S8. The Biology of Breast Cancer in Relation to Efficient Prevention

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The biology of endocrine prevention is based on the cell and molecular biology of the mammary gland and the epidemiology surrounding the development of breast cancer. The major epithelial structures of the breast are the ducts and the lobules. Each lobule comprises two epithelial cell layers, luminal epithelial cells which differentiate under hormonal influences to produce milk during and after pregnancy and basal myoepithelial cells which contain smooth muscle actin and have contractile properties. Experiments where low numbers of tagged mouse epithelial cells are transplanted to the mammary fat pad suggest that the mammary gland can be derived from a single stem cell[1]. Some transplanted epithelial cells give rise to ducts only or lobular like structures only indicating that there are committed progenitor cells for each of these structures.[2] A proportion of single epithelial cells (~ 5%) when dissociated from reduction mammoplasty tissue give rise to colonies which contain cells with markers for both luminal and myoepithelial cells suggesting a single progenitor for both cell types.[3] There is also evidence for a proliferating transit population of cells between the single precursor cell and differentiated luminal and myoepithelial cells. Luminal epithelial cells are of at least two types based on their oestrogen receptor (ER) status. The nucleus of approximately 20% of cells stains with antibodies to ER using the methods of immunocytochemistry. These same cells also contain progesterone receptors (PR). However, the cells which express ER and PR are differentiated and rarely divide and it is probable that oestrogen and progesterone exert their proliferative effects by inducing paracrine growth factors which produce their proliferative effects on adjacent ER/PR – ve cells.[4,5] There is evidence that the separation between ER/PR + ve steroid hormone sensor cells and ER/PR – ve effector cells is reduced with age indicating a transit population of ER/PR + ve proliferative cells which could potentially be targets for carcinogenesis. It is known that the numbers of ER/PR + ve proliferating cells are markedly increased in ER + ve breast cancers and moderately increased in hyperplasia of usual type and atypical ductal hyperplasia. Thus, as the female ages, ER/PR + ve proliferating cells can be detected suggesting that these cells may be a target for malignancy and that this population of cells expands in ER + ve premalignant and malignant lesions. Rats treated with the carcinogen methylnitrosurea (MNU) show increased numbers of ER/PR + ve proliferating cells and this increase can be prevented by mimicking pregnancy with high dose oestrogen and progesterone for 21 days before administration of MNU.[7] The data outlined above suggest a model for the action of preventive endocrine therapy. Wellings[8] and others suggest that breast cancer arises in a terminal duct/lobular unit. Under normal circumstances these units comprise a series of progenitor cells which give rise to luminal (ER/PR + ve and – ve) and myoepithelial cells. The control of cell production of cell types is probably regulated by feedback to the progenitor cell from the ER/PR + ve sensor cell. Preventive endocrine therapy (eg, SERMs or ovarian ablation) given under these normal circumstances would reduce proliferation (and putatively) malignant transformation in ER + ve and ER – ve cells by a feedback mechanism, thus potentially suppressing all tumour types. However, if preventive endocrine therapy is given after the early stages of malignancy have developed lesions with a predominant ER/PR + ve phenotype will be suppressed whereas those with an ER – ve phenotype will not. In the NSABP P1 tamoxifen prevention trial and the raloxifene prevention trial (MORE), only ER/PR + ve tumours were prevented suggesting that treatments were suppressing early malignancy rather than preventing it. Attempts to induce differentiation by, for example, mimicking pregnancy using chorionic gonadotrophin (HCG) or high dose reproductive[9] steroids may be effective when lobules are normal but relatively ineffective after the malignant process has been initiated since induction of differentiation in mammary tumours has proved to be difficult. Follow up data of women given an oophorectomy in their thirties or early forties for benign conditions and the results of the P1 and

MORE studies indicate that approximately one half of tumours are to be prevented or suppressed. Elimination of the other half may require endocrine measures implemented at an earlier age.

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