**New technologies in the myeloma gene mine**

The new gene expression profiling technologies are redefining malignancy. In a previous article published in Blood (2002;99:1745-1757), Dr. Shaughnessy’s group published gene expression profiles of malignant plasma cells and included comparisons with normal plasma cells that were arduously sorted from normal tissues. In a report here, Tarte et al (page 1113) approach the limitation of obtaining normal plasma cells by developing a method to differentiate normal peripheral blood B cells to polyclonal plasmablastic cell populations. They demonstrate with extensive genetic and phenotypic characterizations that normal polyclonal plasma cells can be obtained not only from healthy volunteers but also from the myeloma patients. This provides a novel gene profile comparison of malignant and normal plasma cells from the individual patient, thus reducing population heterogeneity that can confound normal versus malignant profiles. By including data from the Shaughnessy studies these authors demonstrate gene expression patterns of the in vitro-generated polyclonal plasmablasts are very similar to those of bone marrow-derived plasma cells. Thus, this approach provides both comparison of normal and malignant cells gene profiles and also a powerful tool to identify genes involved in plasma cell differentiation.

The approach was validated by the differential expression of genes known to be restricted in the various cell populations. From these studies the authors conclude that (1) there is no intrinsic defect of the nonmalignant B cells from MM patients to differentiate into plasma cells, (2) the model described may allow identification of gene expression alterations involved in MM pathogenesis, and (3) an in vitro differentiation model may be useful to investigate, using gene transfer, the role of deregulated genes to transform normal cells to malignant ones. The true effort comes in identifying the functional relevance of sets of genes that distinguish stages of development in normal cells versus malignant plasma cells. Of 50 myeloma-specific genes, 5 cancer/testis tumor antigen genes were noted in a subset and represent potential tumor-specific therapeutic targets. One limitation of such studies is the nagging concern that the true transformed cell progenitor in myeloma may be derived from B cells earlier in differentiation than the plasma cell, and until that controversy is resolved, the exact relevant pairs of comparisons that may identify critical myeloma-specific genes may have to be carefully considered. Moreover, there is likely a complex interplay in intracellular communication, and the challenge is to attribute functional consequences of the patterns identified. With that comes not only an understanding of the disease but additional potential therapeutic targets. The current report by Tarte et al provides another step in technical development to produce and mine the data.

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**An animal model for myelofibrosis**

Idiopathic myelofibrosis (IM) is an acquired, insidious disorder characterized by collagen deposition in the bone marrow, splenomegaly, and extramedullary hematopoiesis. Marrow fibrosis, the hallmark histologic feature, is believed to represent a reaction toward underlying clonal proliferation of hematopoietic cells. Indeed, progressive accumulation of some lineages, especially atypical megakaryocytes, has long been recognized in IM, and other syndromes of megakaryocyte hyperproliferation in man and mice are frequently associated with secondary fibrosis. Although it is often assumed that megakaryocyte products induce local collagen deposits, the molecular basis of IM is unknown and is likely to be multifactorial. Moreover, there is considerable heterogeneity in the extent and speed with which myelofibrosis develops in response to diverse forms of megakaryocyte hyperplasia.

One mouse model of megakaryocytosis results from deficiency of the transcription factor GATA1. Vannucchi and colleagues (page 1123) now extend observations first hinted at by Takahashi et al (Blood. 1998;92:434-442) that, with age, GATA1-deficient mice develop a clinical disorder that resembles IM. The phenotype is variably severe and affected mice show no evidence for the most fearsome complication of human IM, transformation to acute leukemia. This accurately reflects the fundamental difference in underlying pathophysiology between the human disease and the mouse model: the root cause of IM is clonal cell proliferation, whereas GATA1-deficient mice principally model the late sequelae, presumably, of nonclonal megakaryocyte excess. These findings highlight the complex effects of GATA1 in regulating megakaryocyte maturation, including the extracellular milieu associated with incomplete differentiation.

Identifying the factors that drive collagen deposition in IM represents an important challenge, and a genetically defined animal model could prove invaluable in focused molecular studies. But the results reported by Vannucchi et al suggest that many candidates may need to be considered before the key molecular defects are known. Regarding the question of pathogenic molecular lesions, it will also be interesting to know whether and how acquired, clonal loss of GATA1 function may contribute to a whole range of megakaryocyte hyperplastic states.

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