Bypassing the requirement for MYC in lymphoma progression

Recent studies in mice engineered to express regulatable alleles of MYC, RAS, and other oncogenes support the general principle that the genetic lesions that initiate tumorigenesis are often essential to maintain the malignant phenotype. The general design of many of these experiments may be criticized on theoretical grounds because, unlike human cancer, the inciting mutation is expressed widely in a field of cells and this may result in polyclonal proliferation that obviates the need for one or more cooperating mutations. But studies in human patients with chronic myeloid leukemia (CML) who demonstrate resistance to imatinib provide strong support for the idea that genetic lesions that initiate tumorigenesis remain essential in at least some human cancers (reviewed in Shannon, Cancer Cell. 2002;2:99-102).

In this issue Karlsson and coworkers (page 2797) describe an interesting series of experiments in which they performed spectral karyotype (SKY) analysis in lymphomas from mice in which the tetracyclene regulatory system was used to conditionally express the MYC oncogene in B cells. They then correlated these data with the propensity of these tumors to bypass the requirement for MYC in vivo. The authors emphasize that tumors from these mice are genetically complex yet consistently regress when MYC expression is repressed. This is a fair point, but I find other aspects of this work more interesting. First, a significant proportion of tumors in this model relapse despite continuous inhibition of MYC expression and no longer require the inciting oncogene. Second, there was an intrinsic difference in the propensity of individual tumors to relapse; that is, the intrinsic genetic characteristics of the primary lesions correlated with whether the tumor had a high, intermediate, or low probability of becoming independent of the requirement for MYC. Finally, specific new recurring chromosomal translocations were identified in resistant lymphomas.

To physicians who treat patients with hematologic malignancies, this sounds very much like what occurs in the clinic. These data and other recent studies (see, for example, Le Beau et al, Blood. 2002;89:2985-2991) underscore that careful molecular and cytogenetic analysis of tumors that develop in mouse cancer models may offer new ways of identifying cooperating mutations and of uncovering the molecular mechanisms that underlie disease progression and treatment resistance.

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Fishing for evolutionary clues to globin gene regulation

The pufferfish has a compact genome that is well suited for finding many protein-coding genes by fish-mammal sequence comparison. In this issue Gillemans and colleagues (page 2842) also turn to pufferfish for insights into the evolution and function of long-range regulatory elements, such as the locus control region (LCR) found upstream of mammalian beta-globin genes and the major regulatory element (MRE) found upstream of mammalian and avian alpha-globin genes. They find that matters are more complex than anticipated, but they also uncover clues that may prove productive in the long run. Pufferfish have 2 globin-gene loci, one with only alpha-globin genes (Flint et al, Hum Mol Genet. 2001; 10:371-382) and one with an active beta-globin gene plus an active and a likely inactive alpha-globin gene (the alpha/beta locus). Gillemans et al searched the latter for a long-range regulatory element similar to a mammalian LCR, but none was found by sequence searches, DNase hypersensitive site mapping, or gene transfer into transgenic mice. Thus, either pufferfish do not have a regulatory element similar to the mammalian beta-globin LCR, or it is considerably further away on the chromosome. Interestingly, detailed analysis of the genes flanking the pufferfish globin loci showed a homologue to the Rhomboid gene of Droso phila close to the globin genes in both loci, as well as upstream to the human alpha-globin genes and close to a recently discovered, widely expressed globin gene (encoding cytoglobin) on human chromosome 17. This Rhomboid-globin gene arrangement appears to be ancient, predating the gene duplications leading to the genes encoding hemoglobins. Such conservation of synteny and breaks from it likely will be helpful guides to better understanding the evolution of globin gene families and deriving clearer insight into the origins of long-range regulatory elements.

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