Abstract

STUDIES ON BIOCHEMICAL AND CELLULAR, LET DEPENDENT EFFECTS OF IONIZING RADIATIONS IN SYNCHRONOUS MAMMALIAN CELL SYSTEMS

by

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Variations of the linear energy transfer (LET) of ionizing radiations produce profound variations of biological response, and such effects appear to be ubiquitous. We, therefore, studied LET dependent endpoints of ionizing radiation at the biochemical and cellular levels. The endpoints specifically selected for study were nucleic acid synthesis and hepatoma induction.

In the study of effects on nucleic acid synthesis, RNA transcription was of particular interest because of its possible relationship to both cell death and carcinogenesis. The uptake of RNA precursor into HeLa cells, synchronized by the vinblastine technique of Pfeiffer and Tolmach, was significantly depressed immediately following 750 rads of gamma irradiation at highly specific cell ages (G_1- S and late S). Asynchronous cells, however, exhibited no such radiosensitivity. We interpret these results as evidence that RNA synthesis is, in synchronized cells, a cell cycle dependent, radiosensitive process with low LET irradiation.

These studies were extended to the parasynchronous regenerating LAf_1 mouse liver system where there was no

significant depression of the rate of RNA synthesis immediately following X-irradiation (450 R and 950 R) during any phase of the cell cycle studied (G_o, early G_1, G_1- S, and G_2- M). However, 2.6 meV cyclotron neutron irradiation (for doses between 250 and 520 rads) caused immediate depression of the rate of RNA synthesis during G_o, G_1- S, and G_2- M ($p < 0.05$) and probable depression during early G_1 ($p < 0.10$), suggesting cell cycle <u>independence</u> of RNA synthesis with <u>high</u> LET irradiation. Thus, considering both the HeLa and regenerating liver cell results, transcription may be a radiosensitive process which is cell cycle <u>dependent</u> for <u>low</u> LET radiations and cell cycle <u>independent</u> for <u>high</u> LET radiations.

Because of known latent damage to chromosomes by fission neutron irradiation and because of possible relevance to the carcinogenic endpoint, it was of interest to consider the possibility of latent, LET dependent effects of ionizing radiation on nucleic acid synthesis in the LAf_1 mouse liver system. We noted that G_o liver cells exposed to X-rays (550 R or 300 R) demonstrated no significant inhibition in the rate of RNA or DNA synthesis when these cells were stimulated to proliferate by partial hepatectomy, at 1 day or 9 months following the irradiation. However, the data does suggest that prior irradiation of G_o liver cells with either fission neutrons (300 rads) or 2.6 meV cyclotron neutrons (150 and 370 rads) caused a decrease in the rate of RNA synthesis (at 5.5 hours and 32 hours after partial

hepatectomy) when the neutron irradiation was given 1 and 9 months prior to surgery. A 38% decrease in the rate of DNA synthesis, stimulated by partial hepatectomy at 9 months after the neutron irradiation (175 rads) of G_0 liver cells, was also suggested. In addition the data showed a delayed onset of DNA synthesis following partial hepatectomy for 1 year old control mice (compared to 3 month old control mice). We interpret these data as suggestive of latent biochemical defects in neutron irradiated G_0 cells, which might interfere with the G_0 cells' ability to respond to a proliferative stimulus. (Further speculations regarding possible implications of these biochemical effects to radiation induced cell death and carcinogenesis, and to high LET radiotherapy, are discussed.)

As a pertinent cellular endpoint and as a followup on the work of Cole and Nowell, we also studied the cell cycle dependence of high and low LET radiations on hepatoma induction in male LAf_1 mice. Although partial hepatectomy (either 24, 36.5, or 48 hours before, or 2 to 3 months after 200 rads of fission neutron or gamma irradiation) significantly enhanced the carcinogenic endpoint, no significant cell cycle dependence for either type of radiation was noted. The data also established that fission neutron irradiation is 2 to 3 fold more effective for hepatoma induction than γ-irradiation.

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