Cancers are believed to arise through multistep accumulation of somatic mutations in the progeny of a single cell of origin. In colorectal carcinoma molecular events have been identified at various stages of tumor development along the way from adenomas to metastatic cancer (1). We would like to propose that in tumors in which precursor lesions are either ill defined or not readily available, another approach, analysis of DNA samples taken in parallel from different areas of a tumor specimen, may similarly permit dissection of early and late mutational events. Mutations acquired at an early stage of carcinogenesis would be expected to be common to all tumor cells, while late clonal genetic changes would be restricted to particular areas.

We investigated several separate DNA samples of a gastric adenocarcinoma from a female patient, including three different areas of moderate and one area of poor differentiation. Tumor samples from all four areas showed the same clonal X-inactivation pattern (Fig. 1A) (2). However, clonal loss of heterozygosity at 1q21, frequently detected in stomach (3) and breast cancers (4), was in this case only seen in the poorly differentiated area, but not in the other tumor samples (Fig. 1B).

It is of course possible that the various regions of this tumor might have arisen independently and would exhibit the same clonal X-inactivation pattern simply by chance [probability of 0.5^n-1, where n is the number of tumor samples examined; (cf. Ref. 5)]. However, X-inactivation analysis in these tumor samples is fully consistent with their common origin from a single somatic cell. In contrast, loss of heterozygosity at 1q21 may have occurred at a later stage in carcinogenesis, since it was limited to a single poorly differentiated tumor area. Clonal heterogeneity within a tumor as seen here must be taken into account when reporting the prevalence of gene mutations. For example, allelotypes have been reported in a variety of different cancers based on assessment of the extent and variation of allelic loss with the use of polymorphic DNA markers (6, 7). We believe that it would be rewarding to complement such studies by examining intraindividual tumor heterogeneity. Our approach could also be valuable in tracing the hierarchy of mutational events in those cancers in which no premalignant lesions can be studied.

References

Studying Clonal Heterogeneity in Human Cancers

Martin F. Fey, Arthur Zimmermann, Bettina Borisch, et al.


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