Menghong Sun
Dr. med.

Molecular Characterization of Gastrointestinal Tumors Using Tumor Suppresser Gene Associated Microsatellite Markers and their Relationship to Pathological and Clinical Features

Geboren am 15. März, 1960
Studiengang der Fachrichtung Medizin vom SS/WS 1978 bis SS/WS 1983 (Bachelor of Medicine), vom SS/WS 1985 bis SS/WS 1988 (Master of Medizin)
Klinisches Studium in Anhui Medizinische Universität
Staatsexamen am 05, 07, 1988 an der Anhui Medizinische Universität

Promotionsfach: Chirugie
Doktorvater: Prof. Dr.Med. M.v. Knebel Doeberitz

Tumors are the result of clonal stepwise alterations in multiple genes. Most of our knowledge on the genetic nature of carcinogenesis has been derived from the studies of gastrointestinal tumors. Current models provide strong evidence for the existence of genetically heterogeneous preneoplastic cell populations which furtheron lead to genetic heterogeneity in the tumors. These findings outline the events responsible for determining the natural history of gastrointestinal tumors. The prognostic impact of reading molecular profiles of individual cancers is unclear at present. We addressed the question whether a molecular profiling approach by analyzing allelic imbalances of specific tumor suppressor gene loci as an evidence for allelic loss (loss of heterozygosity) might correlate with the prognosis of the respective cancers.
Matched tumor and normal DNA from CRC (colorectal cancer) of 79 patients (1986 until 1988); 10 adenomas obtained from 10 FAP (familial adenomatous polyposis loci) patients and two rare esophageal carcinosarcomas were obtained after microdissection. 11 tumor associated loci were amplified by PCR using fluorescein labeled microsatellite primers. PCR products were analyzed on a DNA sequencer (A.L.F.) and allelic loss (LOH) was determined using the Fragment Manager software.

In 86% (68/79) of the tumors frequent LOH was observed at the tumor suppressor gene loci 5q12 (38%), DCC (72%), p53 (74%), NF2 (30%) and RB (25%), as well as in loci not directly associated with colorectal carcinogenesis such as 17q (BRCA1, 31%), 15q13 (ß2-microglobulin, 34%) and 6p21 (TAP1, 27%). Patients showing with LOH in RB or 5q12 had a better prognosis than patients without LOH at these loci. In 14% (11/79) of colorectal tumors genome wide instability was observed in more than two loci, reflecting a high level of genetic instability. In an early adenoma LOH at the 5q12 (D5S107) locus was detectable in tenascin positive crypts. Adenomas of a second patient displayed variable LOH at the 18q12 (D18S34) locus, i.e. LOH in one

tenascin positive adenoma but wildtype in a different tenascin positive adenomas. Such adenomas display genetic heterogeneity suggesting temporally and spatially different mutagenic events.

In two esophageal carcinosarcomas LOH was also detected at the p53 locus, hMLH1 and other loci. A rare splice donor site mutation at the boundary of exon-intron 6 was detected in both carcinomatous and sarcomatous tumor components which is a strong hint for the clonal origin of both tumor elements.

We have established a complex LOH profile for sporadic colorectal tumors. Molecular profiling of tumors represents a novel approach in defining different types of genetic alterations arising during tumorigenesis.