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## Preface

Cellular dormancy refers to the cell entering a state of quiescence where growth is arrested in the G0-G1 phase of cell cycle. In this phase the cells are inactive and asymptomatic. The micrometastasis model defines tumor cell dormancy as a state of balanced apoptosis and proliferation of micrometastasis resulting in no net increase in the tumor mass. Cancer dormancy is referred to (in clinical terms) in connection with recurrence of cancer systemically or locally a long time after removal of the primary tumor in a patient who has been clinically disease free. Occurrence of cancer dormancy is a characteristic of all migrating tumor cells. Once tumor cells disseminate and start migrating to a new site to metastasize, the interaction of the tumor cells with the microenvironment determines whether the cells will proliferate and form metastases or undergo growth arrest and enter cancer dormancy. The disseminated cells will opt for dormancy if the new environment is not permissive such as absence of available growth factors and angiogenesis, and cellular stress. However, such dormant cells can exist in a quiescent state for many years, but start proliferating and form metastases that are incurable. For example, in breast cancer, 20% of clinically disease-free patients relapse 7–25 years after mastectomy.

It is suggested that metastasis-initiating cells are cancer stem cells or such cells revert to this functional state upon infiltrating a target organ. It seems plausible that primary tumors shed tumor cells at an early stage into the blood circulation, and a subset of these disseminated cells may persist in a state of dormancy. Molecular characterization of disseminated tumor cells in bone marrow and circulating tumor cells in blood opens a new avenue for understanding cancer dormancy and might contribute to the identification of metastatic stem cells.

Cellular quiescence is opposite to cell proliferation and is considered to be in a non-dividing state, but is reversible. It is a reversible growth/proliferation arrest process induced by diverse anti-mitogen signals, each of which regulates a group of genes; these genes play a key role in the cessation of cell growth and division. Different genes involved in this process can be identified.

In contrast to quiescence, senescence is essentially an irreversible cell growth arrest, which occurs when cells that can divide encounter oncogenic stress. Cellular senescence is a crucial anticancer mechanism. Premature senescence functions as a tumor suppressor mechanism in response to oncogenic stimuli. It is characterized by irreversible cell cycle arrest mediated

by tumor suppressors such as p53, Rb, and the promyelocytic leukemic (PML) protein. However, senescence is both tumor promoter and tumor suppressor. With the exception of embryonic stem cells and some tumor cells, most division-competent cells can undergo senescence when stimulated. DNA double strand breaks are one of the potent senescence inducers. Other stresses implicated in the induction of senescence include oxidative damage, telomerase dysfunction, and aberrant oncogene-dependent proliferative signaling. Senescence cells increase with age, which may give rise to cancer.

Although some evidence indicates that autophagy induction accelerates the development of senescence, the opposite has also been reported, i.e., autophagy suppression does not alter senescence induction. In other words, presence of senescence does not depend on the prior induction of autophagy. Some other studies report that autophagy and senescence occur in parallel, but are not interdependent. It is apparent that the exact relationship between autophagy and senescence is very complex, and contradictory results have been reported. Furthermore, because apoptosis is induced when autophagy is inhibited, the correct interpretation of the relationship between autophagy and senescence becomes difficult.

This is volume 3 of the multivolume series discussing Tumor Dormancy, Quiescence, and Cellular Senescence. The role of tumor dormancy and senescence in a number of diseases, including breast cancer, ovarian cancer, and leukemia, is discussed. Also is discussed the role of senescence and autophagy in the age-related cardiovascular diseases. The enchantment of autophagy seems to retard cardiac senescence. The role of cancer dormancy in breast cancer is discussed, indicating that tumor cells are able to persist in the dormant state until they become active and cause distant metastases. It is pointed out that cancer stem cells exist within breast tumors, which possess the ability of self-renewal and differentiation in a deregulated manner, resulting in tumor progression. The wntless related protein (Wnt) pathway plays a significant role in the “awakening” of dormant tumors.

Ovarian cancer is the most deadly of gynecological malignancies, and the long-term survival rate is quite poor, especially in patients having Type II high grade ovarian cancer with defective TP53. It is pointed out that Type II tumors are phenotypically heterogeneous, and a subpopulation of tumor cells is relatively resistant to chemotherapy. The resistant tumor cell population persists after chemotherapy in a state of dormancy, with recurrent tumors arising upon transformation of such dormant cells back to malignant growth. How lineage, histological subtypes, and grade influence the differential response of ovarian cancer resistance to platinum drugs is explained. Also is discussed the role of angiogenesis, growth arrest and autophagy in human ovarian cancer xenograft models for tumor dormancy.

By bringing together a large number of experts (oncologists, neurosurgeons, physicians, research scientists, and pathologists) in various aspects of this medical field, it is my hope that substantial progress will be made against a terrible human disease and injury. It is difficult for a single author to discuss effectively the complexity of cancer diagnosis, therapy and prognosis. Another advantage of involving more than one author is to present different points of view on a specific controversial aspect of cancer metastases and

therapy. I hope these goals will be fulfilled in this and other volumes of the series. This volume was written by 26 contributors representing 7 countries. I am grateful to them for their promptness in accepting my suggestions. Their practical experience highlights their writings, which should build and further the endeavors of the readers in these important areas of disease and injury. I respect and appreciate the hard work and exceptional insight into the role of dormancy, quiescence, and cellular senescence in various diseases and stem cell functions provided by these contributors. The contents of this volume are divided into five subheadings: General Applications, Role in Breast Cancer, Role in Ovarian Cancer, Role in Leukemia and Role in Cardiovascular Disease.

It is my hope that subsequent volumes of the series will join this volume in assisting in the more complete understanding of the major human diseases and their treatments. There exists a tremendous, urgent demand by the public and the scientific community to address to cancer diagnosis, treatment, cure and hopefully prevention. In the light of existing cancer calamity, government funding must give priority to eradicating deadly malignancies over military superiority.

I am thankful to Dr. Dawood Farahi and Phil Connelly for recognizing the importance of medical research and publishing through an institution of higher education. I am thankful to my students for their contribution to the preparation of this volume.

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