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NEWS AND COMMENTARIES

Cancer Genetics

Finding the right mix

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In this month's *Nature Genetics*, Stanford scientists report on the development of new experimental models of melanoma that may facilitate the identification of cooperating transforming mutations.

Cancer is the end product of the accumulation of multiple genetic lesions. Most epithelial human cancers harbor complex karyotypes that reflect cycles of genomic instability. Although much progress has been made in identifying and characterizing cancer-associated mutations, the complexity of the cancer genome often makes it difficult to connect a cancer genotype to specific malignant phenotypes.

Over the past few years, several groups have created cell and animal models of cancer with the goal of deciphering the roles of specific pathways implicated in oncogenesis. Human cell models have proven quite useful in this regard.[1] However, these experimental systems have typically assayed tumorigenicity via subcutaneous implants in immunodeficient mice. Reliance upon these protocols raises the concern that such systems fail to incorporate critical features of cancer such as the input of tissue-specific stromal cells. Moreover, since such cell-based models require some period of culturing *ex vivo*, an additional concern is that the process of culturing imposes artificial requirements for transformation.

A recent report from Chudnovsky *et al*[2] describes the development of melanocyte transformation models that not only provide insight into genes that cooperate to induce tumorigenicity but also recapitulate key features of human malignant melanoma. By using genetically engineered human melanocytes and primary human keratinocytes, these investigators generated a facsimile of the human dermis in immunodeficient mice. By introducing mutations associated with patient-derived tumor samples into this model system, they were able to create tumors that displayed both clinical and histological features of invasive melanoma. Importantly, the histopathologic features of the tumors correlated with the particular combination of genes introduced into the engineered cells.

Specifically, Chudnovsky *et al*[2] perturbed the p53 and RB pathways that govern cell-cycle control and survival, the Ras signaling pathway that regulates several pathways involved in growth regulation, and the pathway(s) regulated by the catalytic subunit of human telomerase (hTERT). The authors show that the simultaneous disruption of these pathways in melanocytes drives the formation of invasive melanoma. Since they also generated parallel cultures in which only some of these pathways were disrupted, they were able to investigate the contributions of individual cancer-associated mutations to melanoma formation. These experiments yielded several interesting observations that highlight the utility of this model system. For instance, it has long been appreciated that hTERT and telomerase mediate cellular immortality, but recent observations suggest that the hTERT protein may have additional functions in tumorigenesis.[3,4] Indeed, Chudnovsky *et al*[2] found that hTERT overexpression is required to drive invasive melanoma even though this expression of hTERT did not appear to be required for immortality. Therefore, these observations suggest that telomerase may have more complex roles in melanoma than previously appreciated.

A key element of these experiments is the use of untransformed human keratinocytes to create an environment closer to that which surrounds premalignant melanocytes *in vivo*. Although many studies have demonstrated the importance of orthotopic implantation in tumor formation,[5] this system provides a foundation with which to study melanoma mutations in the appropriate microenvironment. Similar studies in human keratinocytes[6] and prostate epithelial cells[7] reinforce the notion that reassembling the tumor environment permits the development of improved cancer models. Since recent work suggests that stromal cells contribute to tumor development,[8] such systems promise to allow one to dissect the interactions between tumor cells and stromal cells in transformation. Taken together, these types of model systems will allow us to understand how individual genes influence the behavior of specific human tumors.

This new model system represents one tool in a growing arsenal of experimental systems that will facilitate our understanding of melanoma initiation and progression. Since anatomical as well as cell biological differences between murine and human skin tissue architecture complicate direct comparison between murine and human model systems of melanoma, these orthotopic models enable the rapid generation of matched human melanocytes, while avoiding the laborious and expensive procedures required to generate a similar cohort of genetically engineered mice. Indeed, such cell-based studies should help identify specific combinations of genetic alterations around which new murine models can be developed. Such murine systems will then make it possible to analyze the effects of development and the immune system on tumorigenesis in undisturbed tissue.

The findings of Chudnovsky *et al*[2] support the notion that it may one day be possible to screen groups of mutations efficiently and rapidly to determine if they suffice to induce melanoma. Importantly, this coculture and grafting protocol does not appear to require genetic instability, facilitating the study of particular mutations without the potential confounding effects of other mutations. Although further experiments are neces-

sary to determine the widespread utility of this system in assaying the contribution of newly identified mutations to melanoma, this experimental model provides an interesting new platform that will not only help to delineate critical pathways in transformation but may also be leveraged for drug discovery and validation efforts that target these pathways

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Demography

Peopling the Americas

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A new study by Jody Hey,[1] published in *PLoS Biology*, sets new standards in the analysis of human genetic data. Using new statistical methods and a combined analysis of nine genes, Hey provides a detailed picture of the events associated with the first migration of Asians into the Americas.

Explorations into the use of DNA sequence data for human demographic inferences began in the late 1980s and early 1990s.[2,3] The research was focused on testing the out-of-Africa hypothesis and the main inferential tool was the estimation of gene trees. However, it soon became apparent that demographic inferences cannot easily be made on the basis of an estimated gene tree, mainly because the relationship between particular demographic models and gene trees is very complex. The same gene tree may arise from multiple different demographic models. A method for connecting gene trees with demographic models was needed. Coalescent theory[4] turned out to provide this link. Using coalescent theory it is possible to calculate how likely a particular gene tree is under a particular demographic model. The coalescent framework was used to estimate population growth rates, and methods for inferring migration rates and other parameters were developed.[5–8] Unfortunately, most of the models were so demographically naïve that they hardly were applicable to real human data. The fundamental problem has been that the effects of various factors, such as changes in population sizes, gene flow between populations (migration), and divergence of populations from a shared ancestral population, are intertwined, making it impossible to determine the effect of one factor without taking the other into account. The only solution to this problem is to construct complex models that take all (or as many as possible) of the relevant factors into account.

The study by Hey, Rutgers University, sets the bar for such studies. His model incorporates changes in population size, gene flow, and divergence – allowing new explorations into human genetic demography. Inferences are made in a coalescent-based statistical framework that takes into account the uncertainty in the data regarding the gene tree (no gene tree can be estimated with 100% accuracy) and can combine the information from many different loci. He applied this method to data from nine loci from East-Asians and Amerind-speaking Native American populations. The major objective was to determine the timing of the earliest migrations into the Americas from Asia, and determine the effective population sizes of past and present populations. The results suggest that the first wave of migration occurred relative recently but that the effective number of migrants was about 90.

Although much emphasis has been put on the exact number of migrants populating the Americas, it is should be noted that the estimates obtained in genetic studies are of the *effective* population size at the time of migration. The actual number of people could be substantially higher than the effective number. For example, Hey found the effective population size of the number of people in the ancestral Asian population to be approxi-