Identification and characterization of new potential oncogenes and tumor suppressor genes in human colorectal cancer

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ABSTRACT

The study was carried out at the Molecular Diagnostic Laboratory, Dept. of Clinical Biochemistry, Aarhus University Hospital Skejby Sygehus, Denmark. The purpose of the study was to identify new genes associated with colorectal cancer. The basis of the study is the transcript profiling done on tissue samples of normal colon mucosa and tissue from colorectal adenocarcinomas of Dukes' stages A-D (proximal and distal colon) using Affymetrix GeneChips. Analysis of the transcript profiles revealed several hundred genes and ESTs to be differentially expressed in the colon adenocarcinomas compared to the normal colon mucosa, but only thirty genes were in common as differentially expressed genes in both proximal and distal colon adenocarcinomas.

Among the genes and ESTs found above ten ESTs were chosen for further analysis in this study, and they were all found to represent genes in the human genome. All ten genes were cloned and over-expressed in COS7 cells. Of these ten cloned genes one was chosen for more detailed analysis, namely the gene *hFKBP10* encoding the hFKBP65 protein. The levels of both gene transcript and protein were shown to increase dramatically in colon adenocarcinomas compared to normal colon mucosa in both proximal and distal colon. The protein was also shown to be increasingly expressed in the early lesions of the colon such as hyperplastic polyps and adenomas, in addition to being detected in liver metastases from colon adenocarcinomas. The hFKBP65 protein was then showed to have a molecular mass of approximately 72kDa, to be localized in the endoplasmic reticulum of COS7 cells as well as being N-glycosylated.

hFKBP65 protein expression has been shown to be elevated in many human cancers such as invasive ductal carcinoma of the breast and adenocarcinoma of the lung, by immunohistochemical analysis of a multi-cancer tissue microarray .

hFKBP65 overexpression in a colon cancer cell line did not affect the proliferation rate of the cells, but the expression of many genes were found to be affected.

The next step would be to initiate an iterative approach with over-expression and knock-down of the genes affected by hFKBP65 over-expression/knock-down. When followed by microarray analysis and phenotypic assays on the transfected cells, this could elucidate whether the genes are in fact downstream targets of the hFKBP65 protein, based on whether the same phenotypic effects are seen.