Comment on “Tumor Response to Radiotherapy Regulated by Endothelial Cell Apoptosis” (I)

Garcia-Barros et al. (1) reported innovative experiments demonstrating that for two murine tumors, the growth rate, endothelial cell apoptosis, and radiation response, at dosages of 10 to 15 grays (Gy), were affected by acid sphingomyelinase levels in the endothelial cells of acid sphingomyelinase--deficient (asmase$^{-/-}$) and control (asmase$^{+/+}$) mice. They stated that the studies “indicate that microvascular damage regulates tumor cell response to radiation at the clinically relevant dose range,” and noted, referring to a previous study (2), that they had “recently reported that microvascular endothelial apoptosis is required for clonogenic cell dysfunction” in interpreting radiation response of jejunal crypt cells. These are powerful assertions, especially in the absence of data or discussion on tumor cell killing mediated by mechanisms other than apoptosis of endothelial cells—for example, direct radiation tumor cell killing.

In addition, Garcia-Barros et al. (1) provided no discussion of the mechanism by which endothelial cell apoptosis would cause tumor cell death. Radiation has been extensively documented as effective in killing of normal and malignant cells in vitro, with colony formation as the endpoint for survival and inactivating spheroids (3–5). These in vitro systems are free of capillaries. Further, the dose to inactivate experimental tumors has been well predicted by the measured number of tumor clonogens and radiation sensitivity (6).

Garcia-Barros et al. (1) reported that the MCA/129 tumor in asmase$^{-/-}$ mice was “completely resistant to 15 Gy” but that 15 Gy conferred 50% tumor control (TCD$_{50}$) (7) for that tumor in asmase$^{+/+}$ mice. At 20 Gy, however, the response was the same for MCA/129 in asmase$^{+/+}$ and asmase$^{-/-}$ mice. These remarkable findings were not supported by TCD$_{50}$ values, nor was there discussion of the relevance of these findings to the fact that single-dose TCD$_{50}$ values of 15 to 20 Gy for spontaneous tumor transplants in syngeneic hosts are virtually unknown, other than lymphomas or germinal tumors. Growth rates of tumors are not known to predict TCD$_{50}$ values.

TCD$_{50}$ values for each of three human and six murine tumors were the same when growing in the highly radiation sensitive severe combined immunodeficient (SCID) or the normally sensitive NCr/Sed (nu/nu) nude or C$_{3}$H/Sed mice. TCD$_{50}$ doses for the individual tumors ranged from 37 to 104 Gy (8). Further, the TCD$_{50}$ values of methylcholanthrene-induced fibrosarcomas in SCID and C$_{3}$H/Sed mice differed by factors of 2.6. In vitro radiation sensitivities of their cell lines differed similarly (9). These results indicate that the TCD$_{50}$ values were dominated by the sensitivity of the tumor cells, not of the host tissues. Garcia-Barros et al. (1) stated that “tumors may regulate the baseline apoptotic level and the radioresponsiveness of their own microvascular endothelium.” Were this proposal valid, each of these nine tumors would have had to have modified the radiation sensitivity of the endothelial cells in the SCID mice to achieve the same TCD$_{50}$ as obtains for that tumor in nude or C$_{3}$H mice. We accept that one may postulate that the radiation sensitivity of endothelial cells (as distinct from cells of other tissues) of SCID mice may not be affected by their deficiency in DNA repair. A crucial experiment to determine which target cell dominates the tumor response would be the assessment of the radiation response of tumors differing widely in TCD$_{50}$ when implanted in asmase$^{-/-}$ and asmase$^{+/+}$ mice. Such an experiment would help to clarify whether endothelial cell sensitivity is the predominant determinant of tumor response, as was stressed by Garcia-Barros et al. (1).

Herman D. Suit
Henning Willers
Department of Radiation Oncology
Massachusetts General Hospital
Harvard Medical School
Boston, MA 02114, USA

References and Notes
7. TCD$_{50}$ is the dose that, on average, achieves local control in 50% of the irradiated tumors.