a recent study (Schrappe et al., 2008). Should future studies demonstrate that the concomitant use of a NOTCH1 inhibitor with glucocorticoids can enhance the response of resistant leukemia, lower doses of dexamethasone could be used to treat such patients, sparing them from the toxicity of intensified chemotherapy. The protective effect of glucocorticoid therapy against the gastrointestinal toxicity of γ-secretase inhibitors might also renew interest in γ-secretase inhibitors as therapy for patients with Alzheimer's disease, for whom the drugs were first introduced to inhibit the production of amyloidogenic β-amyloid peptides.

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The Stem of Cancer

Riccardo Fodde[1,*]
[1]Department of Pathology, Josephine Nefkens Institute, Erasmus Medical Center, Rotterdam 3000 DR, The Netherlands
*Correspondence: r.fodde@erasmusmc.nl
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Despite great advances in our understanding of tumor initiation and progression, the identity of the "cell of origin" of cancer remains elusive. Two recent publications provide experimental evidence that normal intestinal stem cells are the cells of origin of intestinal cancer in the mouse.

Colorectal cancer (CRC) represents a unique model to study mechanisms underlying tumor formation and progression. However, notwithstanding our detailed understanding of the initiating and rate-limiting mutation at the *APC* tumor suppressor gene and the subsequent genetic hits that accompany the adenoma-carcinoma sequence, the identity of the CRC cell of origin is still obscure.

The epithelium lining the gastrointestinal (GI) tract represents a unique stem cell niche where different cell types are spatially organized, each dedicated to a specific function. As recently shown by the Clevers laboratory, intestinal stem cells exist at the base of the crypts and, at least in the mouse, are earmarked by expression of the *Lgr5* gene in both the proximal and distal (colon) intestinal tract (Barker et al., 2007). These crypt base columnar cells divide about once per day, and their progenies, the transient amplifying (TA) cells, divide at an even higher rate and migrate up the crypt until they reach its midportion, where they differentiate into specialized intestinal functions. When the differentiated cells reach the top of the crypt-villus axis, they undergo apoptosis and are shed into the intestinal lumen. In such a hierarchical tissue architecture, it would be predicted that cancer cells would arise from (epi)genetic mutations in stem or early progenitor cells because of their long-term proliferation capacity and their ability to differentiate and acquire more specialized functions. However, an alternative model has been proposed in which the initial transformation occurs in an epithelial cell located in the intercryptal zone and in which the dysplastic process proceeds downward (Shih et al., 2001).

Two recent studies have provided evidence for normal intestinal stem cells as the cells of origin of intestinal tumors in the mouse (Barker et al., 2008; Zhu et al., 2008). Barker et al. bred a floxed *Apc* allele into the *Lgr5*-Cre mouse line, which expresses Cre recombinase controlled by the endogenous *Lgr5* locus, to selectively inactivate *Apc*, which leads to constitutive activation of the Wnt/β-catenin signaling pathway in the stem cells. Within days, these Wnt-activated stem cells generate transformed progeny that rapidly expand to the TA compartment. Eventually, multiple

adenomas form in the small intestine and the colon, in agreement with the authors' previous report on *Lgr5* expression marking the stem cells of both the proximal and distal GI tract (Barker et al., 2008). In contrast, induction of Cre in TA cells does not result in the formation of frank neoplasia.

In the second study (Zhu et al., 2008), Cre was driven by the endogenous prominin (*Prom1*) gene, which encodes the cancer stem cell (CSC) marker CD133 (O'Brien et al., 2007; Ricci-Vitiani et al., 2007). The authors show that *Prom1* expression is restricted to cells located at the base of the crypt, predominantly overlapping with the *Lgr5*$^+$ stem cells in small intestine. This specific expression pattern is not conserved in the colon, where differentiated cells in the crypt also express *Prom1*. Lineage-tracing experiments provided more conclusive evidence that *Prom1* specifically marks stem cells capable of generating all of the differentiated cell types of the small intestine. Hence, small-intestine stem cells located at the crypt base are *Lgr5*$^+$*Prom1*$^+$, whereas stem cells of the colon epithelium are apparently *Lgr5*$^+$*Prom1*$^-$. Accordingly, breeding of *Prom1*-Cre mice with animals carrying a floxed mutant allele of the β-catenin gene resulted in massive dysplasia in the small intestine, but in not the colon.

Overall, both of these studies provide evidence that a small window of opportunity exists for mutations in intestinal epithelial cells to efficiently cause tumor formation. Nevertheless, although the vast majority of human CRCs are triggered by *APC* mutations (and to a much lesser extent by oncogenic activation of β-catenin), the underlying genetic mechanisms are quite different from the abrupt loss of *Apc* function (or β-catenin activation) achieved by Cre-Lox technology in the mouse. In adenomatous polyps, the benign precursors of colorectal cancer, the first and second hit at the *APC* gene appear to be selected so as to retain some residual β-catenin regulating activity (Albuquerque et al., 2002). According to this "just-right signaling" model, tumor formation in the intestine requires a specific degree of Wnt/β-catenin signaling activation, different from the constitutive and full-blown activation predicted to result from total *APC* loss. Whether specific intestinal stem and/or progenitor cells are differentially susceptible to specific dosages of Wnt/β-catenin signaling is at present unclear. Moreover, as the two hits at a tumor suppressor gene occur in a sequential fashion, one should also consider possible selection advantages provided to the stem cell upon the first mutation event, i.e., before the rate-limiting and tumor-initiating somatic hit at the remaining wild-type allele takes place. Indeed, individuals with heterozygous germline *APC* mutations have been shown to have pretumor intestinal crypt changes consistent with enhanced stem cell survival (Kim et al., 2004).

A similar observation that the adult stem cell represents the cell of origin of cancer has recently been made in chronic myeloid leukemia (CML): restricted expression of the *BCR-ABLp210* oncogene in the mouse hematopoietic stem cell compartment is sufficient to induce CML formation that recapitulates the human disease (Pérez-Caro et al., 2009). Notably, in these three studies, evidence points to the existence of a cellular hierarchy within the tumors arising from mutations in stem cells. In the case of *Lgr5*$^+$ initiating cells (Barker et al., 2008), TA cells, which do not express *Lgr5* but accumulate β-catenin, are visible 5 days after induction of the *Apc* mutation. In more advanced adenomas, only 6.5% of the tumor cells express the intestinal stem cell marker. Likewise, only 15.5% of tumor cells retained CD133 expression in the prominin study (Zhu et al., 2008). This is reminiscent of human colorectal cancers in which CD133 was shown to mark a subpopulation of CSCs with tumor-initiating capacity when transplanted in immunodeficient recipient mice (O'Brien et al., 2007; Ricci-Vitiani et al., 2007). Finally, in the CML mouse model expressing *BCR-ABLp210* under the control of the *Sca1* promoter, leukemogenic potential was only observed in tumor-derived *Sca1*$^+$ cells, but not in the more mature *Sca1*$^-$ parenchymal cells (Pérez-Caro et al., 2009). Overall, these observations support the CSC model that predicts a cellular hierarchy within malignancies in which cells with self-renewal and differentiation ability coexist with more specialized and mature cells. However, the CSC model has been challenged by showing that non-CSC subpopulations of tumor cells can also recapitulate the diversity of the primary cancer when transplanted in immunoincompetent animals (Kelly et al., 2007; Quintana et al., 2008; Shmelkov et al., 2008). From this perspective, the lineage-tracing experiments presented in the Barker et al. and Zhu et al. papers further confirm the CSC model and bypass the limitations and experimental variability of the transplantation assay.

How do these advancements affect our understanding of cancer and impact on therapeutic approaches? In the CML model, CSC elimination was sufficient to eradicate the whole tumor though treatment with the BCR-ABL inhibitor imatinib could not modify the course of the disease (Pérez-Caro et al., 2009). Of note, *BCR-ABL* oncogene activation in CML and loss of *APC* function in CRC have been shown to cause genetic instability possibly allowing escape from oncogene dependence by accumulating additional somatic changes in CSCs. Future efforts should consider targeting the CSC population as a whole rather than focusing on pharmacological inhibition of the molecular pathways underlying CSC onset. One challenge ahead is to identify cell surface markers that exclusively mark CSCs and that can be targeted without affecting their normal counterparts.

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