Breast cancer stem cells are regulated by cell intrinsic pathways as well as by elements in the tumor microenvironment. New evidence suggests that an important interaction between the interleukin (IL)-8 receptor CXCR1/2 and HER2 is involved in this regulation. Simultaneous targeting of these pathways provides a novel therapeutic approach. Clin Cancer Res; 19(3); 511–3. ©2012 AACR.
ERK1/2 phosphorylation and reduced tumor sphere formation. These findings are consistent with previous studies showing that Src stimulates transcriptional activation of NF-kB via Stat3/CYLKD signaling cascade leading to the generation of an inflammatory feedback loop (9) as shown in Fig. 1. The studies of Singh and colleagues suggest that in addition to the previously described inflammatory feedback loop involving NF-kB and IL-6 there exists an additional positive feedback loop involving IL-8 and HER2. A recent report showing that HER2/HER3 activity leads to overexpression of IL-8 (10), combined with the reports of Singh and colleagues, supports the existence of such a positive feedback loop.

The studies of Singh and colleagues also have important clinical implications. Their data showing a correlation between levels of IL-8 in metastatic fluids and BCSCs frequently support previous studies showing a correlation between serum levels of IL-8 and poor patient outcome in patients with metastastic breast cancer (11). Apoptosis induced by chemotherapeutic agents may also increase intratumoral levels of IL-8 stimulating the cancer stem cell population (12). We previously have shown that reparaxin, a small-molecule inhibitor of CXCR1/2, inhibits BCSC in mouse xenografts (3). On the basis of this, we have initiated a phase I clinical trial combining reparaxin with chemotherapy in women with advanced breast cancers. The studies of Singh and colleagues suggest that combination of HER2-blocking agents may synergize with CXCR1/2 inhibitors in targeting the BCSC population. The recent developments of HER2-blocking agents with increased clinical efficacy such as T-DM1 may provide highly potent agents to test such approaches. The simultaneous targeting of interacting extrinsic and intrinsic CSC regulatory pathways may result in more efficient targeting of BCSC populations improving patient outcome.

Disclosure of Potential Conflicts of Interest
H. Korkaya receives research support from MedImmune. M.S. Wicha has commercial research grants from Dompe and MedImmune; ownership interest (including patents) in Oncomed Pharmaceuticals; and is a consultant/advisory board member for MedImmune, Veratem, and Paganini.

Authors’ Contributions
Conception and design: H. Korkaya, M.S. Wicha
Writing, review, and/or revision of the manuscript: H. Korkaya, M.S. Wicha

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Breast Cancer Stem Cells: We've Got Them Surrounded

Hasan Korkaya and Max S. Wicha


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