

Molecular Mechanisms of Cancer and Aging in Mammals

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Activities 2007. One major focus of our group is to generate appropriate mouse model systems of human cancer for the validation of emerging concepts in tumor biology, e.g. the hierarchical organization of tumors as abnormal tissues which originate from, and are maintained by, transformed stem cells.

Solid evidence supporting this model has been recently generated for the human leukemias, breast cancer, neuroblastomas and glioblastomas. It is likely that similar results will be obtained for the majority of all other tumors. If validated, the concept of cancer stem cells will profoundly influence both fundamental cancer research and our strategies to improve cancer treatment. From the point of view of the basic understanding of cancer development, the possibility that tumors arise from tissue stem cells questions our view of the early steps of carcinogenesis, namely the immortalization step. Infact, stem cells express telomerase and are near-immortal.

The focus of our investigations, therefore, will be more and more switched toward self-renewal regulation in normal and cancer stem cells. The existence of a small population of cancer stem cells that maintain the bulk of the tumor might explain the failure of many anti-cancer strategies. Most cancer therapies, infact, are designed to kill dividing cells, while stem cells divide unfrequently. Cancer stem cells might, therefore, escape the cell-killing effects of standard therapies. Mouse model systems tailored at exploiting these new concepts of tumor biology are not available. They will be, however, critical to assess the function of the known tumor suppressor pathways and to set-up novel anti-cancer strategies.

We plan to use some model systems to evaluate whether activation of critical checkpoint pathways in stem cells leads to altered tissue homeostasis, organism ageing and increased cancer incidence. Stem/progenitor cells ensure for tissue and organism homeostasis. Although they are potentially immortal, their life span is restrained by signaling pathways (ARF-p53; p16-Rb) that are activated by DNA damage (telomere dysfunction, environmental stresses) and

lead to senescence or apoptosis. Therefore, execution of these checkpoint programs might lead to stem cell depletion and organism aging.

Our lab has made, in the past, original and seminal contributions to the understanding of the molecular basis of cancer, particularly in the field of human acute leukemias, and molecular mechanisms of aging in mammals.

Our major achievements are: i) cloning of the Acute Promyelocytic Leukemia t15;17 breakpoints and molecular characterization of the PML-RAR translocation product; ii) identification of mutations of nucleophosmin (NPM) in myeloid leukemias; iii) biological and molecular characterization of the leukemogenic potential of PML-RAR, AML1-ETO and mutant NPM (effects on ARF-p53 and apoptosis; effects on chromatin and differentiation); iii) definition of the molecular basis of targeted treatment of leukemias (retinoic acid; inhibitors of HDACs); iv) isolation of a family of signal transduction proteins (Shc, Rai, Sli) and definition of their role in the cytoplasmic propagation of mitogenic and pro-apoptotic signals; v) identification of the p66shc splice variant as a critical determinant of the life span control mechanisms in mammals; vi) characterization of the red-ox properties of p66Shc.

Presently three major levels of efforts are being pursued in the lab:

Hematopoietic stem cells and Acute Myeloid Leukemias

Our major ongoing projects are: i) identification of the leukemic target cell and the leukemic ii) stem cells (as mouse models of leukemias we are using PML-RAR, AML1-ETO, PRDM16 and mutant NPM transgenic mice); iii) analysis of the effects of leukemia-associated mutants on the senescence program of stem cells (ARF-p53; p16-Rb and telomerase); iv) analysis of the roles of quiescent leukemia stem cells and the haematopoietic niche in the maintenance of the leukemic phenotype; v) characterization of the molecular mechanisms of altered gene expression by leukemia-associated mutants.

Breast stem cells and breast cancer

Our major ongoing projects are: i) in vitro propagation of murine breast stem cells and in vivo reconstitution experiments; ii) prospective identification of normal and neoplastic breast stem cells (as mouse models of breast cancer we are using MMTV-Ras and MMTV-erbB2 transgenic mice); iii) transformation of breast stem cells.

Effects of checkpoint activation on tissue homeostasis and molecular mechanisms of aging

Our major ongoing projects are: i) analysis of stem cell functions in progeric mice and long-living mouse strains; ii) analysis of the effects of increased oxidative stress and activated checkpoint pathways in tissue degeneration and cancer formation; iii) molecular dissection of oxidative stress signaling in differentiated and stem cells; iv) molecular and biological functions of recently identified members of the Shc family of signaling proteins (Rai, Ralp).