Parallel Symposium No. 10

Gene Alterations in Human Cancer Cells

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PS 10.1

THE *c-MET*/HGF RECEPTOR GENE

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The proto-oncogene c-MET encodes a transmembrane protein with structural features of a tyrosine kinase receptor. The c-MET protein ($p190^{c\text{-}MET}$) is a heterodimer of two disulfide linked chains: α of 50 kd and β of 145 kd. The c-MET product is first synthesized as a single chain precursor of 170 kd which undergoes a rearrangement of disulfide bonds before being cleaved. Northern analysis of specific transcripts reveals the presence of four major mRNA of 9.0, 7.0, 5.2 and 3.4 kilobases. Monoclonal antibodies directed against the extracellular domain identify at the cell surface the $p190^{c\text{-}MET}$ heterodimer and a truncated form of receptor (140 kd) whose β chain lacks the cytoplasmic kinase domain. A truncated form is also released from the cells. In the search for a ligand we and others have recently found that Hepatocyte Growth Factor (HGF), a two-chain polypeptide of 70 kd, binds to the receptor and stimulates its intrinsic tyrosine kinase activity. The MET oncogene is expressed in a variety of tumors of epithelial origin. Amplification and over-expression have been found in a gastric tumor. Rearrangements of the MET gene and expression of structurally altered proteins have also been observed. These findings suggest that the c-MET oncogene encodes the receptor for a growth factor, and thus plays a relevant role in the control of proliferation in normal and neoplastic epithelial cells.

PS 10.2

Molecular Genetics of the Promyelocytic Leukemia t15;17

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APL is characterized by the t15;17. We and others have established that the chromosome 17 breakpoint (bp) maps to the RARa and the 15 to the myl locus. The resulting chimeric gene is transcribed as a myl/RARa fusion mRNA. Mapping of chromosome 15 and 17 bp. In 26/26 APL cases the chromosome 17 bp mapped within RARa intron 2 while chromosome 15 bp mapped within three myl regions, named bcr1,2 and 3. Sequence of several myl/RARa RNA junctions revealed additional heterogeneity due to alternative splicings. Functional characterization of the myl/RARa protein. By isolating many isoforms of the myl and myl/RARa cDNAs, we showed that the myl/RARa RNAs encode for a fusion protein that includes the RARa B to F domains and variable portions of the myl N-terminal region. One of the myl/RARa proteins was tested for its trans-activation potential. It acted as a retinoid-inducible transcription factor with both ligand-independent repressor and ligand-dependent activator functions in transactivation experiments of a retinoic acid-responsive gene. We propose that: 1) the repressor myl/RARa function is implicated in the promyelocytic leukemogenesis and myl/RARa may act as a dominant negative oncogene; 11) the activator myl/RARa function is implicated in the high sensitivity of APL blasts to Retinoic Acid.

PS 10.3

Oncogene Amplification and Tumor Suppressor Genes in Lung Cancer

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Multiple somatic lesions have been discovered in DNA from lung cancer. Some of these involve tumor suppressor genes, such as RB or p53. Oncogenes of the *myc* family are activated predominantly in small-cell lung cancer (SCLC) as result of gene amplification. These findings will be reviewed.
We have recently characterized a gene fusion formed by L-*myc* and part of a novel gene named *rlf* in SCLC. In addition, we have found coamplifications of unrearranged L-*myc* and *rlf* . Our data suggests a role for the fusion protein in the development of these SCLC tumors.
The functional properties of *myc* proteins are modulated by interactions with *max* , a homologous b-HLH-LZ protein (Blackwood and Eisenman, *Science* 251, 1211, 1991). We have identified a naturally occurring truncated version of *max* , which is also able to dimerize with *myc* in the nucleae, but which remains in the cytoplasm in the absence of *myc*. The molecular biological role of this protein will be discussed.

PS 10.4

Cancer genes on chromosome 17: approaches to mapping, using extended cancer families and sporadic tumours

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The short arm of chromosome 17 at p13 has been implicated in a substantial proportion of lung, colon, breast and ovarian tumours and in oestosarcomas, on the basis of loss of heterozygosity (LOH) in sporadic tumour tissue. The p53 gene located at 17p13.1 is the favoured candidate in most of these tumours and in many instances LOH at 17p13 has been shown to coincide with functionally important mutations in the retained copy of p53.

The situation appears to be more complex in breast cancer. Although p53 mutations do occur, a second locus at 17p13.3, shows a higher rate of LOH than p53 itself. Association between elevated p53 mRNA levels and LOH at 17p13.3 suggests the presence of a gene that regulates p53 transcription.

Few breast cancer families show linkage to loci on 17p but specific germ line mutations in p53 have been identified in a minority of Li-Fraumeni and other multi-cancer syndrome families.

Genetic linkage to a locus at 17q21-22 has been demonstrated in some families with early onset breast cancer and in others with breast/ovarian cancer. Allele losses on 17q do occur in sporadic breast cancer, though they are less common than 17p LOH. In sporadic ovarian cancer, however, LOH is even more frequent on 17q than on 17p. It remains to be established which, if any of the recognised candidate genes on 17q accounts for the linkage and/or LOH findings.