Cancer Immunity (6 February 2006) Vol. 6 Suppl. 1, p. 8

CANCER
IMMUNITY
Meeting Abstract

Leukemia and cancer stem cells

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Abstract

In the hematopoietic system hematopoietic stem cells (HSCs) are the only cells, except T and B memory cells, that self renew long term. Self-renewal is also a characteristic of all cancers and leukemias. In fact, it was arguable that the clonal progression that leads to malignancy occurs in stem and progenitor cells, and the properties of the malignant cell are mainly properties of the rare progenitor from which it derived. We proposed that cancers and leukemias are like the tissues from which they derive, and that they have both self-renewing cancer or leukemia stem cells, as well as nonmalignant differentiated progeny. These we call cancer stem cells or leukemia stem cells (LSCs). We also propose that the genes we call protooncogenes include genes that direct or regulate stem cell self-renewal. We have studied the cell developmental stages of myeloid leukemias in mouse models and human diseases, from chronic phases to acute or myeloid blast crisis. Most chronic myelogenous leukemias appear to be at the level of HSCs (LSCs are at the stage of HSCs), but all acute and blast crisis leukemias we have identified have as LSCs downstream daughter cells that have poorly regulated self-renewal. Mouse *JunB* conditional knockouts get a CML that is only transferred with HSCs. In a mouse AML with induced overexpression of *bcl2* and the homozygous *Fas.lpr* mutation, the leukemias are only transferred with purified granulocyte-macrophage progenitors (GMPs). In human CML at myeloid blast crisis phase, the LSC is a GMP that has activated the β-catenin signaling pathway, and used it for self-renewal. We propose that only isolated LSCs and other cancer stem cells are the appropriate targets for immunotherapy, and that a straight path to identifying targets selectively modified and/or expressed in them will begin with their identification and prospective isolation. We also propose that normal stem cells in the tissue sustain the 1 to *n*-1 events of premalignancy, and the final stages (*n* or *n*+1, etc) occur in progeny of the multihit clone, emerging outside the niches of normal stem cell regulation of self-renewal.