HHS Public Access

Author manuscript

Cell Stem Cell. Author manuscript; available in PMC 2017 July 05.

Published in final edited form as:

Cell Stem Cell. 2016 February 04; 18(2): 168–169. doi:10.1016/j.stem.2016.01.011.

CDX2 - Linking Cell and Patient Fates in Colon Cancer

Eric R. Fearon[1,2,3] and **Emina H. Huang**[4]

[1]Division of Molecular Medicine and Genetics, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan 48109 USA

[2]Department of Pathology, University of Michigan, Ann Arbor, Michigan 48109 USA

[3]Department of Human Genetics, University of Michigan, Ann Arbor, Michigan 48109 USA

[4]Departments of Stem Cell Biology and Regenerative Medicine, Colorectal Surgery, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio 44195 USA

Abstract

Administering adjuvant chemotherapy to stage II colon cancer patients is controversial due to poor benefit observed for the population as a whole. Recently, Dalerba et al identified a subgroup of stage II patients that might benefit from adjuvant chemotherapy based on lack of CDX2 expression in their cancer stem cells.

Preview

Adjuvant chemotherapy, which refers to secondary treatments meant to support a primary surgical intervention, is known to improve survival of patients with stage III (lymph node-positive) colon cancer (Wolpin et al., 2007). However, the value of adjuvant therapy is unclear for stage II colon cancer patients (Varghese, 2015). In a recent issue of the New England Journal of Medicine, Dalerba and colleagues identify a subset of stage II colon cancer patients that may benefit from adjuvant chemotherapy after surgery (Dalerba et al., 2016). This subset is based in part on in-depth studies of the presumptive stem/progenitor subset of colon cancer cells expressing the stem cell protein marker ALCAM/CD166. The absence of CDX2 homeobox transcription factor expression in cancer cells defines the subset.

Recommending adjuvant chemotherapy for stage II colon cancer is problematic because the overall survival benefit is only enhanced 5% or less by treatment with the single most commonly used agent – fluoropyrimidine (Varghese, 2015). The minimal benefit likely stems from a variety of factors including, the heterogeneity of clinical-pathological features and disease course and multiple adverse aspects of chemotherapy (toxicity, inconvenience, and cost). As a result, the risk-benefit ratio for treating all stage II colon cancer patients is unfavorable. Major clinical groups, including the American Society of Clinical Oncology and the National Comprehensive Cancer Network have highlighted selected clinical and

Correspondence to: Emina H. Huang.

laboratory criteria that may predict a benefit for adjuvant chemotherapy in stage II colon cancer patients, including tumor stage, pathologic T4 disease, poorly differentiated histology, and sampling <12 lymph nodes (Dienstmann et al., 2015). Some molecular features that indicate poor prognoses in stage II colon cancer patients and that might be useful as decision aids for adjuvant chemotherapy in stage II patients are the identification of $BRAF^{V600E}$ mutations in the cancer, especially in the setting of microsatellite stability or in distal colon cancer, and KRAS mutants in the BRAF wild-type cancers (Diestmann et al., 2015).

Dalerba and colleagues use a combined analytical approach based on their prior successes in studying colon cancer stem cells (Dalerba et al, 2007). They previously demonstrated the additive enrichment potential in defining a subpopulation of cancer cells with cancer stem cell-like functional properties provided by the detection of $ALCAM/CD166^{high}$ expression, beyond that provided by CD44 high ($CD44^{high}$) expression alone. Expression of ALCAM/CD166 is inversely correlated with survival in colon cancer patients (Weichert et al., 2004;). In their original colon cancer stem cell studies (Dalerba et al., 2007), co-expression of CD44 and ALCAM/CD166 in a subset of cells in primary colon cancers was linked to enhanced cancer stem cell self-renewal. The authors focused on potential biomarkers not expressed in ALCAM/CD166-positive tumors but that were present in ALCAM/CD166-negative tumors, and they thus identified the CDX2 protein. Unlike a prior study, where nearly 30% of colon cancers lost CDX2 protein expression (Baba et al., 2009), Dalerba et al found only ~4% of colon cancers had lost CDX2 expression. In both their initial patient cohort and the validation patient cohorts, loss of CDX2 was associated with reduced 5-year disease-free survival, independent of tumor grade or patient stage, age, or sex. In the rare stage II colon cancer patients treated with adjuvant chemotherapy and whose cancers lacked CDX2 expression, they found improved five-year disease-free survival compared to those not receiving adjuvant chemotherapy (91% vs. 56%, p=0.006). While several prior studies indicated that loss of CDX2 expression is associated with poor prognosis (Bae et al., 2014), the work from Dalerba and colleagues now shows that CDX2-expression status is strongly linked to responses to adjuvant chemotherapy in patients with stage II colon cancer.

CDX2 is a homeobox transcription factor with critical functions in distal intestinal development during later stages of embryogenesis and in appropriate cell fate specification and differentiation in postnatal intestinal epithelium. Several CDX2-regulated genes in intestinal epithelial cells have been defined, including genes encoding liver intestine-cadherin, hephaestin (HEPH) iron transport protein, multidrug resistance 1 (MDR1) protein, and the pregnane X and farnesoid X receptors (Takakura et al., 2010). The functional significance of these genes in mediating CDX2's effects in normal and tumor tissues is poorly understood. Not unexpectedly, the functional effects of reduced or absent expression of these genes and proteins in colon cancer stem cells lacking CDX2 expression are also poorly understood. However, based on the well-known role of MDR1 as an ATP-dependent drug-efflux pump, it is possible that reduced MDR1 levels and function in CDX2-negative colon cancers might enhance responses to adjuvant stage II colon chemotherapy regimens that include agents (oxaliplatin), as MDR1 mediates drug efflux.

The findings of Dalerba and colleagues highlight several concepts and issues deserving further study. *First*, the authors' use of the presumptive colon cancer stem cell surface marker ALCAM/CD166 to define high-priority cancer cell subpopulations for in-depth analytical studies have implications for pre-clinical and clinical work on colon cancer, based on genetic and biological heterogeneity of tumor cell subpopulations in primary colon cancers. *Second*, the bio-informatics efforts to uncover robust biomarkers of colon cancer differentiation were followed by straight-forward immunohistochemical confirmation supporting the utility of assessing CDX2 expression for prognosis and prediction of therapeutic response in stage II patients. Advanced approaches and biomarkers that can realistically be used in clinical work are critical. *Third*, the association of (i) the expression of a transcription factor controlling appropriate cell fate specification of intestinal cells with (ii) clinical outcomes in stage II colon cancer patients is a biologically intriguing and potentially quite important clinical advance. Roughly 25% of patients with colon cancer present with stage II disease, and the authors' findings indicate that the subset (~4-5%) of stage II patients whose cancers lack CDX2 expression may benefit from adjuvant chemotherapy. As the authors acknowledge, a prospective study is needed to establish that CDX2 expression is an independent determinant of the response to adjuvant chemotherapy and that CDX2 expression analysis is useful in guiding therapeutic decisions in stage II colon cancer. In-depth efforts to define potential mechanisms, such as reduced MDR1 expression, through which CDX2 loss might contribute to differential patient responses to adjuvant chemotherapy are also needed. Should further studies provide functional evidence that CDX2 directly regulates the response of colon cancer cells to adjuvant chemotherapy, strategies to antagonize CDX2 expression and function in CDX2-expressing colon cancers could be beneficial.

Acknowledgments

Work in this area is supported by NCI R01 CA082223 to ERF and by NCI R01 CA142808 and R01 CA157663 to EHH.

References

Baba Y, Nosho K, Shima K, Freed E, Irahara N, Phillips J, Meyerhardt JA, Hornick JL, Shivadasani RA, Fuchs CS, Ogino S. Clin Cancer Res. 2009; 15:4665–73. [PubMed: 19584150]

Bae JM, Lee TH, Cho NY, Kim TY, Kang GH. World J Gastro. 2015; 7:1457–1467.

Dalerba P, Sahoo D, Paik S, Guo X, Yothers G, Song N, Wilcox-Fogel N, Forgo E, Rajendran P, Miranda S, Hisamori S, Hutchison J, Kalisy T, Dalong Qian, Womark N, Fisher G, van de Rijn M, Clarke MF. NEJM. 2016 xxxx.

Dalerba P, Dylla SJ, Park I, Liu R, Wang X, Cho RW, Hoey T, Gurney A, Huang EH, Simeone DM, Shelton AA, Parmiani G, Castelli C, Clarke MF. PNAS. 2007:10158–10163. [PubMed: 17548814]

Dawson, H., Koelzer, V.H., Lukesch, A.C., Mallaev M., Inderbitzin, D., Lugli A., Zlobec, I.

Dienstmann R, Salazar R, Tabernero J. J Clinical Oncology. 2015; 33:1787–1796.

Varghese A. Clinic Colon Rectal Surg. 2015; 28:256–261.

Weichert W, Knosel T, Bellach J, Dietel M, Kristiansen G. J Clinical Path. 2004; 57:1160–1164. [PubMed: 15509676]

Weidle UH, Eggle D, Klostermann S, Swart GW. Cancer Genomics Proteomics. 2010; 7:231–243. [PubMed: 20952758]

Winn B, Tavares R, Matoso A, Noble L, Fanioan J, Waldman SA, Resnick MB. Hum Path. 2010; 41:123–128. [PubMed: 19800103]

Wolpin BM, Meyerhardt JA, Mamon HJ, Mayer RJ. CA Cancer J Clin. 2007; 57:168–85. [PubMed: 17507442]