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Evaluation of Aldehyde Dehydrogenase 1A1 (ALDH1A1) in colorectal cancer in relation to prognosis and response to chemotherapy

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ALDH1A1 has been described as a colorectal cancer stem cell marker and there is some evidence for its value as a prognostic marker in a number of cancer entities. However, no study so far has shown any prognostic value of ALDH1A1 in colorectal cancer. The objective of this dissertation was therefore to shed more light on the role of ALDH1A1 as a prognostic marker for overall, disease-free and progression-free survival in tumors of the colon and rectum. This should help to stratify patients to therapy according to their individual risk as well as identify possible targets for therapeutic intervention.

The expression of ALDH1A1 was evaluated in a cohort of 997 newly diagnosed colorectal cancer patients and a second cohort of 44 palliatively treated colorectal cancer patients who had developed liver metastases. Immunostaining against ALDH1A1 was performed on a paraffin-embedded tissue microarrays including 659 primary colon cancer samples and 338 rectal cancer samples and on whole-mount tissue slides of 44 inoperable patients with chemonaive liver metastasis resected during exploratory surgery. Slides were scanned and cytoplasmic immunohistochemical staining was assessed automatically with a protocol established by using the VisioMorph software. An immunoreactive score was calculated for each patient. Patients were sorted into seven groups according to their immunoreactive scores. Nuclear and stromal expression of ALDH1A1 were assessed semi-quantitatively as present or absent. These data were merged with clinical and histopathological data.

Both primary cancer tissue and liver metastasis displayed cytoplasmic and, to a small degree, nuclear staining. Only the primary tumors displayed some stromal staining. Nuclear ALDH1A1 staining in colorectal cancer tissue is a new finding which has not been described so far.

No correlation between any histopathological and clinical data with cytoplasmic or stromal ALDH1A1 staining was detected in any of the cohorts. Furthermore, cytoplasmic and stromal ALDH1A1 staining is neither significantly associated with overall and disease-free survival in colon or rectal cancer, nor with response to chemotherapy and overall or progression-free survival in patients with liver metastasis. A novel finding to be noted is that nuclear expression of ALDH1A1 in the subgroup of colon cancer patients is significantly associated with lymph node status and grading. Furthermore, it is significantly associated with shortened overall and disease-free survival by univariate and multivariate analysis and might therefore be of prognostic significance in this patient group.

While most of the prognostic studies for different cancer entities to date conclude that ALDH1 and ALDH1A1 respectively have a negative prognostic value, the data are inconsistent within different tumor entities as well as between different types of tumors. For some cancer entities data are limited to one study. Studies to date used various staining evaluation methods and statistical cut-off points, which aggravate comparison of data and final conclusions on the value of ALDH1 and ALDH1A1.

The present findings for the cytoplasmic staining in primary colorectal cancer are consistent with three other studies on the value of ALDH1A1 as a prognostic marker in colorectal carcinoma, none of which detected any prognostic value of ALDH1A1 cytoplasmic staining. Those studies, together with the present study comprise more than 2400 patients. Despite different methodology, they all

conclude that expression of ALDH1A1 is not associated with survival rates. Therefore, it is reasonable to state that in colorectal cancer ALDH1A1 staining expression based on percentage and/or intensity of cytoplasmic staining has no prognostic value.

While there is reasonable evidence suggesting that ALDH1 is a cancer stem cell marker in various cancer entities including colorectal cancer, a growing number of studies shows that a combination of different markers, which differ from cancer to cancer entity, improves definition of cancer stem cells and therefore the prediction of patient prognosis. The high percentage of tumor cells displaying ADLH1A1 activity in the present study raises the question whether all of these cells could really be regarded as cancer stem cells. Furthermore the selective expression of ALDH isoenzymes in cancer tissues may be tumor- or organ specific and ALDH1A1 may not be the ideal candidate for colorectal cancer tissue.

There is convincing evidence that ALDH1 positive cells are chemotherapy resistant to cyclophosphamid due to its activity as a detoxifying agent. However, cyclophosphamid is not a chemotherapeutic agent used in colorectal cancer. While there is some evidence that ALDH1 positive cells are resistant to other therapeutic regimes, there are also some data supporting that ALDH1 positive cells are even more chemo sensitive. The rationale for this is yet unclear. Resistance to chemotherapy involves many different stem cell pathways. While ALDH1 can be valuable in defining these cells it is not always a mediator of chemoresistance.

The present results, together with existing evidence, suggest that ALDH1A1 expression alone in tumor cell cytoplasm and stroma of colorectal cancer patients is not ideal to define cancer stem cells and has no prognostic value. The new finding, that patients with colon cancer expressing nuclear ALDH1A1 staining have a marked lower overall and disease-free survival rate, justifies further studies to prove this result. Knowing more about the function of ALDH1A1 in the nucleus may lead to specific therapeutic interventions of value for this specific patient group.