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THE ROLE OF TYPE 1 GROWTH FACTOR RECEPTORS IN HUMAN CANCER
W.J. Gullick
ICRF Oncology Unit, Hammersmith Hospital, Du Cane Road, London W12 0NN, U.K.
Several lines of evidence support the hypothesis that growth factor receptor overexpression is a contributory factor to cell transformation. Equally, overexpression represents a target for new therapeutic agents. Conceptually, these may be either directed at reducing receptor activity or designed to exploit overexpression relative to normal tissues. Monoclonal antibodies to growth factor receptors have been developed which take advantage of the latter phenomenon. We have made an antibody to c-erbB-3 which has been employed in ADEPT in a preclinical model of tumour growth inhibition. We have also prepared antibodies to the type III mutant EGF receptor found commonly in glioblastoma multiforme. Their specificity and tumour localisation *in vivo* has been explored. These represent an ideal model system as they are directed against a tumour specific antigen expressed at very high levels on brain tumours.

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EGF-RELATED PEPTIDES IN CANCER
D.S. Salomon
Tumor Growth Factor Sect., Lab. Tumor Immunology & Biology, NCI, NIH, Bethesda, MD. U.S.A.
Epidermal growth factor (EGF), transforming growth factor α (TGFα), amphiregulin (AR), heparin-binding EGF (HB-EGF), betacellulin (BTC), heregulin (HGR), epiregulin, and cripto-1 (CR-1) belong to a large family of structurally and functionally related peptides. With the exception of HRG and CR-1, these peptides bind to and activate the EGF tyrosine kinase (c-*erb*) receptor which is a member of the type I receptor tyrosine kinase family. HRG can bind to two other type I tyrosine kinase receptors, c-*erb* B-3 and c-*erb* B-4 which can in turn heterodimerize with c-*erb* B-2. All of these peptides are mitogens for normal and malignant epithelial cells. Also, these peptides can modulate various aspects of cell differentiation. The expression of these peptides is differentially regulated during early development in the mouse. Hormones such as 17β-estradiol, progesterone, androgens, thyroxine and angiotensin can enhance the expression of TGFα, AR, HB-EGF and EGF in a tissue specific manner. The expression of TGFα, AR and HRG can also be upregulated by various oncogenes such as an activated c-Ha-*ras* gene or by overexpression of c-*erb* B-2. An autocrine role has been formally demonstrated for TGFα, AR and/or HB-EGF in oncogene transformed mammary epithelial cells, in transformed keratinocytes and in several different human breast, colon, gastric, lung and pancreatic carcinoma cell lines. TGFα and CR-1 can function as dominant transforming genes in mammary epithelial cells and in keratinocytes. This is supported by the observation that TGFα transgenic mice have a high incidence of developing hepatocellular carcinomas, mammary carcinomas and gastric and pancreatic dysplasias. The expression of TGFα, AR, HRG and CR-1 has been detected at an elevated level and frequency in primary human glioblastomas, bladder, breast, cervical, colon, esophageal, gastric, hepatic, lung, ovarian, pancreatic and prostate carcinomas and in premalignant bladder, breast, cervical, colon and gastric lesions.

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ONCOGENES AND ONCO-SUPPRESSOR GENES AS PROGNOSTIC INDICATORS IN HUMAN CANCER
D.A. Spandidos
Medical School, University of Crete, Heraklion, Greece
Recent progress in the field of oncogenes and onco-suppressor genes has produced valuable information concerning the molecular and cellular biology of the cancer cell and its implication in clinical oncology. Some oncogenes such as *ras*, *myc* and *erb*B-2 and the onco-suppressor gene p53 have been extensively investigated in the progression of carcinogenesis in several types of human tumors. *Ras* mutations have been found to occur frequently in variety of cancers and p53 mutations are the most common genetic abnormality found in all neoplasias. In certain cases the incidence of aberrant gene expression and genetic alterations of oncogenes and onco-suppressor genes have been shown to be important in the progression of these cancers and may be of use as prognostic indicators and form the basis for a successful therapy.

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TYPE I RECEPTOR TYROSINE KINASES AS TARGETS FOR CANCER THERAPY
N.E. Hynes, R. Beerli, D. Graus-Porta, W. Weis
Friedrich Miescher Institute, P.O. Box 2543, 4002 Basel, Switzerland
The Type I family of receptor tyrosine kinases (RTK) has four members: EGFR, ErbB-2, ErbB-3 and ErbB-4. Interest in these proteins is high since altered expression of the receptors has been implicated in the development of human cancer. We have taken two approaches to inhibit growth of tumor cells using ErbB-2 and EGFR as targets. First, genes encoding single-chain antibodies (scFv) were expressed intracellularly in tumor cell lines. scFvs represent the smallest high affinity binding domain of an antibody. The scFvs were provided with an N-terminal hydrophobic leader and a C-terminal KDEL ER retention signal. Expression of the ErbB-2 specific scFv FRP5 in ErbB-2 transformed cells prevents transit of the receptor through the ER and its appearance on the plasma membrane. This results in functional inactivation of the receptor and reversion of the transformed phenotype. Second, we have used recombinant DNA technology to produce scFv-toxin fusion proteins which specifically bind ErbB-2 and EGFR. The scFv-encoding sequences were joined to a cDNA encoding a truncated Pseudomonas exotoxin A (ETA) protein. A TGFα-ETA fusion protein has also been produced. The bacterial produced recombinant proteins bind with high affinity to the appropriate receptor and display potent *in vitro* and *in vivo* cytotoxic effects selective for tumor cells expressing ErbB-2 or EGFR.

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RECURRENT REARRANGEMENTS IN THE *MAG* LOCUS IN A VARIETY OF BENIGN MESENCHYMAL TUMORS
W.J.M. Van de Ven[1], H.F.P.M. Schoenmakers[1], S. Wanschura[2], R. Mois[1], H. Van den Berghe[1], J. Bullerdiek[2]
[1] Center for Human Genetics, University of Leuven, Belgium
[2] University of Bremen, Germany
Translocations involving human chromosome segment 12q13–q15 have been observed in a variety of benign solid tumors. Among these are subgroups of uterine leiomyoma, lipoma, and pleomorphic adenoma of the salivary glands. In recent molecular cytogenetic studies, the chromosome 12 breakpoints of these three tumor types were found to duster in a 1.7 Mb breakpoint region, which was designated MAR (Multiple Aberration Region). Subsequent studies indicated that the majority of the chromosome 12 breakpoints in these tumors mapped within a 445 kb subregion of MAR. Furthermore, evaluation of other mesenchymal tumors with aberrations involving chromosome segment 12q14–q15, such as hamartoma of the lung, hamartoma and fibroadenoma of the breast, and angiomyxoma, revealed that in these tumors the 445 kb subregion of MAR was also directly affected, which might point towards a common genetic denominator; e.g. a multiple aberrant growth (*MAG*) gene. Using a positional cloning approach, we identified a candidate *MAG* gene within a 175 kb segment of MAR and characterized its genomic organization. By FISH, we pinpointed within this gene the majority of the breakpoints of the seven different benign solid tumor types. By Southern blot and 3′-RACE analysis, we demonstrated consistent rearrangements in *MAG* and/or expression of altered *MAG* transcripts. Implications will be discussed.

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INVOLVEMENT OF NF2 GENE ALTERATIONS IN TUMORIGENESIS
G. Thomas
INSERM U434, Institut Curie, 75231 Paris Cedex 05, France
Neurofibromatosis type 2 (NF2) is a monogenic dominantly inherited disease characterized by a susceptibility to develop nervous system tumours, particularly schwannomas and memingiomas. The genetic defect causing NF2 has been shown to map to chromosome 22q12. The gene which when mutated causes NF2 was isolated in 1993. Point mutations in the constitutional DNA of affected individuals can be found in over a third of the patients. Frequent, somatic mutations in sporadic or familial schwannomas and meningiomas were also found. They were frequently associated with loss of the other NF2 allele. Thus functional inactivation of the NF2 gene by a two hit mechanism is expected to operate in the tumorigenic process of both schwannomas and meningiomas, strongly suggesting that NF2 may be a tumor suppressor gene. Mutations in the NF2 gene were rare or absent in the other tumor types tested with the notable exception of mesothelioma recently reported by Sekido *et al.* The NF2 gene codes for a product called schwannomin (also merlin) which has significant homology with proteins known to link membrane