The evolution of genetically engineered mouse models of cancer

Kristopher K. Frese and David A. Tuveson

Mouse models of cancer have taught us much about how cancer develops. They have been instrumental in, and would argue essential for, verifying theories of cancer biology that were initially developed in cultured cells. However, as our understanding of the complexity of tumour biology has increased, the limitations of using mice to model human cancer have become evident. But mice still offer the promise of testing a new hypothesis under replicated in vivo conditions, and few would question that findings from in vitro studies need to be verified in vivo. So how can we improve genetically engineered mice (GEM) so that they are more relevant to the conundrums we are now trying to resolve? GEM need to evolve further to accurately reflect all the components of a human tumour if they are to have a greater role in the bench-to-bedside continuum. Humanizing GEM, alongside the insightful use of current genetic technology, should ensure that this progression is successfully achieved.

Animal culture

Although initially useful, xenograft models of human cancer do little to recapitulate the real disease and are essentially in vitro Petri dish. Xenografts show loss of the normal tumour architecture and often consist of a dominant clone that was not evident in the primary tumour. Moreover, the vascular and lymphatic systems are not well established in xenografts and there is an aberrant immune response. It is therefore not surprising that xenografts have an altered response to chemotherapeutic drugs. The time for reliance on such models to determine the response to a new therapy has passed.

Genetically engineered mice (GEM)

GEM are now many and varied. Initial GEM relied on the overexpression of a transgene (either an oncogenic or dominant-negative tumour-suppressor gene) within a specific tissue through the use of ectopic promoter and enhancer elements, such as the immunoglobulin heavy chain enhancer in p-MSL or p-FK transgenes. The capacity to regulate the function of a transgene through the use of exogenous ligands, such as dexamethasone to regulate transcription (the Tet system), or to confer ligand-regulated protein function, has enabled the temporal regulation of oncogene expression and the demonstration of ‘oncogene addiction’ in a tissue. For example, the regulation of Kras and Bcl2 by dexamethasone demonstrated a role for these oncogenes in the induction and maintenance of lung cancer and melanoma, respectively. However, such models are still under the regulation of an ectopic promoter. Advanced and breakthrough technologies heralded the era of endogenous GEM, in which mutant genes are under the control of the endogenous promoter and enhancer sequences. Such technologies also enabled the loss of tumour-suppressor genes in cancer, such as those observed in human familial syndromes, to be replicated in mice. However, most studies to date have not reproduced the human condition (for example, loss of TP53 does not induce neurofibromatosis type 2 in mice). Conditional models have shown more promise. These enable the deletion or expression of a gene within a specific tissue, under the control of endogenous promoter through the use of recombinases such as Cre, Lox, FLPeR. This can also be combined with ligand-dependent activation of Cre through the use of the floxed-dependent Cre-ERT to achieve greater temporal control.

Genetics of GEM

• Basic cancer biology
  - Biology of epithelial tissues and early stages of cancer development
  - Interactions between cancer cells and normal cells
  - Mechanisms of faulty gene control

• New technology-driven research
  - Molecular imaging
  - Genomics
  - Bioinformatics and bio-molecular computing

• Clinical research
  - Solid tumours (including breast, prostate and pancreatic)
  - Blood cancer
  - Solid tissues
  - Regenerative medicine (tissue engineering and kidney applications)

• More advanced GEM
  - Human tumours are thought to arise from a cell sustaining one initial mutation, from which more mutated cells arise. However, the oncogenic events in many GEM occur in all cells of the tissue, and the tumour cells do not evolve in the context of normal surrounding cells. The Cre-expressing viruses at low titres has enabled the acinarisation and silencing of genes in just a few cells, resulting in hyperplastic foci surrounded by normal cells. Cre-mediated technology is also being used to introduce and model the effects of genetic changes within the tumour microenvironment.

• Humanized mice
  - Human tumours (or ‘true’ xenografts) are standing in as a model of genetically engineered mouse models of cancer that important physiological processes in mice differ substantially from those in man. So, why not make GEM more human? Currently, mice are engineered to harbour human genomic loci including non-coding regulatory elements, genes involved in the immune response and genes that regulate drug metabolism and protein glycosylation. All of these modifications should enable not only allograft, xenograft and human cells.

Acknowledgements

Kristopher K. Frese and David A. Tuveson are at the University of Cambridge, Dynamic Imaging and the Cambridge Research Institute, Cancer Research UK, 15 King's Parade, Cambridge, CB2 0DZ. The perspectives expressed here are those of the authors, not of the University.