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Sounding Board

Intermediate Estrogen Receptor Levels in Breast Cancer

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USING a microsample technique [1] to determine estrogen receptor (ER) levels in different regions of breast cancer [2], we have detected a group of tumors which appear to contain a rather homogeneous low/moderate ER distribution when sampled from four different regions of the same tumor. In contrast to this group are tumors that also measure low/moderate in ER level but express a very heterogeneous ER distribution in different areas. We should stress that this assay corrects ER levels for the amount of viable carcinoma per sample so that the problem of variations in cellularity between samples is largely eliminated. There are at least three possible explanations for the existence of this group of homogeneous tumors: (1) such tumors contain unstable receptors that degrade rapidly during processing or (2) such tumors consist of a "checkerboard" of cells with alternate high receptor levels and with absence of receptors, or (3) such tumors contain cells with truly intermediate ER levels.

Studies on experimental mammary tumors suggest that high ER levels per cell correlate with hormone dependency while lower levels may only minimally influence the rate of cell division [3]. If this is also true for human tumors, it is clinically important to detect tumors with such a homogeneously reduced ER level. Most currently employed assays are not likely to detect such tumors. Biochemical analysis on a single tumor sample will not differentiate such tumors from those that are heterogeneous for ER levels since both types probably measure a low/moderate level for ER on routine analysis. On the other hand, immunohistochemical techniques are presently not able to quantitate ER levels with great precision and have difficulty differentiating this type of tumor from that which is homogeneously high for ER [4]. It would seem that a combined biochemical/immunohistochemical analysis is needed to properly identify such tumors. Indeed, some of the paradoxical responses of ER positive breast tumors to hormonal manipulations seen clinically may be clarified by identification of this type of tumor.

In addition, the phenotype of a tumor is not stable and may evolve over a period of time [2, 5, 6, 7]. In breast cancer it is thought that the progression of hormone dependent tumors towards autonomy is paralleled by a reduction in ER level of the tumor as a whole [2, 8, 9]. Tumors with intermediate receptor levels may represent a transition state between hormone-dependent and autonomous variants and consist of a mixture of tumor cells some with, and some without ER as the phenotype changes.

Of 14 tumors from which we obtained 4 microsamples per tumor, we identified 7 tumors with overall intermediate ER levels. Of these, 3 were classified as heterogeneous and 4 as homogeneous for ER [2].

The tumors with heterogeneous intermediate ER

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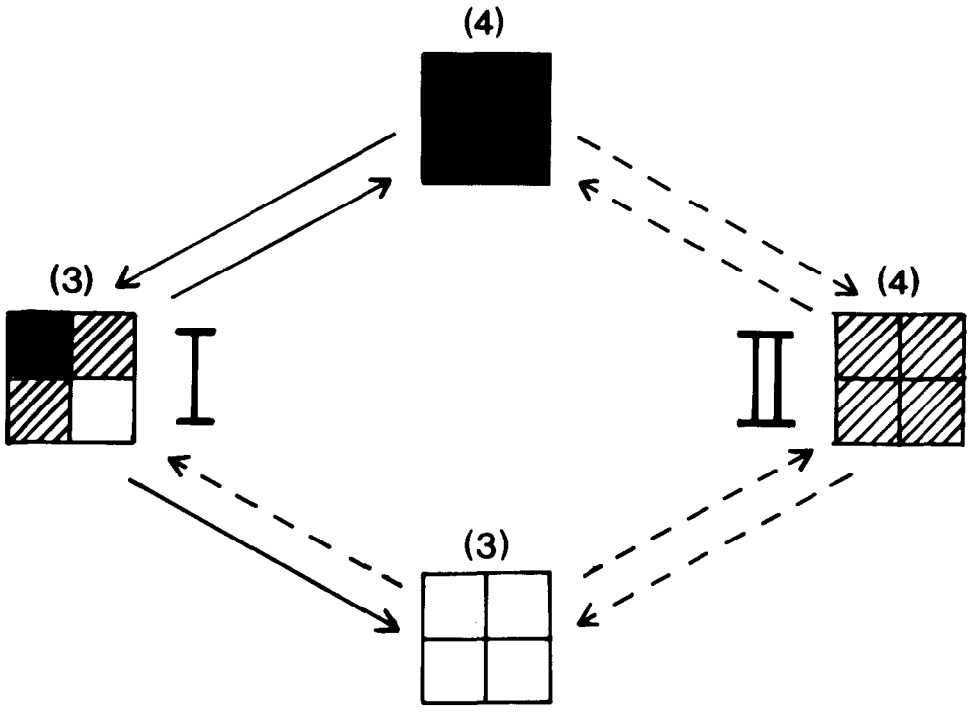

Fig. 1. Possible pathways of progression of receptor positive to receptor negative tumors, and vice versa. *Four samples of 14 individual tumors were analysed for estrogen receptors (quadrants). ■ High receptor level, ◪ intermediate receptor level, □ absence of receptors. Figures in brackets represent number of tumors in each general category. Solid arrows are probable pathways, dotted arrows are less likely.*

levels can be viewed as good candidates for a transition state between the hormone-dependent and autonomous variants by developing ever increasing numbers of ER negative cells that have escaped the endocrine control system. Although it is difficult to visualize how the homogeneous intermediate tumor woud fit into such a progression scheme this possibility cannot, as yet, be ruled out (Fig. 1).

Reports in the literature [10–12] apparently noting ER negative tumors becoming ER positive after some period of time are an enigma. If such tumors consist of mixtures of ER positive and negative cells, with the positive component below the detection range available with currently employed methodology, then pathway I (Fig. 1) may best explain this phenomenon. However, if these tumors are truly negative, it is equally difficult to rationalize the appearance of ER via either pathway. Such a shift would involve the apparent "capture" of an endocrine control system by a tumor, rather than the more common escape from it.

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