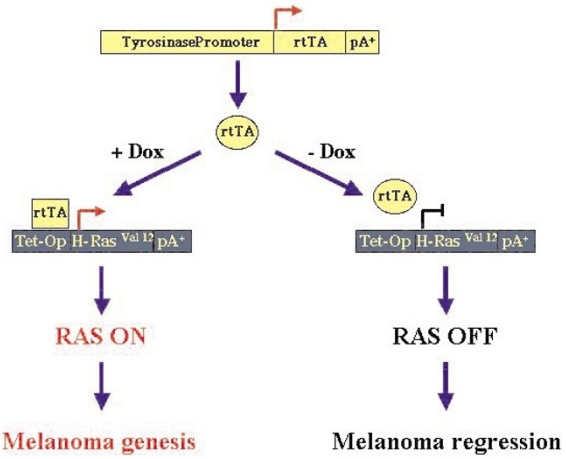

Fig. 1 Inducible H-Ras^{V12G} control of tumorigenesis. Dox, Doxycyclin; rtTA, reverse tetracycline transactivator; Tet-Op H-Ras, Tet operator controlling H-Ras expression; pA; polyadenylation signal.

more effective than strategies designed to target Ras or Myc. However, TAg inactivates p53, and it is possible that prolonged inactivation of p53 by Tag in these tumors may have caused chromosomal instability and the development of highly mutated tumor cell subsets that grow independently of TAg. In circumstances in which tumor-initiating mutations also cause slow tumor growth, there is selective pressure for additional alterations in the same pathway, which make the tumor to become less dependent on the early mutations. This theory is supported by studies with tetracycline—repressible BCR/ABL transgenic lines, which develop acute B cell leukemia (B-ALL) in permissive conditions (Table 1). Multiple rounds of tumor induction and regression can occur, indicating that 'escapes' are rare in this apparently single oncogene disease. Intriguingly, however, animals from one founder line that show a prolonged latency period all relapse, developing a BCR/ABL-independent leukemia after having undergone a complete remission upon tetracyclin administration. It is likely that additional mutations were acquired by a subset of tumor cells during the latency period.

The recent development of regulatable tumor models will be useful for unraveling the fundamental mechanisms of tumor initiation and development. They have already shown that tumor regression can be induced by targeting a single oncogene product, which alternative approaches involving transgenic mice and inhibitors of the Ras pathway[7,8] have not been able to conclusively establish. It will also be important to study the impact of genetic instability on regression in the new inducible models, given that human epithelial tumors are almost invariably aneuploid or deficient in mismatch repair. Studies using this approach to observe the combined effects of mutations in signaling molecules, such as Ras, Myc, and BCR/ABL with mutations in genes involved in controlling genomic stability such as p53 and Msh2 will be useful in answering these questions. Other important areas of investigation include identification of the secondary mutations that allow tumors to escape oncogene targeting—do these include mutations within the same oncogenic pathways? The Tet-inducible systems also offer us the opportunity to titrate the 'oncogenic dose' and measure its effect on treatment outcome. More surprises undoubtedly lie ahead, but the latest data from these models raises our expectations for drugs designed to target specific components of the molecular cancer machinery.

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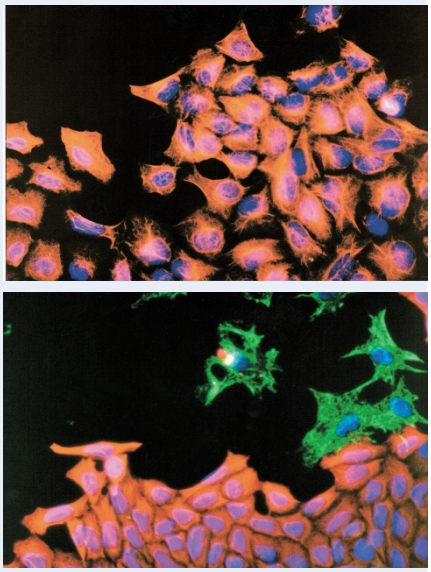
Another tetracycline - induced transformation



Tetracycline (Tet) -inducible and repressible expression systems have provided important information about the roles of various tumor-associated enzymes in cancer progression. In the 23 July issue of *Cell*, Sternlicht *et al.* used a Tet - regulated expression system of the metalloproteinase (MMP) stromelysin-1 (Str-1) to investigate its role in carcinoma development. MMPs typically promote tumor cell invasion by disrupting extracellular matrix barriers, but are also believed to affect cell signaling. The authors observed that in the presence of Tet, when Str1 expression is repressed, mammary epithelial cells grow as a sheet, expressing the protein cytokeratin (upper panel–red stain). These cells develop into normal duct and gland-like structures when injected into mice. Removal of Tet (lower panel) induces Str1 expression, causing an epithelial to mesenchymal transition characterized by downregulation of cytokeratins and upregulation of the mesenchymal cell marker vimentin (green stain). Str1 expression therefore converts normal mammary epithelial cells into highly infiltrative mesenchymal tumor cells both *in vitro* and *in vivo*. Sternlicht and colleagues think that MMPs such as Str1 promote this differentiation by activating the E-cadherin/β-catenin signaling pathway involved in both normal development and abnormal neoplastic progression.

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