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Induction of differentiation may stimulate invasiveness in subpopulations of tumor cells

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In tumor cells, malignant behavior and differentiation potential appear to be correlated inversely. A similar relationship may exist in a normal invasive cell type, the human trophoblast. We have tested this hypothesis by modulating differentiation and by correlating this with invasiveness in normal and malignant trophoblast cells. Normal trophoblast cells isolated from first trimester or term placentae as well as malignant trophoblast cell lines (BeWo, Jeg-3, and JAr choriocarcinoma cells) were treated with substances known to modulate the expression of differentiation markers in these cells, i.e. retinoic acid (RA), methotrexate (MTX), dibutyryl-cAMP (cAMP) or phorbol-12-myristoyl-13-acetate (PMA). The production of chorionic gonadotrophin (hCG) and the activity of cellular streptolysate (STP) were monitored as an equivalent for differentiation. The invasiveness of the different cell types was examined in a Matrigel penetration assay. The expression of hCG was (with few exceptions) well stimulated by all substances in all cell types. Changes of STP activity (measured only in choriocarcinoma cells) showed the same trend. In contrast, invasiveness was affected heterogeneously: in both types of normal trophoblast cells and also in BeWo cells invasiveness was decreased by all effectors in an inverse correlation with hCG production. In Jeg-3 cells cAMP had no effect. In Jeg-3 and in JAr cells, however, treatment with PMA (in JAr cells also RA treatment) resulted in an increase in the rate of Matrigel penetration. These results suggest that in normal trophoblast and BeWo cells invasiveness and differentiation may be correlated inversely. However, the data obtained with Jeg-3 and particularly with JAr cells imply different regulation mechanisms for both processes. Considering BeWo, Jeg-3, and JAr cells equivalents of different subpopulations in a tumor one would conclude that induction of differentiation — as intended in certain strategies for tumor therapy — may have the unwanted effect of stimulating invasiveness in certain subpopulations of tumor cells (at least in trophoblast tumors).