REVERSING HEMATOPOIETIC TUMORIGENESIS THROUGH ONCOGENE INACTIVATION

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Cancer is a consequence of genomic catastrophes that initiate the process of tumorigenesis by activating oncogenes or inactivating tumor suppressor genes. These mutant gene products usurp physiologic programs and mandate a neoplastic program with many stereotypical features including: relentless cellular proliferation, unrestrained cellular immortalization, blocked differentiation, abrogation of apoptosis, infidelity of genomic integrity, capacious invasiveness, robust angiogenesis and transience to evade host mechanisms. Hence, cancer is largely defined by a constellation of mutant gene products. These observations beg the question, can the neoplastic process be reversed through the targeted inactivation or repair of these mutant genes?

A priori, there appear to be several reasons why the targeted inactivation of any single oncogenes may not be effective. First, cancers are a consequence of many genetic events. Thus, no single event - even an event considered essential for the initiation of tumorigenesis - may remain essential to sustain a neoplastic phenotype once acquired. Second, cancers are genomically unstable greatly facilitating their ability acquire new genetic events that could compensate for the loss of any particular event. Finally, cancer is not solely a consequence of genetic events, epigenetic features may be more important for the maintenance of a neoplastic phenotype.

Contrary to expectation, compelling recent evidence illustrates that not only can cancer be reversed through the inactivation of a single oncogene, additionally, pharmacological agents have been identified that specifically fulfill this purpose. Perhaps even more demonstrative is the observation that in transgenic mice engineered to conditionally express particular oncogenes, tumors caused by these oncogenes almost uniformly undergo sustained regression promptly upon oncogene inactivation. Thus, cancers appear to be generally *addicted* to oncogenes.

Results will be presented demonstrating how from novel conditional transgenic mouse models the mechanisms by which oncogene inactivation results in the regression of hematopoietic tumors. Interesting, both cell autonomous and cell dependent mechanisms appear to be essential. The results of these studies will be useful towards the better understanding of the mechanisms by which oncogene initiate and sustain tumorigenesis and the development of new therapeutic approaches for the treatment of cancer.

MODELING HUMAN MATURE B CELL LYMPHOMAS WITH CONSTITUTIVE NFκB ACTIVITY IN THE MOUSE

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Constitutive NFκB signaling is a hallmark of several classes of mature B cell lymphomas in the human and there is evidence that it plays a critical role in the survival of the malignant cells. In accord with this view, NFκB signaling is essential for the survival of mature B cells in normal physiology. We have generated a system of conditional gene activation by Cre-mediated recombination and used it to target canonical or alternative NFÎB activity into mature B cells. We show that this makes the cells completely independent of BAFF-BAFF-receptor interaction and extends their life span in vitro and in vivo, without driving them into proliferation. However, upon mitogenic stimulation the mutant cells proliferate massively, far beyond what is seen in wild-type cells. This translates into the regular development of oligo- or monoclonal mature B cell lymphomas upon transfer of the mutant cells into syngeneic wild-type recipients. We are searching for the nature of the molecular events responsible for the transformation of the mutant cells and assessing a possible role of antigen in their selection. Our insights into these issues will be discussed together with the limitations and possible improvements of this mouse model.

MIR GENES IN LYMPHOID MALIGNANCIES

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Over the past five decades, a plethora of non-random chromosomal abnormalities have been consistently reported in malignant lymphoid cells facilitating the identification of lymphoid malignancies-associated protein coding oncogenes and tumor suppressors. The genetic dissection of hot spots for chromosomal abnormalities in the age of the sequenced human genome resulted in the discovery that microRNA genes, encoding for a class of small non-coding RNAs, frequently resides in such genomic regions. The combination of non-random chromosomal abnormalities and other types of genetic alterations or epigenetic events contribute to down-regulation or over-expression of microRNAs. The consequent abnormal expression of miRNAs affect cell cycle, survival and differentiation programs and selective targeting of these non-coding genes could provide novel therapeutic options for killing the malignant cells.