179. Immunohistochemical localization of sex-hormone-binding globulin in normal breast tissue and breast carcinoma

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The development of breast cancer is at least partially related to the action of estrogens. Concepts of identifying a role for increased biological activity of estrogens in breast tumor patients are based on the classical view that sex steroids enter their target cells via passive diffusion and thus only the free fraction is biologically active. This concept has been challenged by an alternative hypothesis, suggesting that SHBG steroid hormone complexes might bind to specific membrane receptors [1, 2] and become internalized by receptor-mediated endocytosis [3]. In a previous study we found intracellular SHBG in prostatic tissue, in benign prostatic hypertrophy and in endometrium [4, 5]. To further elucidate the role of SHBG in endocrine target tissues, we studied the intracellular localization of SHBG in normal and neoplastic breast tissue.

Materials and methods: Paraffin blocks from 19 breast carcinomas were examined. (4 intraductal, 11 infiltrating, 4 both intraductal and infiltrating carcinomas.) In 10 cases normal breast tissue was additionally evaluated. From the paraffin blocks 6 μm slices were cut and placed on glass slides. The sections were incubated with a 1/600 diluted monospecific rabbit antiserum against highly purified human SHGB followed by incubation with a biotin-labeled secondary antibody and the addition of an avidin-biotin-peroxidase complex. The sections were developed by 3,3′-diaminobenzidine and counterstained with hematoxylin or methyl green. Every run included a negative and a positive control.

Results: In normal breast the distribution of SHBG was confined to the cytoplasm of epithelial cells, the nuclei were unreactive. Normal breast ducts and ductules stained positively for SHBG with some enhancement in the apical parts of some of these epithelial cells. Stromal cells were unstained. In neoplastic tissues the staining was heterogeneous. 8 of 19 cancers were SHBG-positive in the majority of the tumor cells, 9 were negative in all tumor cells and 3 showed a different distribution in different parts of the neoplasm, being positive in the intraductal and negative in the infiltrating component. All 8 intraductal but only 4 out of 15 infiltrating carcinomas were SHBG-positive.

Discussion: The cytoplasmic staining of SHBG in epithelial cells was present in all normal breast tissues. It seems to be a normal feature of non-neoplastic breast tissue. In neoplastic tissue we found a striking difference between intraductal and infiltrating tumor components. While the overall positive staining of intraductal carcinomas is similar to the finding in normal breast epithelium, infiltrating carcinomas stained positively only in about 30% of the cases.

The existence of a specific recognition system for SHBG has been reported for endometrial tissue [2]. It might be speculated that a similar mechanism exists in human breast epithelium. The sequestration of SHBG or a SHBG steroid complex from the blood circulation onto the cell membrane and the subsequent internalization of this complex into the cytoplasm may be a specific cell function. Thus the disappearance of SHBG-positive staining in transformed cells may be explained by the dedifferentiation and change of the cell membrane properties of the breast cancer cell.
The appearance of SHBG exclusively in the cytoplasm of epithelial cells agrees with the idea that steroid hormone action is controlled by this protein.

References

180. Effects of two antigestagens (ZK 98.299, ZK 98.734) on prostaglandin (PGF$_{2\alpha}$ and PGE$_2$) synthesis in fibroblast monolayer cell cultures of human endometrium


In subcultured monolayer cell cultures of fibroblasts from proliferative human endometrium, PGF$_{2\alpha}$ and PGE$_2$ synthesis was measured with and without addition of increasing amounts of antigestagens.