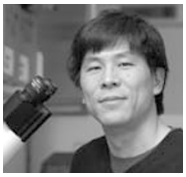
PERSPECTIVE



A model disease

Despite its rarity, multiple myeloma is an ideal testing ground for cancer biology, says **William Matsui**.

The study of multiple myeloma has provided exceptional insights into several areas of tumour biology. Findings in multiple myeloma have not only improved the understanding of human carcinogenesis, but have also pioneered its translation into the clinic.

Genomic techniques have dramatically improved our understanding of the pathogenesis of many human cancers, although the clinical impact of these findings has been limited in most of them. In myeloma, however, these techniques have helped to identify which patients are most at risk. Initial studies examining gross chromosomal alterations identified two subsets of patients based on the presence of unique chromosomal translocations or increased numbers of chromosomes. The development of fluorescence *in situ* hybridization subsequently enabled the evaluation of specific cytogenetic events in most patients and made it possible to further delineate specific risk categories. Treatments for other diseases also depend on risk assessments based on specific cytogenetic changes or gene mutations, but multiple myeloma has had the benefit of more global and detailed analyses — especially the pioneering work in array-based gene expression profiling (GEP), which has helped to evaluate specific biological and clinical risk[1].

As new anti-myeloma agents have emerged, GEP has also helped to identify which patients are most likely to respond to particular therapies. Moreover, by assembling large databases that combine GEP data and patient outcomes, the potential importance of the overexpression or mutation of specific genes can be clinically validated. In this way, technologies such as single-nucleotide polymorphism and comparative genomic hybridization arrays, as well as next-generation sequencing, can be used to characterize genetic changes at the single-nucleotide level. These studies are likely to influence clinical care in the future.

A DEEPER UNDERSTANDING

The bone-marrow microenvironment has long been recognized as a critical factor in the pathogenesis of multiple myeloma[2]. Extracellular matrix proteins, soluble growth factors and cytokines all have a profound influence on the growth, survival and drug resistance of tumour cells. Similarly, the interaction between malignant plasma cells and a wide range of other cell types, including bone-marrow stromal cells, fibroblasts, osteoblasts, osteoclasts and endothelial cells, has been shown to mediate both tumour growth and the bone disease that commonly affects myeloma patients. The impact of the extracellular environment on tumour biology is not unique to this type of cancer, but these complex interactions have been defined at a particularly detailed level in multiple myeloma.

Cancer stem cells (CSCs) are distinguished by their ability to produce tumours that recapitulate the malignancy from which they are derived and then maintain this tumorigenic potential through the process of self-renewal. Although CSCs have been identified and characterized in many solid tumours and haematological malignancies, studies in multiple myeloma have made a significant contribution to the understanding of CSC biology[3]. For example, findings from myeloma studies were among the first to demonstrate that CSCs may be more resistant than bulk tumour cells to typical anti-cancer agents. Several processes that protect non-cancer stem cells from toxic injury are responsible for this multidrug resistance, including the increased expression of proteins that allow them to pump drugs out or convert them into inactive metabolites. The implication is that CSCs persist after treatment, mediate tumour regrowth and play a central role in disease relapse.

Given the potential role of CSCs in the pathogenesis of multiple myeloma, it is not surprising that several strategies to target them have been identified. Cellular processes regulating all kinds of stem cells are a major focus of investigation. For example, the exploration of pathways involved in normal embryonic development, such as the Hedgehog signalling pathway, have paved the way for similar findings in a broad range of tumour types. Similarly, studies of multiple myeloma identified ways of targeting CSCs by cellular processes that regulate postnatal stem-cell and tissue homeostasis, involving telomerase for example, and these are now being applied to other tumour types.

NEW INFORMATION ABOUT THE BASIC BIOLOGY OF MULTIPLE MYELOMA HAS LED TO MARKED IMPROVEMENTS IN PATIENT OUTCOMES.

CLINICAL BENEFITS

Beyond basic research, multiple myeloma has also provided a test-bed for translating the CSC hypothesis into the clinical setting. Several clinical trials explicitly targeting CSCs in myeloma are underway. Because CSCs constitute a minority of tumour cells in many cancers, the typical means of evaluating drug efficacy, such as following changes in tumour size and bulk after treatment, are unlikely to detect whether the rare CSCs have been affected. These challenges have made it difficult to demonstrate that CSCs are clinically important. Biomarker strategies capable of serially quantifying myeloma CSCs have been developed, however, and results correlating the relative number of myeloma CSCs with clinical outcomes have provided evidence supporting the relevance of these cells[4].

The wealth of new information regarding the basic biology of multiple myeloma has led to marked improvements in the outcomes of patients that represent some of the greatest gains in clinical oncology over the past decade. It is also clear that novel findings in myeloma have made possible similar discoveries in many other cancers. In this way, multiple myeloma serves as a model to improve cancer treatment as a whole. ■

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