Targeting the Journey: From Embryogenesis to Cancer Stem Cell

S. Percy Ivy, Guest Editor; National Cancer Institute

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Drugs That Target the Stemness Pathways

When Michael Clarke (1) reported data for the existence of breast cancer stem cells, he introduced a new paradigm with the notion that at the heart of our failure to eradicate cancer is the continual repopulation of tumors by a small number of phenotypically distinct cells. In time, the stem cell characteristics became longevity, asymmetric cell division, self-renewal, quiescence and drug resistance. The offspring of these stem cells, often labeled progenitors, were following a failed path to differentiation and constituted the bulk of the tumor mass. This model, termed a hierarchical model, has been held in opposition to the traditional stochastic model, which held that one random cancer cell gives rise to two daughter cells, although it was understood by any cell biologist that at any given moment most cancer cells were quiescent and therefore also drug resistant, and that some cells in a heterogeneous population had managed to differentiate more than others. While the articles in this CCR Focus argue for the hierarchical model as opposed to the stochastic model, the jury is still out. And regardless of which model is accepted in time, the concept of “stemness” has prompted the introduction of at least 4 important new pathways to target. Embryonic stem cell pathways are dysregulated in cancer, and drugs targeting these pathways are in development. In the overview of this issue of CCR Focus by Guest Editor Percy Ivy, and in an elegant elaboration by Catherine O’Brien et al, the stem cell hypothesis is debated. But the lead compounds and potential drugs described, respectively, by experts Fumi Takahashi-Yanaga, Antonio Pannuti, Akil Merchant, Mark LaBarge and co-authors in the Wnt, Notch, Hedgehog, and Niche pathways make this critical point: we will have new drugs for cancer. Speaking to this are the responses in basal cell carcinoma and medulloblastoma observed with the Hedgehog inhibitor. The opportunity for drug development is the key contribution of the cancer stem cell hypothesis. As always, it is hoped that this issue of CCR Focus will challenge the expert, inform the interested nonexpert, and inspire strategies for the future.

Susan E. Bates, M.D.
Deputy Editor, CCR Focus
National Cancer Institute

Reference

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Susan E. Bates

Clin Cancer Res 2010;16:3105.