabled the identification of elements of this neoplasm even when present in minute foci not otherwise identifiable by conventional stains within seminoma or embryonal carcinoma. Occasionally some tumour cells in embryonal carcinoma and endodermal sinus tumour also stained for cytokeratins 4 and 17, indicating a potential for squamous epithelial differentiation. In agreement with the observations of Damjanov et al. (1990) syncytiotrophoblastic cells within these tumours stained for cytokeratin 7. Tumour cells in embryonal carcinoma, endodermal sinus tumour and choriocarcinoma also expressed vimentin, pointing to mesenchymal differentiation. Furthermore neurofilaments were demonstrated in a case of endodermal sinus tumour. In teratomas each type of tissue present expressed the appropriate IF protein.

Of particular interest in the above study was the observation that the expression of cytokeratins 8, 18 and especially 19 appeared to parallel the level of differentiation of the tumour closely. Thus in embryonal carcinoma, a neoplasm of low differentiation, cytokeratins 8 and 18 were frequently weakly expressed, while cytokeratin 19 was not detectable in the majority of the tumours. In endodermal sinus tumour and choriocarcinoma, which are neoplasms of extra-embryonic differentiation, the expression of cytokeratins including cytokeratin 19 was generalized and strong. In the epithelial elements of teratomas, the germ cell tumour showing the highest degree of differentiation, cytokeratin expression was the most intense. These conclusions were also supported by results obtained in seminoma (Fogel et al. 1991), which is considered to represent the most primitive germ cell tumour in which, as mentioned before, cytokeratin expression was either absent or only focal.

In conclusion, differentiation patterns in human testicular germ cell tumours as studied by IF proteins have shown a striking heterogeneity in all the neoplasms, including seminomas. In addition, a certain parallelism between the level and extent of cytokeratin expression, especially cytokeratin 19 and the level of differentiation of the tumour cells, was evident. Aside from elucidating the histogenesis and interrelationship of these neoplasms, studies of the differentiation patterns in human germ cell tumours may also contribute to our understanding of normal human embryogenesis.

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