

RECONSTRUCTING THE EVOLUTIONARY HISTORY OF NEOPLASTIC CELLS

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Cancer progresses through the generation and selection of mutant clones in genetically heterogeneous neoplastic tissues. Since all mutant cells derive from a normal cell through a series of mutations and mitoses, their evolutionary relationships form a phylogenetic tree. By reconstructing the phylogeny of mutant clones in a patient's neoplastic tissue, we can deduce the branching sequences of mutational events that led to the set of observed clones.

We have taken a set of biopsies from 62 Barrett's esophagus patients with high grade dysplasia. The samples were separated by ploidy and proliferation through flow cytometry and a Ki67 assay. The relatively homogeneous subpopulations were then screened for loss of heterozygosity (LOH) in 10 short tandem repeat (STR) markers along chromosome 17 and 9 STR markers along chromosome 9. We then reconstructed the phylogenies from the LOH data in two steps. We first constructed a "framework" phylogeny of the observed clones alone. This framework then constrained the inference of ancestral clones through the application of both parsimony and consensus tree algorithms to the data. These techniques for reconstructing the phylogenies of mutant clones should be applicable to all forms of solid tumors.

The set of unique phylogenies, one for each patient, begins to sketch the boundaries of what is possible in the evolution of neoplastic cells. In addition, regularities in the phylogenies point to any systematic orderings of the mutations. Analyzing multiple phylogenies helps us separate out the systematic constraints from the historical accidents in the evolution of the neoplastic cells. We found that the most common sequences of mutations often begin with LOH near CDKN2A. We also found evidence for LOH in chromosome 17q that typically precedes LOH in the other markers on chromosome 17 as well as aneuploidy.