CANCER STEM CELLS

A remarkable paradigm shift has occurred in recent years regarding the biological origins of cancer. The cancer stem cell hypothesis has challenged the foundational notions of cancer, and the therapeutic implications have been profound. Compelling evidence indicates that errors in the development of a small subset of adult stem cells can lead to cancer. Only this small subpopulation of cells has the inherent ability to form tumors and metastasize. This book discusses the emerging field of cancer stem cell research, with contributions from leading experts on the basic biology, genetic pathways, and potentials for therapeutic targeting of cancer stem cells. It also covers clinical challenges for these new discoveries, namely, that cancer stem cells might be resistant to conventional chemotherapeutic and radiological treatments and may be at the biological core of relapse and therapeutic resistance. This book is an essential concise guide to the latest discoveries and therapies in cancer research.

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Preface

Cancer results from the accumulated effects of somatic or inherited gene alterations that result in the improper function of proteins. An increased understanding of the underlying genetics has shaped the modern hypotheses for the basis of cancer. First was the concept of *oncogenes*, defined as genes that promote a transformed cellular phenotype. The altered activities of this class of proteins are usually due to mutations in the genes themselves, polymorphisms in promoter elements, or aberrant activation of upstream signaling pathways. The next concept with profound implications for the genetic basis of cancer was the discovery of tumor suppressor genes. This class of genes, when genetically silent, essentially takes the brakes off the normal controls of cell cycle, senescence, and apoptosis. From the silencing of genes in cancer emerged the rapidly growing field of epigenetics and how gene silencing leads to the development of cancer. Therefore, for the past several decades of molecular biology, the focus has been on the ON and OFF switching of genes. Engineering of recombinant DNA in model cell systems produced a greater understanding of the underlying biochemistry and molecular biology of cancer. This led to the belief that similar alterations could occur naturally in nearly any somatic cell type, and therefore cancer was believed to be of a stochastic nature.

The *stochastic hypothesis* suggests the clonal evolution model, in which any cell with overexpressed oncogenes and/or downregulated tumor suppressors will eventually form a tumor. This model could explain the multiple aspects of human disease and clinical observations. However, recently, a hypothesis has reemerged to challenge this notion, causing a shift away from the stochastic model. Increasing evidence, initially discovered in hematological malignancies and, later, in solid tumors, suggests that tumors are formed from a subset of cells with unique characteristics that reside within the volume of the tumor. The unique subset of tumor-initiating cells is defined as *cancer stem cells*, a term initially coined by researchers in hematological malignancies and adopted by solid tumor researchers. What is shared in common with diverse cancers is that the unique subsets of tumor-initiating cells have stem cell–like biological and genetic similarities. Most pronounced are unique sets of surface markers, the ability of self-renewal, expression of developmental stem cell–like genes, and biological properties that facilitate tumor development.

The birth of the cancer stem cell hypothesis has generated a large degree of enthusiasm not without profound therapeutic considerations. For the most part, few of the current chemotherapeutic and irradiation strategies have considered the cancer stem cell component of the tumor burden. In fact, there are significant indications that the tumor-initiating cells are resistant to the conventional tools of cancer therapeutics.

This book focuses on the clinical and therapeutic implications of cancer stem cells. We have included chapters concerning the basic science of both leukemic and solid tumor stem cell biology and a practical chapter on the isolation and characterization of cancer stem cells. Because of the initial recognition of cancer stem cells in leukemia, therapeutic strategies may first be employed in this cancer, as discussed by researchers active in the field. Finally, we have included chapters describing stem cell signaling pathways that direct self-renewal and other vital cancer stem cell characteristics. These pathways offer the fodder for molecularly targeted therapeutics and rational drug design.

While this is a rapidly emerging field, the discovery of the cancer stem cell as a subset of cells with unique biological and genetic properties will likely have a substantial impact on cancer therapeutics and prevention as well as on the understanding of the biological origins of cancer.

William L. Farrar, PhD