Melanomas, metastases, and survival

Counselling patients with uveal melanomas can be both a difficult and a traumatic experience: not surprisingly, most individuals are devastated when first told that their eye harbours a tumour. Initially, their thoughts are usually focused on the prospect of losing the eye or, if an alternative to enucleation can be offered, the possibility that some, or perhaps all, visual function in that eye will be lost. With time, the patient’s attention turns, almost inevitably, to the pitiful question of long term survival. The simple truth at present is that it is not possible to predict what the future holds for any given patient who undergoes treatment for a uveal melanoma. Although it seems improbable that we shall ever be able to predict an affected individual’s prospect of cure with absolute certainty, our understanding of the factors which may influence survival is crucial if we are to compare critically the results of different treatment techniques and ultimately develop new ones.

In this issue Coleman et al present the results of a study into those factors which may influence prognosis following enucleation for a uveal melanoma. Their results suggest that tumour size, histological cell type, and the presence of secondary glaucoma are important prognostic factors in determining survival. While the latter appears a novel observation, both size and cell type are well recognised prognostic indices. It is, perhaps, not surprising that tumours containing appreciable numbers of epithelioid cells have the greatest metastatic potential. These cells resemble the primitive neural crest precursors of the uveal melanocyte and can be considered as an undifferentiated or anaplastic phenotype. Lack of cell tumour differentiation is widely recognised as a poor prognostic feature for many other tumours. Similarly, the fact that large tumours have a significantly worse prognosis than their smaller counterparts would seem logical.

Unfortunately, a proportion of patients who have received treatment for tumours with apparently favourable characteristics, such as small size or pure spindle cell composition, still develop metastases. Deiner-West et al have reported recently a 5 year mortality rate of 16% for small tumours, based on a pooled analysis of data published during the period from 1966 to 1988. This agrees closely with the results presented in this month’s issue of the journal. Clearly, size is not everything.

Our inability to predict survival with a high degree of confidence mirrors an inherent failure in our understanding of the fundamental factors which initiate and control the metastatic process in uveal melanomas. To complicate matters further some authorities have suggested that treatment could actually potentiate the development of metastases instead of preventing them. They argue that surgical manipulation of the eye during enucleation could mechanically squeeze tumour cells into the blood stream, thus enhancing dissemination. If correct, this argument could, equally, be applied to other modes of treatment which involve surgical intervention including local resection, radioactive plaques, and insertion of localising rings for external beam irradiation. Proponents of this hypothesis point to the lack of detectable metastases when the patient first presents and to their increasing appearance in the years following treatment. Although, at first, these arguments may seem persuasive, they considerably underestimate the complexity of the metastatic process. To enter the systemic circulation tumour cells must become motile, locally invade the extracellular matrix, and cross the blood vessel basement membrane and endothelium. Once in the circulation they must evade destruction by the host’s immune system. Upon reaching a distant site, the tumour cells must become attached to and then cross the vascular endothelium and its basement membrane before, again, locally invading the tissues. Finally, the cell must then be capable of unrestrained replication before a tangible deposit can develop. This progressive and complex sequence of events has been called the metastatic cascade.

Recently, several groups of investigators have attempted to identify differences in the uveal melanoma genotype and phenotype which could be responsible for the variations in metastatic potential. Cytogenetic studies recently have demonstrated non-random chromosome abnormalities in up to half the tumours examined. Aberrations of chromosomes 3 and 8 are the most common and appear, almost exclusively, to occur in tumours arising from the ciliary body and anterior choroid. These abnormalities are found extremely frequently in posterior choroidal melanomas, suggesting a fundamental genetic difference between these two tumour groups. Although, at present, we do not understand the full significance of these observations, they may explain, at least in part, the significant difference in survival rate observed between ciliary body and posterior choroidal tumours.

Cottam et al have investigated the secretion of gelatinolytic metalloproteinases by uveal melanomas. These enzymes are important in the degradation of the extracellular matrix and basement membrane, and their production has been found to correlate with tumour invasion and metastasis. They found that all 15 uveal melanoma cell lines secreted a 72 kDa gelatinolytic metalloproteinase and that
nine of them produced an additional 92 kDa species. Experimental animal studies have demonstrated that production of both species of gelatinase correlates with increased metastatic potential. Further studies will be required to assess the impact of these findings.

Both human and animal studies into other tumours would suggest that the production of metastases is a very inefficient process and that, although literally millions of cells may be shed by a tumour into the circulation daily, very few cells have the necessary prerequisites to survive and develop. It is probable that uveal melanomas are equally inefficient in producing metastases; indeed their unusual pattern of dissemination strongly supports this. Beware the patient with a glass eye and a large liver: this axion, known to many, serves to remind us of the curious propensity for uveal melanomas to metastasise to the liver. The majority of patients with metastatic uveal melanoma either present with, or subsequently develop, liver deposits. Why uveal melanoma cells are hepaticophilic is unknown. It cannot merely be a function of simple anatomical accessibility. Circulating tumour cells, once they have left the confines of the eye, must traverse the lungs before reaching the liver, and yet, despite this, pulmonary metastases are relatively uncommon. Presumably the liver provides the necessary environmental conditions for circulating tumour cells to flourish and replicate. The factors which facilitate the tumour’s ability to colonise the liver remain elusive.

At present, we have almost no insight into those crucial events which initiate the development of uveal melanomas and the factors which promote their ultimate dissemination.

The acquisition of this knowledge will provide us with more accurate indices of survival and a greater prospect of cure.

IAN RENNIE

Department of Ophthalmology and Orthoptics, University of Sheffield, Royal Hallamshire Hospital, Sheffield S10 2JF


Macrophages in the pathobiology of epiretinal membranes: multifunctional cells for a multistage process

Epiretinal membranes are proliferations at the vitreoretinal junction and frequently cause traction retinal detachment by virtue of scar-like contraction. Contractile epiretinal membranes typically arise as a complication of proliferative diabetic retinopathy (PDR) or rhegmatogenous retinal detachment. Post-detachment membranes form part of the spectrum of proliferative vitreoretinopathy (PVR). PVR membranes essentially are avascular and have a fibrocellular histological appearance, whereas PDR membranes characteristically are fibrovascular in composition. Nevertheless, both fibrovascular and fibrocellular membranes contain a variety of non-vascular cell types including retinal glia (astrocytes and Müller cells), retinal pigment epithelial cells, and inflammatory cells.

Inflammatory cells have long been recognised as a component of epiretinal membranes. However, epiretinal inflammatory cells have received relatively little attention while much research effort has concentrated on the contribution of non-inflammatory cells like retinal pigment epithelial cells. Indeed, there is evidence that differentiated retinal pigment epithelial cells contribute to some of the macrophage-like cells present in epiretinal membranes. However, PDR and PVR membranes also contain cells with the locomotory characteristics of the mononuclear phagocyte system (MPS), and MPS macrophages may be detected in PVR membranes using immunohistochemical methods.

The introduction of immunohistochemical and tissue culture techniques into the study of epiretinal membranes has marked a shift in the emphasis of research towards the functions, rather than the origins, of cells in the membranes. It is believed that macrophages are involved in both the initiation and the subsequent development of epiretinal membranes. Thus macrophage injections into the vitreous can provoke experimental epiretinal membrane formation. Moreover, epiretinal membrane formation is a multistage process which is likened to wound repair mechanisms elsewhere in the body, a process which is critically dependent upon the multiple activities of macrophages. Apart from their phagocytic functions, macrophages in repair processes are capable of producing a range of enzymes which degrade tissue components. Other macrophage products involved in wound healing include chemotactic agents (for example, the fibronectins), mitogens (such as peptides of the fibroblast growth factor family), and factors which promote extra-cellular matrix synthesis (for example, peptides of the transforming growth factor β family).

Variations in macrophage behaviour are reflected by alterations within a group of antigens expressed by the cells. Two such macrophage activity related antigens are recognised by the monoclonal antibodies 27E10 and RM3/1 respectively. The antigen detected by 27E10 is displayed by macrophages during the early, inflammatory stages of healing wounds but not during the late, fibrosing phases. By contrast, RM3/1 is expressed by macrophages during the late rather than the early phases of wound repair. Although the precise functional significance of the antigens identified by 27E10...