Can ICAM Modulation Prevent Lung Injury From Ionizing Radiation?

Lisa A. Kachnic, Simon N. Powell

Pulmonary fibrosis can develop as a consequence of a multitude of causes, including radiation therapy and chemotherapy, all of which have common physiologic and pathologic responses in the lung. Exposure of normal lung tissue to irradiation has two well-recognized adverse effects: pneumonitis and fibrosis (1). Radiation pneumonitis occurs during the acute injury phase, typically within the first 6 months after treatment. The characteristic histologic finding in patients with radiation pneumonitis is a prominent inflammatory cell infiltrate in the alveoli and in the pulmonary interstitium. Radiation-induced lung fibrosis occurs months to years after irradiation. The pathogenesis of this latter process is less well defined, although some evidence suggests that cytokines and growth factors play a role (2–4).

The target cells of radiation injury in the lung are thought to be the type II pneumocytes, which are found in the alveoli, and the vascular endothelial cells, but inflammatory cell infiltrates also play an accessory role (5–7). Once the injury is sustained by the target cells, the recruitment of inflammatory cells in the alveolar interstitium contributes to the acute inflammatory response, the subsequent deposition of collagen in the lung, and the development of noncompliant lungs. The study reported by Hallahan et al. (8) in this issue of the Journal demonstrates the importance of inflammatory cell recruitment in lung tolerance to radiation. Intercellular adhesion molecule 1 (ICAM-1), an immunoglobulin-related molecule expressed on vascular endothelial cells, has been shown to mediate the adhesion of circulating leukocytes to the endothelium and their subsequent extravasation into the interstitial space in response to lung injury (9,10). Hallahan et al. (8) demonstrated that the lungs of mice, genetically engineered to lack expression of the ICAM-1 gene, had markedly fewer leukocyte common antigen-positive cells after irradiation than did the lungs of mice that expressed wild-type levels of ICAM-1.

Lung injury is initiated within the region exposed to irradiation and results in damage at the capillary–alveolar level, with collagen deposition occurring in the alveolar wall and alveolar spaces. Although the impact of ICAM-1 deficiency is striking in the extent to which the number of inflammatory cells are reduced, it is important to ask if this effect translates into clinically significant end points. The authors found that, when collagen deposition in the lung was assessed more than 12 months after irradiation, there was a clear difference in lung histology between the mice that lacked ICAM-1 and those that expressed it: alveolar septal wall thickening was remarkably absent in the ICAM-1-deficient mice. However, when respiratory distress at 9 or 18 months after irradiation was examined, the authors found that ICAM-1 deficiency resulted in only a small increase in the radiation tolerance of the lung. In other words, whereas the impact of ICAM-1 deficiency is overt at the level of acute and chronic inflammatory changes, the absence of an ICAM-1-mediated inflammatory response does not prevent lung injury altogether. Thus, although modulation of ICAM-1 may well help to improve radiation tolerance of the lungs, it is unlikely to completely prevent lung injury.

Radiation injury to the lungs is a function of the total dose of radiation, the dose per fraction of radiation, and the volume of the lung that is irradiated. In humans, the estimated radiation doses that result in a 1%–5% risk of lung toxicity at 5 years when one third, two thirds, or all of the lung volume is irradiated are 45 Gy, 30 Gy, and 17.5 Gy, respectively (11). In general, damage to the lung increases as the volume of lung irradiated increases. However, there is a threshold effect, such that irradiation of more than 10% of the lung is required to produce pulmonary damage. In clinical settings that use radiation in cancer therapy, lung volume often supercedes radiation dose as the limiting factor for tolerance. If human lung cancers are being treated with radiation doses of 60–70 Gy in 30–35 treatments, normal lung tissue will be exposed to levels of radiation that exceed the tolerance of that sector of lung. The effect of blocking ICAM-1 expression to increase the radiation tolerance of the lung may have little impact on the regions of normal lung that receive doses of radiation above their level of tolerance. With the increasing use of intensity-modulated radiation therapy, in which larger volumes of lung receive lower doses of radiation because the prescribed radiation dose is concentrated within the tumor volume, the impact of modulating the expression of cytokines and cell adhesion factors may become clinically significant. Carrying out this type of preclinical study in genetically engineered mice would be technically difficult but ultimately more relevant to the potential impact of biologic response modifiers on improving the tolerance of the whole lung to ionizing radiation.

During the last decade, the incorporation of chemotherapy into treatment regimens has improved both the local control of lung cancer and the overall survival of patients with inoperable lung cancer who were treated with radiation therapy alone (12). However, combined or sequential therapies can also increase the probability of acute and chronic pulmonary morbidity (13,14). The current clinical trials for lung-derived tumors frequently incorporate concurrent therapeutic approaches. The role of inflammatory cell infiltrates in the development of pneumonitis following combined modality therapy may be more important than following radiation alone and, therefore, the potential for
ICAM-1 deficiency to reduce lung injury may be greater for combined modality therapy than for radiation alone. This extension of the studies of Hallahan et al. would be a straightforward and valuable preclinical experiment.

Future studies will need to integrate the role of ICAM-1 with that of other modifiers of radiation-induced lung damage. Expression of basic fibroblast growth factor has been shown to reduce the extent of radiation-induced apoptosis in endothelial cells (15), and it would be interesting to know whether the effects of this manipulation are additive, synergistic, or inhibitory with ICAM-1 deficiency (16). Whether radiation injury to target cells in the lung produces the inflammatory response secondary to cell death or to radiation-induced changes in intercellular communication is another question worthy of attention. There is considerable potential for experiments that use knockout mice to give important insight into the mechanisms of therapy-induced lung injury. It is hoped that the report of Hallahan et al. (8) spawns such additional experimental studies.

REFERENCES


