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Book Review

Cancer Surveys Volume 24: Cell Adhesion and Cancer Editors: I. Hart and N. Hogg

OVER THE past few decades most efforts in basic cancer research have centred upon the events that regulate transformation from normal to tumorigenic. Thus, recent studies on dominant acting oncogenes, tumour suppressor genes, DNA repair genes and cell cycle control genes all have added to our knowledge of how cells lose the constraints of normal, regulated growth. The changes in programmed proliferative activity, as they relate to the development of transformation, are important considerations in understanding the initial stages in oncogenesis. However, this clearly is not the whole consideration with regard to the biology of neoplastic disease. The later stages in tumour evolution, when the cancer moves from a benign to a malignant phenotype, although clearly of fundamental importance in clinical cancer, have not been subjected to the same intensive scrutiny in the laboratory. It is the capacity of malignant tumours to invade and to metastasise, by migrating from their original site to distant organs, where they will establish secondary tumours, that is responsible for the majority of therapeutic failures. Thus, an understanding of the genes, and the products of those genes which are involved in regulating the phenomenon of tumour spread clearly is of major significance. Hopefully, such knowledge will not only increase our conceptual understanding, but possibly offer strategies for the development of new therapeutic substances.

Cancer cells are not the only cells that migrate throughout the body. Our knowledge of the molecules which regulate the migration of cells in normal physiological processes may well be relevant to the mechanisms utilised by cancer cells to accomplish much the same result. It has been shown that molecules which control cell-to-cell and cell-to-substrate adhesion play important regulatory roles in normal physiological cell migration. It is not unreasonable, therefore, to expect that many of the same adhesion molecules expressed by tumour cells might also be involved in the pathological aspects of cell migration. Changes in levels of expression or activation status of these molecules, resulting in alterations in function, may well regulate the later stages of tumour development and malignant evolution. A new volume of *Cancer Surveys* entitled *Cell Adhesion and Cancer* seeks to address these questions.

It is interesting that the more that is learnt about the biochemistry and biology of these cell adhesion molecules, the less clear cut becomes the distinction between genes involved in the later stages of tumour progression and those involved in the initial stages of oncogenic development. This concordance is covered by two chapters in the forthcoming volume. Thus *DCC*, a tumour suppressor gene which has homology with the immunoglobulin family of cell adhesion molecules, is described in the article by Fearon and Pearsall. Equally, the members of the cadherin family, calcium dependent, homophilic cell-to-cell adhesion molecules, thought to play an important role in maintaining epithelial integrity, frequently have their functional activity down-regulated in cancer and also have been shown to function as tumour suppressor genes [1]. This point is considered by Birchmeier and his colleagues, who point out that the association between putative suppressor products and components of the cell adhesion machinery, as documented by the association between the beta catenin and *APC* gene product [2, 3], may well relate to initial events in transformation.

Since both cell-to-cell and cell-to-substrate adhesion molecules provide a bridge between the external environment of the cell and the internal machinery, signals generated as a consequence of binding to the external portion of the adhesion molecules may be translated into the cell interior and result in alterations in gene expression. These signalling events often occur as a consequence of tyrosine kinase phosphorylation and result in stimulation of mitogenic signals, and aspects of these pathways are discussed by Enrique Rozengurt in his article. Clearly, aberrant mitogenesis in tumour cells as a consequence of either constitutive activation of adhesion receptors or their occupancy by appropriate ligands, is likely to be an area of intense investigation in future years [4, 5].

Evidence that cell adhesion molecules function as modulatory proteins in terms of biological behaviour frequently comes from transfection studies. Introduction of cDNAs encoding for the different cell adhesion molecules into recipient normal or non-tumorigenic cells has not resulted in acquisition of the capacity for neoplastic growth. However, the introduction of the same or related cDNAs into transformed cells can have profound effects upon their malignant, as distinct from their tumorigenic capacity. CD44 or various integrin cDNAs have been introduced into tumorigenic but benign cells, and this has resulted in the acquisition of the capacity to disseminate [6, 7]. This aspect is discussed in the *Cancer Surveys* volume by Drs Gunthert and associates, Danen and associates and Kemperman and associates. Essentially, the results obtained in experimental systems are rather more clear-cut than those resulting from clinical analyses. Most clinical analyses have utilised messenger RNA analysis or monoclonal antibody staining for protein expression simply to detect the presence or absence of the requisite cell surface molecule. Little attention has been paid to the activation status or function of the identified adhesion molecule. Nonetheless, there are good correlative studies which, while documenting the co-expression or lack of expression of specific adhesion molecules with alterations in invasive or metastatic capacity, infer a causal relationship between these two parameters. This approach, which requires great caution in interpretation, has been the province of the pathologist. Drs Danen and associates and Pignatelli and Stamp examine the evidence for these associations in two chapters in the volume. Simply classifying the mere presence, absence, upregulation or downregulation of specific adhesion molecules may represent taxonomy, but it is a basic taxonomy required for the interpretation of subsequent experimental results. Larger studies, using more extensive collections of material, will help to define these categorisations, although they may tell us little about the dynamic reciprocity of such interactions. For this, the researcher may need to turn to the more easily manipulated experimental systems, and the power of this approach is highlighted by the contribution of Dr Simmons.

Unfortunately, an understanding of how tumour cells spread at the basic biochemical level may still provide little opportunity for exploitation in therapeutic terms. The fact that approximately 50% of patients with solid cancers already have occult metastases at the time of presentation suggests that interventionist strategies, designed to interfere with the dissemination pro-

cess, may be somewhat akin to "shutting the stable door after the horse has bolted". Equally, it may be argued that, since metastases can metastasise, the application of strategies based upon an increased understanding of the mechanisms of tumour spread could prevent the build-up of secondary tumour burden by interrupting the cascade of metastatic events. Similarly, if induction of a mitogenic signal results from the utilisation of adhesion molecules or occupancy of adhesion receptors, interference with such an event may have an effect not upon dissemination *per se*, but upon the capacity of newly established metastases to continue to proliferate. For these reasons it is hoped that the contributions in the volume on *Cell Adhesion and Cancer* will stimulate further investigation into these important areas of tumour biology.

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1. Mahoney PA, Weber U, Onofrechuk P, Biessmann H, Bryant PJ, Goodman CS. The *fat* tumour suppressor gene in Drosophila encodes a novel member of the cadherin gene superfamily. *Cell* 1991, **67**, 853–868.
2. Rubinfeld B, Souza B, Albert I, *et al.* Association of the ape gene product with beta catenin. *Science* 1993, **262**, 1731–1734.
3. Su IK, Vogelstein B, Kinzler KW. Association of the ape tumor suppressor protein with catenins. *Science* 1993, **262**, 1734–1737.
4. Chen QM, Kinch MS, Lin TH, Burridge K, Juliano RL. Integrin-mediated cell adhesion activates mitogen-activated protein kinases. *J Biol Chem* 1994, **269**, 26602–26605.
5. Rosales C, Juliano RL. Signal transduction by cell-adhesion receptors in leukocytes. *J Leukocyte Biol* 1995, **57**, 189–198.
6. Chan BMC, Matsuura N, Takada Y, Zetter BR, Hemler ME. *In vitro* and *in vivo* consequences of VLA-2 expression on rhabdomyosarcoma cells. *Science* 1991, **251**, 1600–1602.
7. Gunthert U, Hofmann M, Rudy W, *et al.* A new variant of glycoprotein CD_{44} confers metastatic potential to rat carcinoma cells. *Cell* 1991, **65**, 13–24.