Life and death of multiple myeloma cells

Multiple myeloma (MM) is a B-cell malignancy in which plasma cells have decreased proliferative ability and an extended lifespan. Zhang and colleagues (page 1885) set out to identify the molecular processes responsible for this extended survival (or delayed apoptosis) in MM cells.

First they showed (using inhibitors of transcription and protein turnover) that survival of MM cells appeared to require the continuous expression of a protein with a high turnover rate. MM cells express a number of survival proteins (of the Bcl-2 family), but changes in levels of one of these, myeloid cell factor–1 (Mcl-1), paralleled changes in cell survival. Thus when Mcl-1 levels were low, the MM cells underwent apoptosis, while levels of Mcl-1 were high in nonapoptotic cells. This correlation by itself was not sufficient to determine whether changes in Mcl-1 levels were actually driving, or merely reflecting, cell death or survival. They then used antisense oligonucleotides or transfection with Mcl-1 cDNA to specifically decrease or increase, respectively, cellular levels of Mcl-1. These approaches confirmed the earlier conclusions: knocking out Mcl-1 levels induced apoptosis and increasing Mcl-1 levels gave the cells even greater resistance to cell death.

Zhang and colleagues show that increased expression of a single survival protein, Mcl-1, may be sufficient to confer the malignant phenotype in MM cells. Apart from providing important new insights into the molecular pathology of MM cells, this work could lead to the development of new therapeutic strategies for the treatment of MM based on the targeted disruption of Mcl-1 expression.

—Steven W. Edwards
University of Liverpool

Thalassemia gene therapy looks good at one year

In 2000, May and colleagues reported that a lentivirus containing a human β-globin gene and sequences from the locus control region (LCR) could be efficiently transferred into hematopoietic stem cells of mice with β-thalassemia minor. In recipient red cells, the human β-globin mRNA and protein were present at levels of 13% of endogenous β-globin per vector copy, and the red cell indices were significantly improved. This was an important advance for the field, demonstrating that lentivirus vectors could overcome the instability of globin retroviral vectors and that high levels of globin gene expression could be achieved.

Recent work at the Massachusetts Institute of Technology, St Jude, and the University of Washington has confirmed the soundness of the lentivirus approach. These results were only the beginning. Many researchers have found that transgene expression from viral vectors can be silenced over time. It was also not clear whether the secondary consequences of thalassemia could be corrected by the amount of human β-globin produced. In this issue May and colleagues (page 1902) have laid these concerns to rest. Irradiated thal/+ recipients received transplants of thal/+ marrow transduced with either control or globin lentivirus vectors. The recipients were observed for 40 weeks after transplantation, nearly half the life span of a mouse. Human β-globin mRNA and protein levels were consistently 16% of endogenous β-globin throughout the study period, indicating that no silencing had occurred. In addition, a careful study of extramedullary hematopoiesis in the spleen and iron accumulation in the liver demonstrated that transfer of the human β-globin gene restored normal hematopoiesis in the spleen and prevented the accumulation of iron in the liver. These are important findings that demonstrate the feasibility of gene therapy for treating hemoglobinopathies.

Clinical gene therapy of thalassemia has more challenges for May and colleagues. Can gene therapy cure the more severe forms of thalassemia? Are HIV-based lentivirus vectors safe for clinical gene therapy? Preliminary results are promising, but more studies such as this one will be needed to fully answer these questions.

—David M. Bodine
National Human Genome Research Institute
Thalassemia gene therapy looks good at one year

David M. Bodine

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