S3. Approaches to Identify Low Penetrance Cancer Susceptibility Genes Using Mouse Models

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Studies of cancer predisposition have largely concentrated on the role of high penetrance susceptibility genes. Less than 10% of the total human tumor burden, however, is accounted for by mutations in these genes. More genetic variation in cancer risk is likely to be due to commoner but lower penetrance alleles. In man, such modifier genes will be difficult to find since they do not segregate as single Mendelian traits. The mouse offers a powerful system for studying polygenic traits such as cancer and has been widely used for this purpose. However, major problems need to be overcome at several levels in any strategy to find tumor modifier genes: mapping the locus at high resolution, identifying the critical gene, and finding the functional polymorphism. Standard linkage analysis methods for localizing quantitative trait loci (QTLs) detect loci within intervals of at least 10 to 30 cM, and the usual method of refining the region involves generation of congenic mice, in which small portions of a chromosome from one strain have been bred onto the background of another. This is an expensive and time-consuming process that can experience problems due to co-localization of multiple QTLs within the same interval, or because of the presence of interacting genes necessary for the phenotype. Finally, identification of the critical polymorphism is difficult because all of the genes in the immediate vicinity will exhibit sequence variants that correlate with the phenotype. We have developed a novel multi-step strategy that helps to resolve many of these problems by exploiting the genetic diversity between tumor-susceptible *Mus musculus* and both outbred and inbred strains of tumor-resistant *Mus spretus* together with the high recombination and low linkage disequilibrium found in humans. Using this strategy, we identified a polymorphic variant of the *STK6/Aurora2* gene that is associated with increased human breast cancer risk. This approach that exploits the advantages of combining mouse and human genetic strategies to identify human cancer susceptibility genes will be discussed in detail. At present, conventional approaches to identify human modifier genes mostly involve testing of known candidate genes, which means that the unknown and unexpected will be missed. This cross-species strategy may however lead to the identification of novel genes based on the mapping of loci in mouse models. A particularly important feature that is emerging from the mouse studies is the frequency and strength of epistatic interactions between modifier loci that determine phenotypic outcome. It is possible that significant associations will only be detected in humans by investigating the combinations of different alleles at these interacting loci. A key goal of the Human Genome Project is to assemble a comprehensive map of single nucleotide polymorphisms (SNPs) that can be used for association studies, but genome-wide scans for modifier genes are presently prohibitively expensive. The use of appropriate mouse models to guide the prioritizing of candidate loci and genes for testing could greatly accelerate this process, leading to significant advances in understanding the polygenic basis of cancer.

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