Martinez, Maria Elena [52]

Effect of 677 C to T mutations in the methylenetetrahydrofolate reductase gene, folate intake and plasma homocysteine on adenoma recurrence

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The *C677T* mutation of the methylenetetrahydrofolate reductase (MTHFR) gene, associated with the thermolabile form of the enzyme, has been shown to influence risk of colorectal neoplasia. We examined the effect of modification of this mutation on the association between plasma homocysteine or folate intake and adenoma recurrence among 703 individuals with a history of resected adenomas. We analyzed homocysteine at baseline by high-peformance liquid chromatography and assessed dietary folate with a food-frequency questionnaire. The prevalence of the *677TT* genotype was 10.8%. A higher risk of adenoma recurrence was shown among the following groups: individuals with the *677TT* genotype compared with those with the *677CC* wild type (odds ratio [OR]=1.60; 95% confidence interval [CI]=0.93–2.74); individuals in the lowest tertile of folate intake compared with those in the highest (*OR*=1.42; 95% CI=0.96–2.10); individuals with plasma homocysteine levels above compared with those below 9.5 μmol l^{-1} (*OR*=1.49; 95% CI=1.01–2.21). When assessing the interaction of folate and MTHFR, we found the highest risk of adenoma recurrence in individuals with folate intakes of 370 μg day^{-1} or lower and the *677TT* genotype as compared with those with intakes greater than 370 μg day^{-1} and *677CC* or *677CT* MTHFR genotypes (*OR*=2.16; 95% CI=1.00–4.69). For the interaction of plasma homocysteine and MTHFR, the OR for individuals with homocysteine levels greater than 9.5 μmol l^{-1} and the *677TT* variant was 5.87 (95% CI=1.51–22.8) compared with those with levels of 9.5 μmol l^{-1} or lower and *677CC* or *677CT* MTHFR genotypes. These data indicate that the association between folate status and adenoma recurrence is influenced by the MTHFR polymorphism.

Masys, Daniel [53]

Use of controlled terminology hierarchies to detect common characteristics of genes within expression clusters

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A growing variety of statistical analysis approaches are available to identify groups of genes that share common expression patterns; however, the interpretation of the biological characteristics of genes in such clusters remains primarily a manual task. We have developed a data-mining method that uses indexing terms from the published literature linked to specific genes to present a view of the conceptual similarity of genes within a cluster or group of interest. The method takes advantage of the hierarchical nature of medical subject headings used to index citations in the MEDLINE database and the registry numbers applied to enzymes. The results are generated as dynamic HTML with links to the citations whose keywords appear in the term hierarchies. We have applied this method to gene clusters in the publication by Golub *et al.*[1] describing statistical methods for classifying acute myeloblastic leukemia (AML) and acute lymphoblastic leukemia (ALL) without *a priori* biological knowledge. In both sets of genes the most common enzymatic descriptor class is that of complement-activating enzymes. In the ALL-predictive set of genes, these enzyme descriptors include endonucleases, endopeptidases, amidohydrolases and acid anhydride hydrolases. In the AML-predictive set, several plasminogen activators occur as keywords, a finding that may correlate with defibrination syndromes and other hemostatic abnormalities that are associated with AML but not with ALL. Overall, complement activation is a common and potentially clinically significant phenomena in acute leukemias, and the high frequency of this descriptor in the set of highly expressed genes is consistent with our observations that informative genes were not merely markers of hematopoeitic lineage, but encoded proteins important in cancer pathogenesis. These conceptual similarities, revealed by the automated summing and organization of literature keywords associated with these 50 genes, are a new finding that complements the interpretations of the authors of the original paper.

1. Golub, T. *et al. Science* **286**, 531–537 (1999).

McNiel, Elizabeth A. [54]

Characterization of cytogenetic aberrations in feline vaccine-associated sarcoma

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Animal models have contributed significantly to understanding carcinogenesis and cancer-related genes and to evaluation of therapeutic approaches. Most animal studies are conducted in inbred laboratory species with induced or implanted tumors, but this approach has inherent scientific limitations. Spontaneous tumors in dogs and cats are clinically well characterized and very prevalent, and they have great potential to contribute to understanding carcinogenesis and tumor biology in animals and humans. Although progress has been made in the characterization of the genome in dogs and cats, very little is known about cancer genetics in these species. We have initiated efforts to characterize the genomic alterations in animal cancers through cytogenetic evaluation of tumors. Causative chromosome rearrangements are recognized in human tumors, and many cancer-associated genes have been identified with cytogenetic study. Our initial efforts in characterizing cytogenetic aberrations in animals have focused on feline vaccine-associated sarcoma. Epidemiological evidence strongly associates vaccination of cats for rabies and feline leukemia virus with the development of soft-tissue sarcomas at the site of administration. The stepwise progression of this tumor from inflammatory lesion to invasive tumor and finally to metastasis is coupled with a short latency and overall time course for progression, providing a powerful model to study progressive genetic lesions. The genes involved in carcinogenesis are those associated with fundamental cellular regulation and are likely to be conserved between species. We present our preliminary characterization of cytogenetic aberrations in feline soft-tissue sarcomas using classical banding, chromosome painting probes and comparative genomic hybridization.