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ON RADIATION DAMAGE TO NORMAL TISSUES AND ITS TREATMENT

I. Growth factors

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Abstract

The first part of the review outlines the classical interpretation of radiation damage to normal organs based on dose-response relationships for clonogenic cell survival and tissue kinetics. Proliferative organization of critical cell lineages (three-compartmental or H-type and one-compartmental or F-type) is considered as an additional determinant in the development of overt radiation injury. This leads to testable predictions concerned with divergent outcomes of stimulation of cell proliferation after radiation exposure using polypeptide growth factors. The prediction of favourable effects of such stimulation in H-type lineages is borne out by recent experiments on treatment with cytokines of radiation-induced haemopoietic insufficiency. The second prediction of deleterious effects of proliferative stimulation in recently, heavily irradiated F-type cell lineages remains to be verified or refuted.

Key words: Ionizing radiation, radiation damage, normal tissues, proliferative organization, growth factors, colony-stimulating factors, interleukins, interferons, tumour necrosis factor.

Over the last three decades, the radiobiology of normal tissues has been dominated by the composite hypothesis stating that the severity and timing of non-carcinogenic somatic effects of ionizing radiation are determined respectively by the degree of sterilization of clonogenic cells and the cell turnover rate of their differentiated progeny; that cells react to radiation autonomously and, consequently, any lesion or malfunction is induced directly and caused by damage to a single ('target') cell lineage which reflects a reduction of the functional cell number. The hypothesis implies that radiation injuries are essentially not amenable to posttreatment other than replacement of the depleted cells or their products. It is my intention to argue that this hypothesis is insufficient to account for the observed phenomena; to specify additional determinants and factors involved in radiation responses; and to consider some rational and practical approaches to prevention and management of overt radiation damage to normal tissues.

The commonly accepted views on the cellular events underlying radiation reactions have been worked out in studies of early responding cell lineages such as the bone marrow, epidermis and the epithelial lining of the alimentary tract (1, 2). These cell lines each consist of three compartments: that of non-functional stem cells with unlimited proliferative potential; the amplification/differentiation compartment; and the fully functional postmitotic cell compartment. The irradiated cells are assumed to die and be lost only during, or after, mitotic division, in addition to normal wear-and-tear which is not influenced by radiation. Such three-compartmental or hierarchical (H-type) cell lineages, therefore, are said to consist of a minority of radiation sensitive proliferating cells and a majority of mature cells which are quintessentially radioresistant (the latter are exemplified by circulating polymorphs or enterocytes covering the intestinal villi). Depletion of functional cells after irradiation is represented as due exclusively to the interference with their otherwise continuous replacement; as long as there is no new mature cell production, the number of functional cells will continue to decrease linearly with time at a rate determined by their normal life-span. Consequently, a given level of cell depletion will be reached after a time characteristic of the lineage and largely independent of radiation dose.

Growth factors in the treatment of radiation damage

Postirradiation stimulation of cell proliferation in the bone marrow—a representative of H-type cell lineages—was predicted by Lajtha (3) to be advantageous since it would result in quickening of the expression of radiation

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Table 1

*Cytokine treatment of radiation-induced haemopoietic failure**

Cytokine	Species	Effect	Reference
rhG-CSF	Mouse	Faster replenishment of myeloid progenitors (spleen, bone marrow) and circulating granulocytes	4
rhG-CSF	Dog	Reversion of otherwise lethal myelosuppression	5
rhG-CSF	Mouse	Accelerated repopulation of bone marrow stem and progenitor cells, circulating leukocytes and platelets	6
rhG-CSF	Mouse	No change in animal survival rate**	7
rmGM-CSF	Mouse	Prolonged median animal survival time and decreased mortality after TBI	8
rmGM-CSF	Mouse	2–3-fold extension of median animal survival time after lethal TBI	9
rmGM-CSF	Mouse	No change in animal survival rate**	7
rmGM-CSF	Mouse	Accelerated repopulation of circulating leukocytes and platelets	6
rhGM-CSF	Monkey	Earlier repopulation of bone marrow granulocyte-macrophage progenitor cells and circulating granulocytes and platelets	10
rhGM-CSF	Man	Rapid rise in circulating granulocyte number	11
rmIL-1	Mouse	No change in animal survival rate**	12
rhIL-1α	Mouse	Increase in animal survival rate**	7
rhIL-1α	Mouse	No change in animal survival rate***	13
rhIL-1α	Mouse	Prolonged median animal survival time and decreased mortality after TBI	8
rhIL-1α or β	Mouse	No change in animal survival rate or median survival time**	14
rhIL-1β	Mouse	Earlier increase in number of bone marrow myeloid/macrophage precursors and circulating neutrophils; delayed replenishment of T and B lymphocytes	15
rmIL-3	Mouse	Increase in erythroid and myeloid progenitor cell number	16
rmIFNγ	Mouse	Increase in animal survival rate**	7
rhTNF	Mouse	Increase in animal survival rate and median survival time after TBI****	17
rhTNFα	Mouse	Increase in animal survial rate**	7

Abbreviations: CSF = colony-stimulating factor; G = granulocyte; GM = granulocyte-macrophage; IFN = interferon; IL = interleukin; rh = recombinant human; rm = recombinant murine; TBI = total body irradiation; TNF = tumour necrosis factor.

** A single i.p. cytokine injection within 3 h after TBI, *** a single i.m. injection 1, 4 or 13 h after TBI or **** a single i.v. injection 24 h after TBI, as opposed to multiple doses or prolonged infusion applied in the remaining studies.

damage limited to the immature cells capable of mitotic divisions and lead to more rapid replenishment of stem cells and earlier resumption of input into the functional cell compartment. Recent animal experiments using haemopoietic growth factors and the clinical experience from treatment of accidental radiation exposure in Brazil are supportive of this far-sighted prediction (Table 1). Cytokine treatment is undoubtedly effective in assisting haemopoietic recovery from radiation damage, and particularly so when commenced soon after exposure and given repeatedly or continuously for a week or two. However, the cytokines listed in Table 1 are not limited in their action to the proliferative stimulation of immature, mostly progenitor, haemopoietic cells; they also promote precursor cell differentiation and functional activation of mature cells (18, 19). Nevertheless, the treatment also proves to be advantageous when judged by the more stringent and relevant criterion of replenishment of stem and progenitor cells, although it may temporarily lead to their abnormal bodily distribution (extramedullary haemopoiesis).

In all the work summarized in Table 1, the polypeptide regulatory factors were administered after irradiation. In addition to their therapeutic action, several cytokines changed the intrinsic radioresponsiveness of lympho- and haemopoietic progenitor cells in vitro (20–26) and, when given before radiation exposure, were shown to be radioprotective in vivo (12–14, 17, 27–33). The last two properties are relevant to the possible future application of growth factors prior to, and during radiotherapy. Administration of cytokines to patients after bone marrow transplantation has been reviewed recently (34–39).

Can the above scheme of radiation responses be applied to all normal self-renewing cell lineages? I thought it could not (40). Firstly, it is by no means certain that all self-renewing tissues have a three-compartmental or H-type proliferative structure. Although the mitotic indices are ordinarily very low, we nevertheless do see mature dividing cells, e.g. in the liver, kidney and endothelium; clearly, these functional cells are not irreversibly postmitotic and, consequently, are radiosensitive in contrast to the mature cells in the H-type lineages. Moreover, in many slowly turning over tissues there is no obvious morphological differentiation gradient which is so characteristic of, say, the bone marrow and which naturally leads one to postulate the existence of a discrete stem cell compartment.

The second reason for doubting the applicability of the

H-type scheme to all radiation responses is simply that it does not always seem to work well. The lag period for many late reactions to irradiation is strikingly dose-dependent, as exemplified by the lung: within the range of low lethal doses given to the mouse thorax, a small dose increment leads to a marked shortening of latency, with a 3–5-fold difference between the extreme values for the duration of the lag period (Ref. 41, Fig. 4). The thyroid gland provides another impressive example for a dose-dependence of latency: in the treatment of thyroid cancer, a high dose of radioiodine leads to ablation of the gland within weeks of its administration whereas hypothyroidism following beam radiotherapy in the neck region takes up to many years to develop.

These two reasons led me to consider radiation responses of a hypothetical one-compartmental or flexible (F-type) proliferative organization in which all cells are equally capable of divisions and cell line specific functions. With the additional stipulation that the number of cells in the lineage is under strict homeostatic control such that cell depletion is met with commensurable increase in cell proliferation, I arrived at a scheme for radiation response which differs from that characteristic of an H-type cell lineage (40). The rate of expression of radiation damage to an F-type cell line, when assessed in terms of the number of its constituent cells, is both radiation dose- and time-dependent. The higher the dose, the more rapid average cell depletion and for a given high dose, the rate of cell loss initially accelerates with time elapsed from exposure (the 'avalanche'). The first characteristic feature of an F-type cell lineage provides a possible explanation for a major dose-dependence of the lag period seemingly typical of late radiation responses. The predicted time-dependent increase in the rate of cell depletion may perhaps be illustrated with weight changes of the irradiated kidney in mice (Ref. 42, Fig. 1).

Radiation responses of both H- and F-type cell lineages have been subsequently mathematically modelled (43) and the models refined (44, 45). The most important practical predictions emerging from this work are that:

1. stimulation of cell proliferation is advantageous for H-type lineages, in accordance with the reasoning of Lajtha (3) addressed to the specific case of the bone marrow and the recently acquired experience (Table 1);
2. stimulation of cell proliferation is detrimental for F-type cell lineages which meet the characteristics specified above.

Provided that these predictions, and especially the second one, will prove to be correct, administration of specific proliferation-inducing factors in management of radiation injuries will call for knowledge of the proliferative organization of the targeted cell lineages, because stimulation of cell divisions in recently, heavily irradiated F-type-like tissues would be strongly contraindicated; it would drive the avalanche and thus lead to earlier and more severe lesions.

Table 2

Polypeptide growth (mitogenic) factors with defined amino acid sequence

Growth factor	Reference
Erythropoietin	46–49
Haemopoietic colony stimulating factors	19, 46–50
Interleukins	19, 46, 47, 51–58
Tumour necrosis factors	19, 46, 47, 59
Epidermal growth factor	46, 47, 60
Transforming growth factors	19, 46, 47
Amphiregulin	61
Fibroblast (heparin-binding) growth factors	46, 47, 62
Keratinocyte growth factor	63
Platelet-derived growth factors	46, 47, 64
Platelet α-granule proteins/melanoma growth stimulatory activity family	65
Platelet-derived endothelial cell growth factor	66
Folliculo stellate-derived growth factor/ vasculotropin/vascular endothelial growth factor	67–69
Vascular permeability factor	70
Insulin-like growth factors	46
Neuropeptides (bombesin, vasopressin, bradykinin, neurokinin)	46, 71
Endothelin	72–77
Hepatocyte growth factor (hepatopoietin A)	78–80

The experiments on correction with cytokines of haemopoiesis affected by irradiation (Table 1) can and should now be extended to other organs and growth factors since the latter are available in large quantities as recombinant products. Their list (Table 2) is lengthening rapidly, and although the effectiveness of cytokines in radioprotection and in treatment of already induced radiation damage has recently attracted greater attention, it would be equally instructive to find out more about how radiation affects the endogenous factor production both in vitro (21, 81–86 and other studies reviewed in Ref. 87) and in vivo or ex vivo (81, 88–100). The work in the last area demonstrated a general tendency for an increased release of cytokines after irradiation but largely relied on bioassays rather than the presently available, more rigorous methods of quantification of the active principles. It would be desirable if, in the therapeutic application of the growth factors, account was taken of their endogenous levels, as well as untoward effects of administration (19, 38, 101–114). Here, the earlier comment on cytokines has to be repeated and extended to the remaining growth factors: their biological actions are not restricted to promotion of cell multiplication and, in addition, the factors tend to function interdependently and form networks.

The second part of this review, which is to be published separately, will deal with the rationale and results of anti-inflammatory drug treatment of radiation damage to normal tissues summarized in (115).

After submission of the manuscript, the following observations related to its topic have been published:

Daily subcutaneous injections of rhG-CSF given to whole body irradiated mice from day 1 to 18 after exposure accelerated recovery of nucleated bone marrow cell and circulating leukocyte numbers (Fushiki M et al., Int J Radiat Oncol 1990; 18: 353–7). In another study, repeated daily subcutaneous injections of rhG-CSF quickened the regeneration of haemopoietic stem cells and circulating leukocytes, erythrocytes and platelets when given to mice after whole-body irradiation; the treatment also increased the animal survival rate (Patchen ML et al., Int J Cell Cloning 1990; 8: 107–22). In vivo protection of haemopoiesis in mice was achieved by administration of rhG-CSF (Uckun FM et al., Blood 1990; 75: 638–45) and rh or rmTNFalpha (Slørdal L et al., Eur J Haematol 1989; 43: 428–34) prior to whole-body irradiation. Pretreatment with rhIL-1 reduced leukopenia which followed radioimmunotherapy of hamsters bearing human tumour xenografts (Blumenthal RD et al., Cancer Res 1990; 50 (suppl): 1003–7). Whole-body irradiation of mice was shown to release a systematic humoral factor which increased the percentage of bone marrow stem cells engaged in DNA synthesis (Grande T et al., Radiat Res 1990; 122: 53–7). Irradiation of the rat liver led to an elevated content of transforming growth factor-beta1 in centrilobular hepatocytes at 9 months after exposure (Anscher MS et al., Radiat Res 1990; 122, 77–85). Various side-effects of GM-CSF (Lieschke GJ et al., Cancer Res 1990; 50: 606–14) and IL-2 (Thijs LG et al., J Immunol 1990; 144: 2419–24; Huang CM et al., Clin Chem 1990; 36: 431–4; Zukiwski A et al., Cancer 1990; 65: 1521–4) were registered in cancer patients.

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