EDITORIAL

Determinants of radiation-induced injury

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Malignant glial tumours are complex heterogenous cellular microenvironments composed of one large aggregation of tumour cells and smaller subpopulations of invading cells distant from the major tumour mass. Local tumour recurrence after radical surgical resection is thought to be related to the failure of adjuvant radiotherapy and chemotherapy to control residual invasive cell populations. When the major tumour mass cannot be resected, treatment failure after adjuvant therapy suggests an inability of present modalities of therapy to control both invasive cells and those of the residual tumour mass. Radiotherapy given to the involved field up to a total dose of 60 Gy significantly prolongs the survival of patients having malignant glioma; however, long-term survival is rare.[1] Intensifying radiotherapy using a multitude of methodologies such as radioactive seeds, brachytherapy and radiosensitizers has not improved outcome.[2] The genetic, molecular and cellular determinants of this radiation resistance are poorly understood.

The biologic mechanism by which ionizing radiation kills tumour cells involves the generation of oxygen-derived free radicals, including the very reactive hydroxyl radical. These can cause a variety of alterations in cell proteins and lipids. However, single- and double-strand DNA breaks are crucial to subsequent reproductive tumour cell death. When a tumour cell sustains radiation-induced DNA injury there appear to be 3 potential outcomes: cell cycle arrest, cell cycle progression or apoptosis.[3,4] The path taken by any individual cell appears to be determined by a complex intracellular signalling and control system, some of whose components have recently been reviewed.[4,5] The *ATM* (ataxia-telangiectasia mutated) gene senses breaks in DNA and encodes a kinase that phosphorylates and thus activates the tumour suppressor *p53* gene, either by activating *CHK2* (a known checkpoint gene with defects in CHK2, conferring radiosensitivity) or directly. The *p53* gene, although critical to monitoring DNA damage, is not essential for cell viability. The phosphorylated p53 protein induces cell cycle arrest, providing the essential time frame for DNA repair. The *ATM* gene plays a role in activating other genes or gene products such a *BRCA-1* and NBS (Nijmegen breakage syndrome), which are important in DNA repair. It may also play an important role in the tumour cell's apoptotic response if DNA cannot be repaired — clearly a desired result. Malignant gliomas develop in patients with Li-Fraumeni syndrome, in which there is a germline *p53* mutation, and over half of the low-grade astrocytic tumours and a smaller percentage of primary glioblastomas have *p53* mutations.[2] Clearly, *p53* has an important role in preventing tumour progression after DNA injury, and malfunction of the *p53* gene product can lead to tumour initiation. Conceptually, tumours with *p53* mutations should be more susceptible to radiation therapy since their DNA repair mechanisms are defective. Unfortunately, this has not been seen clinically or in the study reported by Yee and colleagues in this issue of the journal (page 76).

Radiation therapy is associated with a multitude of cellular responses occurring in residual tumour and invasive cell subpopulations. Oxygen and substrate

availability, free radical scavenging systems, immune and inflammatory responses probably all play roles in determing radiation-induced tumour kill in these 2 populations. Yee and colleagues reported that the imbalance present in a series of immunomodulating components of the cell lines studied is not altered by irradiation or influenced by *p53* status. In 3-dimensional models using collagen type I gels, the response of invasive cells can be separated from those of the major tumour mass. Irradiating C6 astrocytoma spheroids in this model have demonstrated increased apoptosis in invading cells and decreased mitotic activity in both invading cells and those of the major tumour mass, indicating that these different subpopulations may have different responses to irradiation.[6] The decreased invasive activity seen with C6 astrocytoma cells after irradiation in the model was not seen when human malignant glioma cell lines or human tumour explants were used.[7] Elucidating the cellular responses that promote tumour cell death in human malignant gliomas continues to be a major challenge.

Future research needs to define the molecular sensing and repair mechanisms available to both tumour and normal cells after radiation-induced injury, to outline how these signals induce cell death in the diverse populations of cells present in these heterogenous tumours and to elucidate how the immune and inflammatory components of tissue reaction modulate these events.

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