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# Cross-Species Oncogenomics in Cancer Gene Identification


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**The complexity of genomic aberrations in most human tumors hampers delineation of the genes that drive the tumorigenic process. In this issue of *Cell*, Kim et al. (2006) and Zender et al. (2006) demonstrate that cognate mouse tumor models recapitulate these genetic alterations with unexpected fidelity. These results indicate that cross-species genomic analysis is a powerful strategy to identify the responsible genes and assess their oncogenic capacity in the appropriate genetic context.**


Chromosomal aberrations recurrently contribute to malignant transformation. Typically, deleted or amplified genomic regions cover large (rather than focal) areas, thus slowing down the identification of the specific genes driving tumorigenesis. In two papers published in this issue of *Cell* (Kim et al., 2006; Zender et al., 2006), integrative cross-species analysis was used to narrow down the number of candidate oncogenes within amplified DNA segments (amplicons). This approach illustrates the power of genome-wide comparison of cognate mouse and human tumors, as it identified genes found in regions commonly amplified in both species (Figure 1).

To study the genes involved in the metastasis of melanoma, Kim et al. (2006) used an inducible H-Ras nonmetastatic mouse model of melanoma, from which they derived two metastatic cell lines. Array-Comparative Genome Hybridization (CGH, which measures DNA copy-number differences between genomes) showed that these cell lines, relative to their parental counterparts, shared an amplified region of 850 kb on chromosome 13 encompassing eight genes. A region of much larger size, syntenic (preserved as "blocks" of genes across species) with the amplified region in the mouse, is frequently observed in human melanoma. This amplicon is more predominantly present in metastatic variants, suggesting that it might harbor a gene contributing to the metastatic potential of melanoma. Expression analysis in murine melanomas showed that one gene, *NEDD9*, was the most likely candidate to enhance metastasis. Subsequent analyses of NEDD9 levels in human melanoma indicated significant upregulation, with levels increasing as a function of tumor progression. Depletion of NEDD9 by RNA interference (RNAi) reduced the invasive capacity of melanoma cells and impaired experimental metastasis in vivo, as seen for both murine and human cells. Interestingly, the metastatic potential of NEDD9 could be abrogated by knocking down focal adhesion kinase (*FAK*), a gene previously implicated in invasive growth (Hess et al., 2005). NEDD9 and FAK appear to colocalize in focal contacts, which result from NEDD9 overexpression. Therefore, this study not only identified a gene

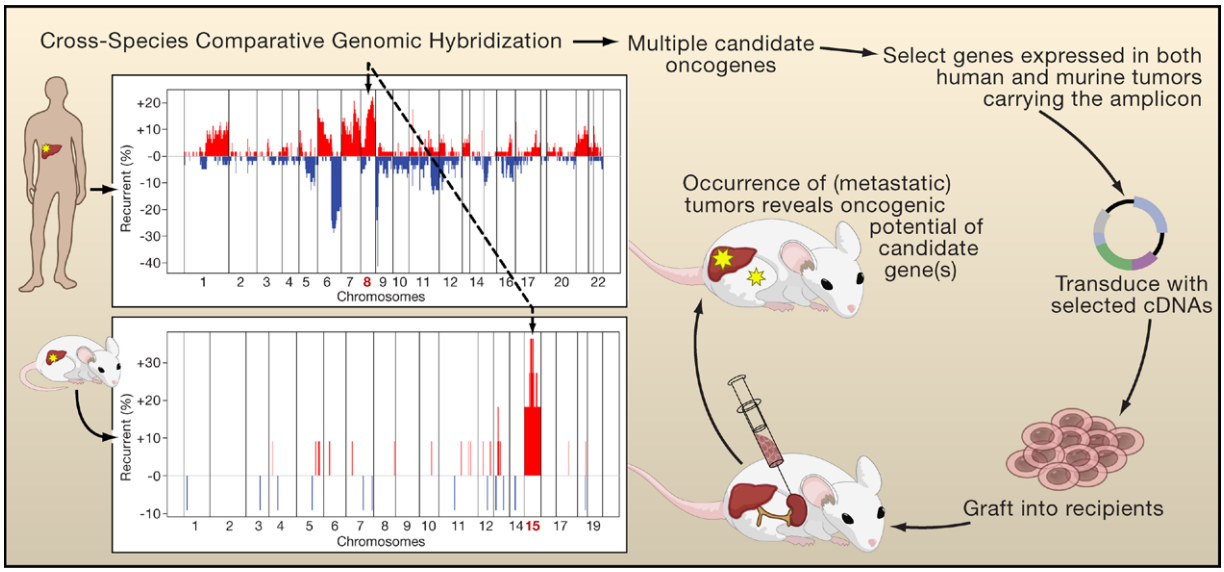


**Figure 1. Cross-Species Oncogenomics Strategy**
To identify candidate oncogenes, array CGH and expression analysis are used to compare genomic abnormalities (e.g., amplicons) between mouse and human tumors. Recurrent events serve as a filter to limit the number of candidate oncogenes. Selected genes (either alone or in combination) are then functionally assessed for tumorigenic or metastatic activity in the same murine genetic setting in which their mutation had occurred originally. Figure adapted from images kindly provided by L. Chin and S. Lowe.

enhancing metastasis in melanoma, it also points to a potential interesting target for intervention, FAK.

Another noteworthy point is that NEDD9 expression is observed not only in metastases but also in primary tumors, indicating that NEDD9 provides a selective advantage to primary tumors as well. In keeping with this, the authors observed that RNAi-mediated depletion of NEDD9 had a significant impact on cell proliferation. This multifaceted feature of certain oncogenes likely represents a frequently occurring phenomenon contributing to both tumor initiation and progression, as previously proposed by Bernards and Weinberg (2002). Indeed, overexpression of NEDD9 stimulated both proliferation and invasive capacity of *Ink4a*;*Arf*$^{-/-}$ melanocytes as well as their metastatic potential in vivo. Interestingly, this was seen only in combination with B-RAF$^{V600E}$ or H-Ras$^{V12}$, illustrating that NEDD9 acts in a context-dependent fashion. Notably, it would have been impossible to reach these conclusions so rapidly without the aid of this mouse model.

A second paper, by Zender et al. (2006), published in this issue of *Cell* describes a new mouse model for liver cancer that permits the identification of genes contributing to hepatocellular carcinomas (HCCs). The authors established hepatoblast cultures allowing in vitro genetic manipulation. As HCCs almost invariably harbor inactivating mutations in p53, the authors infected cultured hepatoblasts from p53-deficient embryos with the oncogenes c-*myc*, *Akt*, or *H-Ras*$^{V12}$. Engraftment of these cells into mice resulted in liver tumors, albeit with different pathologies. Using representational oligonucleotide microarray analysis (ROMA; Lucito et al., 2003) to scan the genome for copy-number changes at high resolution, genes that might contribute to the tumor phenotype were identified. In Akt-induced tumors, no focal genomic alterations smaller than 5 Mb were found. H-Ras-transduced hepatoblasts gave rise to tumors with, in one case, a focal amplification of c-*myc* and, in another, of *Rnf19*. Although *Rfn19* has not been linked to tumorigenesis, c-*myc* alterations are common in human HCC. ROMA of HCCs induced by overexpression of c-Myc revealed a small amplicon on mouse chromosome 9. The amplified segment is syntenic with a region on human chromosome 11q22 that is amplified in a subset of HCC and esophageal cancers. The cross-species comparison limited the number of candidate genes in the region. Most genes encoded by the amplicon, including a number of matrix metalloproteinases, could be excluded as candidates because they were not consistently overexpressed. The remainder of the genes could thus be responsible for the phenotypic effect, e.g., by acting as the "drivers" that stimulate expansion of the cells carrying this amplicon.

Two genes encoding cIAP1 (Imoto et al., 2001), an inhibitor of apoptosis, and Yap (Yagi et al., 1999), a Src-interacting protein, appeared overexpressed in all murine and human amplicon-containing tumors analyzed. Their contribution to HCC was subsequently evaluated in the versatile hepatoblast graft model using combinations of retroviral vectors encoding c-Myc, cIAP1, and Yap. cIAP1 overexpression significantly enhanced tumor growth,