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INSULIN-LIKE GROWTH FACTOR BINDING PROTEINS IN LUNG CANCER CELL LINES

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Binding proteins for the insulin-like growth factors (IGF-BPs) are increasingly recognized as modulators of IGF actions in both inhibitory and stimulatory ways. Previously we have described the existence of different IGF-binding proteins synthesized by small cell lung cancer cell lines (Jaques et al. Exp. Cell Res. 184:396-406, 1989). At least three distinct classes of IGF-BPs are thought to exist differing in their primary structures and binding characteristics. In order to identify the IGF-BPs released by SCLC and NSCLC cell lines we analyzed the mRNA of 14 SCLC and 11 NSCLC cell lines for IBP-1, a low molecular IGF-BP from human placenta, for IBP-2, the human homologue to the rat liver derived BRL-3A cell line and for BP-53, the growth-hormone-dependent IGF-BP from human plasma. All SCLC cell lines which released IGF-BPs expressed IBP-2 while the NSCLC cell lines showed expression for IBP-1 and BP-53. These results suggest, that IGF-BP are probably tumor specific expressed in SCLC and NSCLC and might play an important role in the growth regulation of IGF's.

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COMPARISON OF HEALTHY AND TRANSFORMED HUMAN LYMPHOCYTES KEPT IN CULTURE CONCERNING THEIR DEPENDENCE ON IGF-1

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Healthy human lymphocytes and monocytes were isolated from buffy coats and kept separately in culture without or with the addition of mitogens or antibodies. IGF-1 was determined from the conditioned medium of these cells by means of a RIA. IGF-1 levels were also determined from the culture media of 12 malignant T and B cell lines (ALL) of different stages during their log-phase of growth PHA-stimulated T lymph. produced 1,5 ng/ml, monocytes 1,7 ng/ml and B lymph. between 1-1,8 ng/ml of IGF-1. Only one T-ALL but two B cell lines showed an IGF-1 production 1ng/ml. Three ALL's exhibited a consumption of IGF-1. Additionally the influence of several antibodies (against IGF-1 or insulin / insulin-, IGF-1- or IGF-2-receptor respectively) was tested by the addition of the Ab's to the medium of the cells. T-ALL's of stage I and III and one B-ALL were inhibited by a moAb against IGF-1 and the IGF-1 receptor Ab (aIR3). An antiserum against IGF-1 however stimulated their growth. T-ALL's of stage III were inhibited by the moAb's against the insul.- and IGF-2-receptor.

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TYPE I IGF RECEPTOR EXPRESSION AND CHARACTERIZATION ON HEALTHY AND TRANSFORMED HUMAN LYMPHOCYTES

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In a different experimental approach detailed studies on the IGF-1 receptor expression of the mentioned cell types (see abstract before) were performed. T lymphocytes and monocytes specifically bind IGF-1 (1%) with k_d's of 0,2 nM and express 390 and 310 high affin. binding sites/cell respectively. B lymphocytes show no specific binding of IGF-1. Type I IGF receptor expression is high in early differentiated T as well as B cell lines (3-5%), very low in T-ALL's of stage II (0,3-0,9%) and comparable to PHA-stimulated T lymph. (2,4%) in T-ALL's of stage III (1-2%). The increase in specifically bound IGF-1 is due to a higher number of receptors/cell and not to significantly changed receptor affinities (max. 3x). Extensive affinity-crosslinking studies revealed two ALL's which express smaller a-subunits (HSB-2/REH) of 115 kDa compared to the 130 kDa subunits found in all other cells tested. Under non-reducing conditions the complete receptor ($a_2\beta_2$) can be identified in a SDS-PAA gel with a molecular mass of 300 kDa.

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A NEW TUMOR GROWTH FACTOR: SICRI FROM TUMOR TISSUES

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SICRI:Substance immunochemically cross-reactive with insulin, was observed in the blood and tumors of patients and experimental animals at concentrations up to several times above normal levels of insulin. High levels of SICRI associated with the tumors were not accompained by increased concentrations of circulating C-peptide, indicating either structural differences between SICRI and insulin or different processing of the proform of the molecule or both. SICRI was also detected when primary tumors and tumor cell lines were cultured(in the absence of serum). Murine melanoma B16 and myeloid leukemia were chosen as a suitable experimental model to study the cell content, production and structure of SICRI in vivo and in vitro. SICRI differs from insulin by high molecular weight and isoelectric point. SICRI is a more potent growth factor for different human and murine transformed and normal cells than insulin and IGF I and II. Biochemical and biological data provide evidence that SICRI is a potent growth factor.

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