Aldehyde dehydrogenase-expressing colon stem cells contribute to tumorigenesis in the transition from colitis to cancer.


McKnight Brain Institute, University of Florida, Gainesville, Florida 32609, USA.

Patients with chronic ulcerative colitis are at increased risk of developing colorectal cancer. Although current hypotheses suggest that sporadic colorectal cancer is due to inability to control cancer stem cells, the cancer stem cell hypothesis has not yet been validated in colitis-associated cancer. Furthermore, the identification of the colitis to cancer transition is challenging. We recently showed that epithelial cells with the increased expression of aldehyde dehydrogenase in sporadic colon cancer correlate closely with tumor-initiating ability. We sought to determine whether ALDH can be used as a marker to isolate tumor-initiating populations from patients with chronic ulcerative colitis. We used fluorescence-activated cell sorting to identify precursor colon cancer stem cells from colitis patients and report both their transition to cancerous stem cells in xenografting studies as well as their ability to generate spheres in vitro. Similar to sporadic colon cancer, these colitis-derived tumors were capable of propagation as sphere cultures. However, unlike the origins of sporadic colon cancer, the primary colitic tissues did not express any histologic evidence of dysplasia. To elucidate a potential mechanism for our findings, we compared the stroma of these different environments and determined that at least one paracrine factor is up-regulated in the inflammation and malignant stroma compared with resting, normal stroma. These data link colitis and cancer identifying potential tumor-initiating cells from colitic patients, suggesting that sphere- and/or xenograft formation will be useful to survey colitic patients at risk of developing cancer.

PMID: 19808966

Aldehyde dehydrogenase 1 is a marker for normal and malignant human colonic stem cells (SC) and tracks SC overpopulation during colon tumorigenesis.


Department of Surgery, University of Florida, Gainesville, Florida, USA.

Although the concept that cancers originate from stem cells (SC) is becoming scientifically accepted, mechanisms by which SC contribute to tumor initiation and progression are largely unknown. For colorectal cancer (CRC), investigation of this problem has been hindered by a paucity of specific markers for identification and isolation of SC from normal and malignant colon. Accordingly, aldehyde dehydrogenase 1 (ALDH1) was investigated as a possible marker for identifying colonic SC and for tracking them during cancer progression. Immunostaining showed that ALDH1(+) cells are sparse and limited to the normal crypt bottom, where SCs reside. During progression from normal epithelium to mutant (APC) epithelium to adenoma, ALDH1(+) cells increased in number and became distributed farther up the crypt. CD133(+) and CD44(+) cells, which are more numerous and broadly distributed in normal crypts, showed similar changes during tumorigenesis. Flow cytometric isolation of cancer cells based on enzymatic activity of ALDH (Aldefluor assay) and implantation of these cells in nonobese diabetic-severe combined immunodeficient mice (a) generated xenograft tumors (Aldefluor(-) cells did not), (b) generated them after implanting as few as 25 cells, and (c) generated them dose dependently. Further isolation of cancer cells using a second marker (CD44 (+) or CD133(+) serially) only modestly increased enrichment based on tumor-initiating ability. Thus, ALDH1 seems to be a specific marker for identifying, isolating, and tracking human colonic SC during CRC development. These findings also support our original hypothesis, derived previously from mathematical modeling of crypt dynamics, that progressive colonic SC overpopulation occurs during colon tumorigenesis and drives CRC development.

PMID: 19336570


[Alcohol dehydrogenase and aldehyde dehydrogenase as tumour markers and factors intensifying carcinogenesis in colorectal cancer] [Article in Polish]

Jelski W, Orywai K, Kreda B, Szmitkowski M.

Uniwersytet Medyczny w Bydgoszczy, Zakład Diagnostyki Biochemicznej. wjelski@amb.edu.pl

Numerous experiments have shown that alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are present in cells of various cancers and play role in carcinogenesis. The aim of this study was to compare the capacity for ethanol metabolism measured by ADH isoenzymes and ALDH activity, between colorectal cancer and normal colonic mucosa. We have also investigated the serum activity of these enzymes in colorectal cancer patients as potential tumour markers. MATERIAL AND METHODS: The activities of ADH isoenzymes and ALDH were measured in the: cancer tissue, healthy colonic mucosa and serum of 42 patients with colorectal cancer. For the measurement of the activity of class I ADH isoenzyme and ALDH activity the fluorometric methods was employed. The total ADH activity and activity of class III and IV isoenzymes was measured by the photometric method. RESULTS: The activity of total alcohol dehydrogenase and class I of ADH were significantly higher in cancer cells than in healthy tissues. The other tested classes of ADH had higher activities in cancer tissue but the differences were not statistically significant. The activity of ALDH was significantly lower in the cancer cells. The activities of all tested enzymes and isozenzymes in colorectal cancer tissue were not significantly higher in drinkers than in non-drinkers. Additionally we observed statistically significant increasing activity of class I ADH isoenzymes in the sera of patients with colorectal cancer. For this reason the total ADH activity was also significantly increased. The activities of ADH III and ADH IV isozenzymes and ALDH were unchanged in the sera of patients. There were no marked differences in activities of all tested enzymes and isozenzymes between drinkers and non-drinkers (with colorectal cancer). CONCLUSIONS: The differences in activities of total ADH and class I ADH isozenzymes between colorectal cancer tissues and healthy mucosa might be a factor of ethanol metabolism disorders, which can intensify carcinogenesis. The increased total activity of alcohol dehydrogenase and class I isozenzyme in the sera of colorectal cancer patients seems to be caused by release of this isoenzyme from cancer cells. Total ADH activity or ADH I activity in the serum may be approved as candidates for markers of colorectal cancer.

PMID: 18702331