Symposium

Targeting Cancer Stem Cells

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Towards a Unifying Theory of Stem Cells and Human Diseases: Cancer as a Model System

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Tissue homeostasis is controlled by the balanced equilibrium between the programs of cell growth (cell cycle division) and cell death (apoptosis). Every day in an adult body over two billion cells undergo programmed cell death. The cell as the "unit of life" has been postulated to be the seed for disease initiation in most somatic disorders. In a simplistic but somewhat realistic paradigm, inherited and somatic diseases can be categorized by those with a cell excess phenotype, and those with a cell defect phenotype. The question is "which is the rheostat controlling such precise and critical balance?" We postulate that it is the "stem cell" the one exerting such significant regulation. Using cancer as a disease model we will discuss such hypothesis and present data supporting this groundwork novel concept.

Two major hypotheses regarding tumor initiation have been postulated. The "stochastic model" which predicts that every neoplastic cell can generate an entirely new tumor; and the "cancer stem cell model" which proposes that tumor cells exist in a hierarchical state, and that only a few stem cells possess tumor initiating potential. During the presentation and discussion we will discuss the identification and functional characterization of a human cancer stem cell, which fulfills the following stem cell criteria: 1) self-renewal and differentiation through asymmetrical cell division, 2) tumor initiating capacity, 3) a unique molecular signature, and 4) a multidrug resistance phenotype. Discussion will be mainly based on the discovery of this cancer stem cell in a prostate carcinoma model. The prostate cancer stem cell isolated from human tumors lacks expression of epithelial differentiation antigens (e.g., cytokeratins 19 and 18), organ specific markers (e.g., PSA and PSMA), and immune-surveillance molecules (e.g., class I histocompatibility antigens), while expressing self-renewal/developmental pathways (e.g., WNT/β-catenin, NOTCH and Hedgehog). Treatment with targeted therapies to Notch and Hedgehog pathways attenuated tumor formation, in an experimental murine model. Further studies utilizing this cancer stem cell may lead to a new molecular classification of tumors, development of predictive assays, and design of novel therapeutic strategies. This cancer stem cell has also been isolated from other human tumors, including breast, bladder, colon and lung carcinomas, as well as glioblastomas and certain sarcomas studied; a fact that gives further universality to our findings.

The etiopathogenesis of neoplastic diseases is characterized by its multiple nature. Biological, chemical, and physical agents have been identified as initiating or promoting neoplastic mechanisms. However, they all appear to a have common molecular basis, granting genetic instability and causing somatic derangements to pre-neoplastic and tumor cells. In addition to these somatic mutations, which are the most frequent abnormalities identified in human cancer, germ-line mutations associated with specific familial cancer syndromes have been also characterized. Epidemiologic and molecular genetic

studies have unveiled the underlying mutations of specific genes predisposing patients to distinct cancers, such as certain colorectal and breast tumors. It is therefore conceivable to view cancer as fundamentally a genetic disease entailing germ-line and somatic mutations. However, epigenetic events and altered patterns of protein expression have been also identified in neoplastic lesions, and their identification has become as important in the context of certain tumor classification schemes, as well as in the predicting course of disease.

Alterations in proto-oncogenes and tumor suppressor genes seem equally prevalent among human cancers. Multiple mutations appear to be required to conform the malignant phenotype. Genetic instability leads to a sequence of events that creates phenotypic alterations, granting a selective advantage to specific tumor cells. Metastasis is the ultimate outcome of tumor progression in this selective process. It appears that it is the accumulation rather than the order of these pleiotropic events that confers neoplastic cells the ability for tumor progression.

Tumors are composed of heterogeneous populations of neoplastic cells with different morphologies and phenotypes. The existence of the cancer stem cell has been postulated, this cell being responsible for tumor initiation and giving rise to differentiated progeny, thus capable of generating the heterogeneity observed in tumors and the hierarchical state of these lesions. The identification of this "cancer stem cell" population has important implications for the management of cancer patients. This includes diagnostic and predictive laboratory assays, as well as novel therapeutic strategies specifically targeting the cancer stem cell. Combination of this new therapy with current treatments that target the differentiated, expanding tumor cell subpopulations should eradicate tumors more efficiently, reduce the risk of relapse, and impact on metastatic clones and tumor resistance to conventional therapies.

The discovery of the human cancer stem cell defined above has important clinical implications in diagnostic and predictive laboratory assays, as well as for development of novel therapeutic strategies. These findings and translational clinical applications will be discussed during the presentation.

RECENT CSC PUBLICATION: Suppression of Acquired Docetaxel Resistance in Prostate Cancer through Depletion of Notch- and Hedgehog-Dependent Tumor-Initiating Cells, *Cancer Cell*, Volume 22, Issue 3, 373-388, 11 September 2012 (Copyright © 2012 Elsevier Inc.)