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Correlations between invasiveness and mRNA expression patterns of malignant vs. normal trophoblast cells.

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During embryo implantation and placentation human trophoblast cells develop invasive behaviour comparable to that of tumor cells. In contrast to tumor cells, however, the invasiveness of trophoblast cells appears to be precisely regulated (probably in association with differentiation) and confined spatially to certain areas of the uterine wall as well as temporally to early pregnancy. So far, however, the mechanisms controlling this process are only partly known, but their identification may contribute to better understanding of defects in tumor cells.

In a systematic search for altered gene expression during differentiation of trophoblastic cells we analyzed normal and malignant trophoblast cells with different invasive potential by DDRT-PCR (differential-display-reverse-transcriptase-PCR). A Matrigel penetration assay was used to examine invasiveness of different cell types.

In JAR choriocarcinoma cells, a malignant counterpart of human trophoblast cells, differentiation as monitored by hCG production was induced by treating cells with dibutyryl-cAMP (cAMP) or phorbol-12-myristoyl-13-acetate (PMA). Invasiveness was reduced by cAMP but enhanced by PMA. Normal trophoblast cells were isolated either from first trimester (high invasiveness) or from term placenta (low unvasiveness). Total RNA of treated and non-treated JAR as well as of both types of trophoblast cells was extracted and used for DDRT-PCR.

Minor differences were seen between PCR-amplifications of RNA-preparations from JAR after different treatments. By contrast, considerable differences were detectable between invasive (1st trimester) and "non"-invasive (term) trophoblast as well as between normal and malignant trophoblast cells. PCR-products representing major differences between the two types of trophoblast were reamplified with the same primers as used in DDRT-PCR, cloned in the vector pCRII (Invitrogen), and sequenced. Of several clones, one that was highly expressed in early but not in term trophoblast cells displayed 98% homology to the b1-integrin subunit. Integrins containing this subunit have been suggested to be involved in controlling the invasiveness of trophoblast cells (Damsky et al., 1994, 1995).

These preliminary data demonstrate that differential gene expression can be detected in invasive vs. non-invasive trophoblast cells by DDRT-PCR. Further studies may allow to identify (i) additional molecules that are expressed in correlation with differences in invasive behaviour including molecules with regulatory function and also (ii) corresponding defects in the malignant counterpart.

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