Chromosomal Instabilities and Cancer

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Most types of cancer were found to exhibit very *large-scale genomic instabilities*: deletions of amplifications of entire chromosomal regions. The classical model which views single-gene alterations as causative, and the chromosomal instabilities mainly as a side effect, has been seriously challenged; claims that view these instabilities as the major cause of cancer are forcefully made.

We are participating in several studies that aim at studying the extent to which chromosomal instabilities are prevalent in several kinds of cancer. In addition, the role of DNA copy number changes is also investigated. In particular, we disproved claims about lack of correlations between DNA copy number and mRNA expression levels of the corresponding genes in colon cancer and showed that correlations between SNP chip data and expression are high and statistically significant, not only in colon cancer, but also in glioblastoma and leukemia. These investigations allow a fairly reliable determination of aneuploidy from expression data obtained from clinical samples, a fact that was used to produce a comprehensive map of *CINons* (amplicons and deletons) of colon cancer and to demonstrate their association in with outcome and tumor progression.

In addition to studies that used samples from the clinic, I will describe the results of an in vitro experiment, that started with normal prostate cells that were immortalized and followed during a 600-day long process of cancer initiation and progression. This experiment provided a unique opportunity to observe the timing at which various chromosomal instabilities arose in the course of the malignant transformation and to construct an evolutionary tree of chromosomal instabilities. 20q amplification was identified as a very early event that survived selection, and we identified the pathways that were affected by this aberration. This study supports the viewf chromosomal instabilities playing an active causative role in cancer.