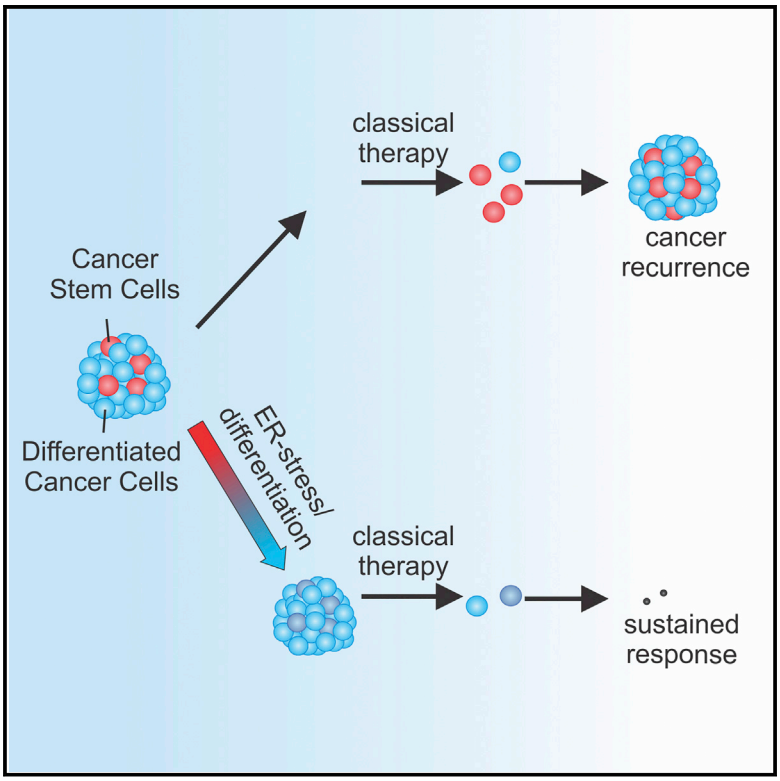
Report

Cell Reports

ER-Stress-Induced Differentiation Sensitizes Colon Cancer Stem Cells to Chemotherapy

Graphical Abstract



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In Brief

Colon cancer stem cells (colon-CSCs) are more resistant to chemotherapy than differentiated cancer cells. Wielenga et al. show that activation of the unfolded protein response (UPR) forces colon-CSCs to differentiate, which augments their sensitivity to conventional chemotherapy.

Highlights

- Colon-CSCs are more resistant to chemotherapy than differentiated cancer cells
- Activation of the unfolded protein response causes differentiation of colon-CSCs
- UPR-induced differentiation enhances response to chemotherapy in vitro and in vivo

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ER-Stress-Induced Differentiation Sensitizes Colon Cancer Stem Cells to Chemotherapy

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SUMMARY

Colon cancer stem cells (colon-CSCs) are more resistant to conventional chemotherapy than differentiated cancer cells. This subset of therapy refractory cells is therefore believed to play an important role in post-therapeutic tumor relapse. In order to improve the rate of sustained response to conventional chemotherapy, development of approaches is warranted that specifically sensitize colon-CSCs to treatment. Here, we report that ER-stress-induced activation of the unfolded protein response (UPR) forces colon-CSCs to differentiate, resulting in their enhanced sensitivity to chemotherapy in vitro and in vivo. Our data suggest that agents that induce activation of the UPR may be used to specifically increase sensitivity of colon-CSCs to the effects of conventional chemotherapy.

INTRODUCTION

In many cancers, a small subpopulation of cells is responsible for tumor initiation, growth, and metastasis (Visvader and Lindeman, 2012). In the colon, these so-called colon cancer stem cells (colon-CSCs) are characterized by the expression of cell surface markers such as CD133 (O'Brien et al., 2007; Ricci-Vitiani et al., 2007), LGR5 (Barker et al., 2009; Kemper et al., 2012), and CD166 (Dalerba et al., 2007). Furthermore, these cells display high levels of ALDH1 enzyme activity (Huang et al., 2009) and Wnt-signaling activity (Vermeulen et al., 2010). Importantly, colon-CSCs show increased resistance to conventional chemotherapies and are believed to be responsible for tumor regeneration after initial response to chemotherapy (Colak and Medema, 2014; Kemper et al., 2010; Rich and Bao, 2007; Valent et al., 2012; Zeuner et al., 2014). Therefore, therapeutic outcomes after chemotherapy may be improved with therapies that specifically target the eradication of colon-CSCs.

Mechanisms that regulate stem cell dynamics in the healthy intestinal epithelium may give fundamental insights into the biology of their malignant counterparts. An important organelle that regulates the homeostasis of normal intestinal stem cells is the ER. Novel proteins that are synthesized in the ER are assisted by chaperones for their proper folding. The major ER chaperone GRP78 is in a dynamic equilibrium between folding proteins and ER transmembrane receptors. An increased load of folding proteins shifts GRP78 away from the transmembrane receptors, a situation termed ER stress that results in the activation of the unfolded protein response (UPR). We have recently shown that activation of the UPR forces normal intestinal epithelial stem cells into differentiation (Heijmans et al., 2013).

RESULTS

Activation of the UPR Reduces Stemness of Colon-CSCs

We hypothesized that, if the differentiating effects of the unfolded protein response (UPR) would be conserved between normal intestinal stem cells and colon-CSCs, then this may be exploited to sensitize colon-CSCs to chemotherapy. To specifically investigate the effects of the UPR on colon-CSCs, we used patient-derived spheroid cultures of colon cancer cells with Wnt-driven GFP expression (Vermeulen et al., 2010). In these cultures, colon-CSCs are marked by high Wnt pathway activity (Wnt^{high}), whereas more-differentiated cancer cells have lower Wnt pathway activity (Wnt^{low}). We have previously established that Wnt^{high} cells exhibit a higher clonogenic potential and are more resistant to chemotherapy than Wnt^{low} cells (Colak et al., 2014; Vermeulen et al., 2010), indicating that the Wnt-driven GFP reporter efficiently distinguishes between CSCs and more-differentiated cancer cells.

The UPR can be activated in vitro with subtilase cytotoxin AB (SubAB), a bacterium-derived protease that specifically cleaves ER chaperone GRP78 (Paton et al., 2006). Gene ontology analysis of SubAB-treated Wnt^{high} cells showed that the top three upregulated gene sets were UPR ($p = 1.3 \times 10^{-36}$), ER-associated catabolic process ($p = 3.9 \times 10^{-23}$), and ER lumen