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CDX2 - A Predictive Biomarker in Stage II Colon Cancer for Adjuvant Chemotherapy?

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Background

Incidence and current issues in stage II CRC

In the United States, colorectal cancer (CRC) is the third most common cancer among men and women. Estimated new cases were 134,490 in 2016, which was 8% of all new cancer cases, while 49,190 deaths were expected [1]. The Tumor-Node-Metastasis (TNM) system of the American Joint Committee on Cancer is the most commonly used system for staging CRC and serves as a predictor of five-year survival [2]. Approximately 28% of patients with colon cancer present with stage II colon cancer [3].

Colon oncotype DX

Recurrence develops in 20%-25% of stage II colon cancer patients. However, the use of adjuvant chemotherapy in patients with stage II colon cancer remains controversial. It is unclear which molecular signature predicts both prognosis and benefit of adjuvant chemotherapy. To address these problems, colon oncotype DX has been used to predict the risk of colon cancer recurrence. This assay was derived from 1851 patients with stage II and stage III colon cancer, in which 761 candidate genes were identified, and a final set of 12 genes were used as validated predictors of recurrence risk. The Colon Recurrence Score value provides quantitative prognostic information for an individual patient. It ranges from 0 to 100, where score of less than 30 is low risk, between 30 to 40 is intermediate risk, and above 40 is high risk [4]. But it does not predict the benefit of adjuvant therapy. Such test is usually costly and has limited adaptability due to its requirement for additional tissues and the mandate of analysis at a central laboratory [5].

In order to easily identify patients with stage II colon cancer who are at high risk for relapse, it is important to use a systemic search for a biomarker that is relatively easy to detect, and feasible for testing in local laboratories. It should be also an actionable biomarker which can predict the benefit of adjuvant therapy.

CRC stem cells

Colorectal cancer stem cells have been chosen for this purpose due to its crucial function in tumorigenicity. There are three theories regarding the origin of Colorectal cancer stem cells. First, Colorectal cancer stem cells is thought to derive from the malignant transformation of normal colorectal stem cells. Second, it may originate from the dedifferentiation of common cancer cells, which may regain stemness even in the stage of terminal differentiation. Third, through regulation of microenvironment, Colorectal cancer stem cells may transform from non-cancer stem cells to cancer-stem cells. Current chemotherapies target mainly actively dividing cells, while quiescent stem cells can escape, the cytotoxic effects of chemotherapy and lead to relapse [6].

CD166 (ALCAM) in CRC

CD166 [activated leukocyte-cell adhesion molecule (ALCAM)], is a mesenchymal stem cell marker. It was found in colon cancer stem cells in CRC xenograft models, which was established by implantation of CRC tissue in non-obese diabetic mice with severe combined immunodeficiency disease [7].

ALCAM is a cell adhesion molecule of the immunoglobulin superfamily, which is physiologically expressed in activated leukocytes, neural cells, epithelial cells, and haemopoietic progenitor cells. In colon cancer, there are two types of ALCAM expression, cytoplasmic and membranous. Membranous type is a physiological condition of ALCAM expression, while cytoplasmic ALCAM was almost ubiquitous in basal parts of colonic crypts of normal mucosa, whereas overexpression was restricted to a fraction of colon cancers, and it is also related to shorter survival time in stage II and III colon cancer patients [8].

CDX2 in a retrospective study ALCAM and CDX2

Piero et al. published an intriguing research study in *New England Journal of Medicine* in 2016. In this study, ALCAM was

used as the example of CRC stem cells to identify biomarkers to predict prognosis in CRC. In this study, 2329 colon genes, which were selected from Human Colon Global Database, were derived from human CRC (2115 samples) and normal colon tissue samples (214 samples), in which 16 genes were identified that fulfilled the criteria of "X-negative implies activated leukocyte-cell adhesion molecule (ALCAM/CD166)-positive". This definition refers to genes that are not present in the presence of ALCAM. This criteria uses Boolean network, which is a software tool, to select genes from microarrays when it meets the cutoff threshold - the false discovery rate <0.0001 (10^{-4}). Among the 16 genes identified, only caudal-type homeobox transcription factor 2 (CDX2) could be measured through immunohistochemical (IHC) analysis, while other 15 genes could not be utilized clinically because no standardized diagnostic tests were available to measure them. CDX2 belongs to caudal-related homeobox transcription factor gene family. Its expressions were inversely related to stem cell properties, and stem cells have been associated with more aggressive cancers [9]. The encoded protein of CDX2 is a biomarker of mature colon epithelial tissues, and it is a major regulator of intestine-specific genes involved in cell growth and differentiation.

CDX2 and DFS in stage II colon cancer

Subsequently, evaluation of relationship between CDX2 and disease-free-survival (DFS) was determined in a discovery data set of 466 patients and a validation data set of 314 patients, respectively. Patients of stage II colon cancer without CDX2 were associated with shorter survival compared to CDX2 positive ones (41% versus 74% in discovery data set, and 48% versus 71% in validation data set, respectively).

CDX2 and benefit of adjuvant chemotherapy

Moreover, the investigators used an expanded database of 669 patients with stage II colon cancer to examine the possibility of CDX2 as a marker for benefits from adjuvant chemotherapy.

Among stage II colon cancer patients without CDX2, adjuvant chemotherapy was associated with higher rate of survival compared to patients without adjuvant chemotherapy (91% versus 56%) [10].

Advantages of CDX2 as a biomarker

CDX2 is a single biomarker that can be detected by widely used IHC analysis and has been widely used as a marker for colon cancer. As a prognostic marker, CDX2 is a much simpler alternative to traditional crude tumor characteristics such as number of lymph nodes removed, vascular or perineural invasion, tumor grade and T-stage. It is also more cost effective than colon oncotype DX by its ability to be easily measured in local medical facilities. More importantly, it has an adding advantage over the prognostic tools with its ability to identify patient population who can benefit from adjuvant chemotherapy.

Disadvantages of CDX2 as a biomarker

The benefit is demonstrated in a retrospective study, which requires prospective validation. In addition, the remaining 15 genes other than CDX2 would potentially identify a different patient population which are a higher risk for relapse and achieve more benefit from chemotherapy. Moreover, these 15 genes may not be a comprehensive panel of stem cell biomarkers in colon cancer.

A recent study using the same gene datasets identified zinc finger E-box binding homeobox 1 (ZEB1) as a new stem cell marker from colon-crypt base. This biomarker could be detected by IHC, and should be studied for its role in both prognosis and predictability of benefits with adjuvant chemotherapy [11].

Genes expressed from cells beyond stem cells, such as stromal cells, might also contribute to poor prognosis and can be used as predictors other than stem cells. In a retrospective study using three CRC transcriptomic data sets containing 916 patients with CRC stage I, II and III, 87 genes were identified to be associated with poor prognosis [12]. The tissue expression patterns of the proteins encoded by these genes using Human Protein Atlas Database demonstrated that Periostin (POSTN) and caldesmon 1 (CALD1) were only expressed in stromal cells. On the other hand, [13] Insulin like Growth Factor Binding Protein 7 (IGFBP7) and Fibroblast Activation Protein Alpha (FAP) showed higher expression in stroma compared to epithelialia of the tumors. This study indicated that elevated expression of CALD1, FAP or IGFBP7 in stromal cells predicted shorter DFS [14]. The roles of non-stem cell markers need further study to understand their roles in prediction of benefit with adjuvant chemotherapy.

Conclusion

CDX2 is a very exciting advancement in the identification of biomarker in stage II colon cancer. It not only identifies prognosis of patients for potential relapse, but also predicts benefit of adjuvant chemotherapy in patients at high risk for relapse. More importantly, it is a marker that has been easily identified in colon cancer diagnostic workup, accessible and inexpensive. However, prospective study is needed to validate these results. In addition, colon cancer stem cell markers beyond CDX2 and markers outside of colon cancer stems cells both have potential to better prediction of prognosis and identification of benefits adjuvant chemotherapy. The feasibility of a simple, accessible and effective biomarker for stage II colon cancer is on the horizon.

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