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Gene Chips: A New Tool for Biology

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The knowledge of many complete genomic sequences has led to a "grand unification of biology," consisting of direct evidence that most of the basic cellular functions of all organisms are carried out by genes and proteins whose primary sequences are directly related by descent (i.e. orthologs). Further, genome sequences have made it possible to study all the genes of a single organism simultaneously. We have been using DNA microarrays (sometime referred to as "gene chips") to study patterns of gene expression and genome rearrangement in yeast and human cells under a variety of conditions and in human tumors and normal tissues. These experiments produce huge volumes of data; new computational and statistical methods are required to analyze them properly. Examples from this work will be presented to illustrate how genome-scale experiments and analysis can result in new biological insights not obtainable by traditional analyses of genes and proteins one by one. For lymphomas, breast tumors, lung tumors, liver tumors, gastric tumors, brain tumors and soft tissue tumors we have been able, by the application of clustering algorithms, to subclassify tumors of similar anatomical origin on the basis of their gene expression patterns. These subclassifications appear to be reproducible and clinically as well as biologically meaningful. By studying synchronized cells growing in culture, we have identified many hundreds of yeast and human genes that are expressed periodically, at characteristically different points in the cell division cycle. In humans, it turns out that most of these genes are the same genes that comprise the "proliferation cluster," i.e. the genes whose expression is specifically associated with the proliferativeness of tumors and tumor cell lines. Finally, we have been applying a variant of our DNA microarray technology (which we call "array comparative hybridization") to follow the DNA copy number of genes, both in tumors and in yeast cells undergoing adaptive evolution during hundreds of generations of growth in continuous culture. These studies suggest a basic similarity in mechanism between adaptive evolution in yeast and tumor progression in humans.