

*review*

## Radiotherapy- and chemotherapy-induced normal tissue damage: the role of cytokines and adhesion molecules

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**Background.** Ionising radiation and cytostatic agents used in cancer therapy exert damaging effects on normal tissues and induce a complex response at the cellular and molecular levels. Cytokines and adhesion molecules are involved in this response.

**Methods.** Published data on the given topic have been reviewed.

**Results and conclusions.** Various cytokines and adhesion molecules, including tumor necrosis factor  $\alpha$ , interleukins-1,-2,-4, and -6, interferon  $\gamma$ , granulocyte macrophage- and macrophage- colony stimulating factors, transforming growth factor  $\beta$ , platelet-derived growth factor, insulin-like growth factor I, fibroblast and epidermal growth factors, platelet-activating factor, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E- and P-selectins are involved in the response of normal tissues to ionizing radiation- and chemotherapy-induced normal tissues damage and are co-responsible for some side effects of these treatment modalities, including fever, anorexia and fatigue, suppression of hematopoiesis, both acute and late local tissue response.

**Key words:** cytokines – radiation effects – drug effects; antineoplastic agents – adverse effects; neoplasms – drug therapy – radiotherapy; cell adhesion molecules – radiation effects – drug effects

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## Introduction

Injury of human tissues and generally of mammalian organism ones, activates a non-specific, but highly complex immune response at the intracellular and intercellular levels, with the aim to protect the tissues and the whole organism against exogenous damage and to regenerate the damaged tissues. Cytokines and adhesion molecules are released during this response and mediate intercellular interactions among effectors of immune and other systems.<sup>1-3</sup>

Cytokines are soluble polypeptides regulating and determining the character of immune response.<sup>1,2</sup> The main source of cytokines are macrophages, but neutrophils, lymphocytes, platelets, endothelial cells, fibroblasts, and microglia, acting as the macrophage of the central nervous system (CNS), are able to release cytokines as well.<sup>3-5</sup> Cytokines are components of a large, complex signalling network. The great variety of cell types that are able to release cytokines and the great diversity of biological effects of each cytokine is confusing. The ability of individual cytokines to induce or inhibit the synthesis of other cytokines and often of its own further complicates the specification of biological functions of individual cytokines.<sup>1, 2, 6</sup>

Adhesion molecules mediate the adherence of leukocytes to the molecules on other cells or to extracellular matrix ligands and are thus involved in leukocyte activation, circulation and localization to inflammatory sites.<sup>7</sup>

Both radiotherapy and chemotherapy exert damaging effects on normal tissues in cancer patients and, consequently, induce an immune response in these tissues. The role of cytokines in this response and the possibilities to modulate it in order to lower the risk of side effects of these treatment modalities are reviewed in this article.

## Ionizing radiation- and chemotherapy-induced cytokines and adhesion molecules

The production of cytokines may result from either DNA damage in cells leading to inhibition in cell cycle progression and resulting in cell death<sup>8,9</sup> or from biochemical changes in cellular environment and metabolism induced by the interaction of ionizing radiation (or chemotherapy) with the target cell (Figure 1).<sup>3</sup>

The cytokines and adhesion molecules that have been observed to be produced in response to ionizing radiation at the mRNA or protein levels in various human or other mammalian cells or tissues both *in vitro* and *in vivo* are summarized in Table 1. The mediators have been shown to respond to irradiation in a dose-dependent manner.<sup>22, 25, 31, 40, 44, 51, 52</sup> The threshold dose of irradiation ranges from 0.5 to 2 Gy for different proteins, except murine brain cells where the threshold dose of 7 Gy has been found.<sup>21</sup> Their production is also time-dependent, peaking usually at 4-24 hours after irradiation with subsequent decrease to normal levels within 24 hours to a few days.<sup>21</sup> Increased intercellular adhesion molecule-1 (ICAM-1) expression persists for at least several days;<sup>46, 47, 51</sup> expression of transforming growth factor- $\beta$  (TGF- $\beta$ ) is often delayed to weeks or months after irradiation and persists for months;<sup>38, 40</sup> in the murine lung and small intestine, increased levels of interleukin-1 (IL-1), IL-4, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and platelet derived growth factor (PDGF) also persist for weeks and months after irradiation;<sup>18, 29, 34</sup> reevaluation of TNF- $\alpha$  at 2-3 months and its continued overexpression more than half a year after irradiation has been observed in brain cells.<sup>21</sup>

Although the immune response to chemotherapeutic drugs has not been studied as extensively as that to irradiation, it is highly probable that the administration of such toxic and aggressive agents as anticancer drugs induces the protective acute phase response in the human organism. Increased producti-

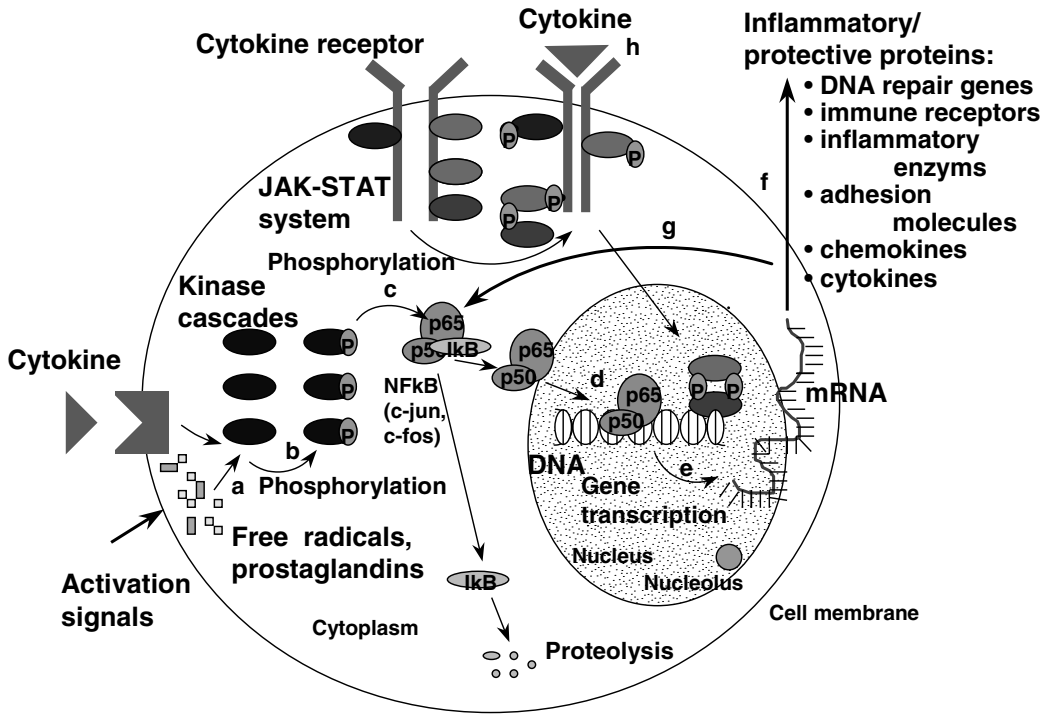


Figure 1. The mechanism of the acute phase response to irradiation at the cellular level. The interaction of ionizing radiation with the target cell induces biochemical changes in the cellular environment and metabolism, generation of free oxygen radicals and arachidonic acid derivatives (a). These changes activate kinase cascades (b) in macrophages and other responsive cells, leading to the activation of transcription factors, such as nuclear factor- $\kappa$ B (NF- $\kappa$ B), c-jun, c-fos (c). Active transcription factors bind to specific recognition elements of DNA in the nucleus and upregulate transcription of genes coding proteins involved in the immune and inflammatory responses (d), leading to an increased formation of messenger RNA (mRNA) and protein (e, f). The proteins released as the end result of this response include cytokines, chemokines, inflammatory enzymes, adhesion molecules, immune receptors and deoxyribonucleic acid repair genes.<sup>7, 9, 10</sup> Some of the cytokines are able to reactivate this cascade through the reactivation of particular transcription factors thus amplifying the response (g). The released cytokines also activate similar response in other cells through binding to the cytokine receptors (h).<sup>3, 7, 9, 11-15</sup> Other mediators of inflammation such as serotonin, histamine, bradykinine, and nitric oxide, and other acute phase proteins are also released. All of this leads to clinical inflammatory manifestations, both at the local level with vasodilation, erythema, edema and pain, and at the systemic level with various behavioral, biochemical and nutritional changes. A part of this response is the release of mediators that attenuate it and cause it to resolve.<sup>3, 6, 11</sup>

on of inflammatory cytokines induced by various anticancer agents has been demonstrated both *in vitro* and *in vivo* (Table 1). Chemotherapy-induced immune system activation *in vivo* is known especially from allogeneic bone marrow transplantation (BMT); conditioning regimens including total body irradiation and high-dose chemotherapy can contribute to the activation of host

immune cells with inflammatory cytokine release and upregulation of adhesion molecules.<sup>69, 70</sup>

It is highly probable that a wide range of other known cytokines, chemokines, adhesion molecules and other mediators of inflammation not studied in this model so far are released in response to ionizing irradiation and chemotherapy.

**Table 1.** Cytokine and adhesion molecule expression in irradiated tissues

Mediator	Irradiated tissue or cell type – animal model	Irradiated human tissue or cells	Induced by CT in vitro	Induced by CT in vivo
TNF-alpha	m. macrophages, lung cells, in vitro (16-19)	PB MNCs, in vitro (23-25)	paclitaxol, CTX, doxorubicine (MNCs) (55-57)	bleomycine (lung) (58)
	m. lung, BM, spleen, brain, in vivo (17-21)	BAL cells, in vivo (25)		CTX (+TBI), CTX+busulfan (serum, BMT CR) (59)
	m. BMT model, serum (22)	serum, BMT pts. (26)		
IL-1 alpha or beta	m. spleen cells, in vitro (27)	lung macrophages, in vitro (31)	paclitaxol (MNCs) (55, 56)	CTX (+TBI, BMT CR; serum) (60)
	m. lung, BM, spleen, small gut, brain, in vivo (18, 20, 21, 27-30)	serum after brain irradiation, in vivo (32)		
IL-2			doxorubicine (MNCs) (61, 62)	
IL-2r		PB lymphocytes, in vitro (33)		
IL-4	m. lung, in vivo (34)			
IL-6	m. BM, spleen, in vivo (20)	macrophages, epithelial cells, lung	MTX, ARA-C (MNCs) (63)	
	m. BMT model, serum (10)	fibroblasts, in vitro (35-37)		
IFNgamma				CTX (serum, BMT CR) (65, 66)
TGF-beta	m. lung, small gut, liver, in vivo (17, 29, 38-40)	PB MNCs, in vitro (23)	5-FU (fibroblasts, ECs) (64)	bleomycine, CTX (lung) (67,68)
	pig skin, in vivo (41)	colon, small gut, in vivo (42, 43)		CTX (+TBI, BMT CR; serum) (60)
PDGF	m. small gut, in vivo (29)	MNCs, BAL cells, in vitro (25)		
IGF-I		MNCs, in vitro (25)		
FGF	bovine ECs, in vitro (44)			
EGF		serum after brain irradiation, in vivo (32)		
PAF		saliva, in vivo (45)		
ICAM-1	m. lung, brain, in vivo (46-48)	ECs, in vitro, in vivo (46, 49-51) skin, in vitro (49, 52)		
VCAM-1		skin, ECs, in vitro (52)		
E-selectin	m. lung, in vivo (47)	ECs, skin, in vitro (51-54)		
P-selectin	m. lung, in vivo (47)			

Abbreviations: CT, chemotherapy; TNF, tumor necrosis factor; m., murine; BM, bone marrow; BMT, bone marrow transplantation; PB, peripheral blood; MNCs, mononuclear cells; BAL, bronchoalveolar lavage; pts., patients; CTX, cyclophosphamide; TBI, total body irradiation; BMT CR, bone marrow transplantation conditioning regimen; IL, interleukin; MTX, methotrexate; ARA-C, cytosin-arabinoside; IFN, interferon; GM-CSF, granulocyte macrophage-colony stimulating factor; M-CSF, macrophage-colony stimulating factor; TGF, transforming growth factor; 5-FU, 5-fluorouracil; ECs, endothelial cells; PDGF, platelet-derived growth factor; BAL, bronchoalveolar lavage; IGF-I, insulin-like growth factor-I; FGF, fibroblast growth factor; EGF, epidermal growth factor; PAF, platelet-activating factor; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

### Role of cytokines in pathogenesis of radiotherapy- and chemotherapy-induced side effects

A simplified list of immune effects of cytokines and adhesion molecules is involved in Table 2.

A variety of changes in normal tissues are induced by ionizing radiation, depending on the total dose, fractionation schedule, and volume treated.<sup>9</sup> Most normal tissue effects can be attributed to cell killing (cytokines mediate repair processes here); some cannot, though. For instance, the nausea and vomiting that can occur within hours after irradiation of the upper abdomen; the acute edema or erythema that results from radiation-induced acute inflammation and associated vascular leakage; the fatigue in patients receiving irradiation to a large volume, especially within the abdomen; the somnolence and headache after cranial irradiation. These are most likely mediated by radiation-induced inflammatory cytokines.<sup>79</sup> Similar symptoms can be observed after chemotherapy. Nausea, vomiting and fever occurring immediately after chemotherapy and the associated anorexia and fatigue are likely to be also mediated by inflammatory cytokines, such as TNF- $\alpha$ , IL-1, and IL-6. Similar symptoms are associated with infectious diseases; immune response is nonspecific.<sup>3</sup>

The hematotoxicity of chemotherapy and radiotherapy has been generally attributed to the direct damage of rapidly dividing hematopoietic progenitor cells.<sup>79, 80</sup> However, several apparently physiological inhibitors of hematopoiesis have been identified that directly or indirectly suppress the proliferative response of progenitor cells to stimulating cytokines; these include TGF- $\beta$ , macrophage inhibitory protein-1 $\alpha$  (MIP-1 $\alpha$ ), TNF- $\alpha$ , and interferon- $\gamma$  (IFN- $\gamma$ ).<sup>81-84</sup> Irradiation can induce IFN- $\gamma$ , TGF- $\beta$  and TNF- $\alpha$  release, and these and other cytokines might be responsible for hematopoiesis suppression after local irradiation not involving large volumes of bone marrow.<sup>66</sup>

Cell-mediated immune response plays a key role in the pathogenesis of the so-called "anemia of chronic disease".<sup>85</sup> This response may also be involved in the pathogenesis of chemotherapy- and radiotherapy-induced anemia. TNF- $\alpha$  and IL-1 reduce proliferation of erythroid progenitor cells by exerting either a direct inhibitory effect or an indirect effect via the action of IFN- $\alpha$  or IFN- $\beta$ .<sup>86</sup> TNF- $\alpha$ , IL-1 and IL-6 are able to induce hypoferrremia by increasing iron uptake into monocytes/macrophages and synthesis of ferritin, thus contributing to efficient storage of the acquired iron.<sup>87, 88</sup> IFN- $\gamma$  and IL-2 enhance strongly the expression of the transferrin receptor, the essential protein for iron uptake.<sup>89, 90</sup> Iron deprivation enhances the activity of cytokines such as IFN- $\alpha$  or TNF- $\alpha$  and cytotoxic effects of macrophages in order to produce a protective response as efficient as possible. However, hypoferrremia reduces hem synthesis in erythroid progenitor cells.<sup>85</sup>

Proinflammatory cytokines are released immediately after CNS irradiation. The basis of demyelination is the interplay of cytokines between endothelial cells, oligodendrocytes, astrocytes and microglia.<sup>21</sup> The disruption of the endothelium leads to the infiltration of lymphocytes into the tissue and initiation of immunologic mechanisms involved in the pathogenesis of encephalopathy and myelopathy.<sup>21, 28, 91, 92</sup>

Apoptosis, i.e. programmed cell death, is a common mechanism of cell death in response to ionizing radiation and anticancer drug exposure.<sup>93-95</sup> The transmembrane forms of TNF- $\alpha$  and TGF- $\beta$  released by peripheral blood mononuclear cells have been shown to be involved in the radiation-induced apoptosis of the endothelial cells.<sup>24, 72</sup> Basic fibroblast growth factor (FGF), on the other hand, protects endothelial cells from radiation-induced apoptosis *in vitro*.<sup>93</sup> The induction of apoptosis is co-responsible for normal tissue damage by irradiation and probably by chemotherapy, too.

**Table 2.** Biologic effects of cytokines and adhesion molecules.

Mediator	Effects
TNF-alpha IL-1, IL-6	principal proinflammatory cytokines with profound effects on the processing of the acute phase response (1, 11); activation of neutrophils, T-, B-lymphocytes, macrophages, ECs, fibroblasts; induction of cytokines and other inflammatory protein release, upregulation of AM expression, activation of the hypothalamus-hypophysis-adrenal gland synthesis, TNF-alpha induced apoptosis in ECs (1, 69, 71-73)
IL-2	activation of lymphocytes and monocytes (74)
IL-4	growth factor of B-lymphocytes; inhibition of the release of mediators of inflammation (1)
IFN gamma	stimulation of phagocytic abilities of macrophages, differentiation of T-lymphocytes, cytotoxic effects (1)
TGF-beta	suppression of the inflammatory response, stimulation of fibroblast proliferation (40)
PDGF, FGF, IGF-I	stimulation of proliferation of fibroblasts (25, 38)
G-CSF, GM-CSF, M-CSF	hematopoietic growth factors playing a pivotal role in regulation of BM progenitor cell proliferation (75)
EGF	stimulation of epithelial proliferation, and differentiation (76)
PAF	involved in transmigration of leukocytes into the site of inflammation in cooperation with adhesion molecules; mediator of angiogenesis induced by inflammatory cytokines (77)
SCF	stimulation of hematopoietic stem cells (78)
AMs of the immunoglobulin family (e.g. ICAM-1, VCAM-1)	mediate firm adherence of leukocytes to ECs with subsequent extravasation (7)
Selectins (E-, P-selectins)	mediate loose contact between leukocytes and ECs, i.e. leukocyte rolling (7)

Fibrosis is a delayed result of radiation- and chemotherapy-associated tissue damage. It represents a reparation process at the time when the damaging insult does not act on the tissue.<sup>79</sup> Fibrosis is more than a mark of tissue damage; it is damaging in itself.<sup>96</sup> In association with fibrosis development, increased expression of TGFs- $\beta$  have been found in the irradiated animal lung, liver and skin tissue and in the lungs of bleomycin- and cyclophosphamide-treated mice.<sup>17, 38-41, 60, 67, 68</sup> Their expression is increased both in early and late stages of tissue reaction.<sup>41</sup> TGFs- $\beta$  have chemoattractive effects on fibroblasts and inflammatory cells and promote cell proliferation; they regulate expression, synthesis and storage of components of extracellular ma-

trix.<sup>40, 97</sup> Other cytokines, such as TNF- $\alpha$ , IL-1, IL-4, PDGF, FGF, insulin-like growth factor-I (IGF-I) are also likely to play an important role in fibrosis development due to fibroblast stimulation.<sup>18, 25, 29, 34, 38</sup>

Proinflammatory cytokines and adhesion molecules are involved in the pathophysiology of BMT-related complications. In an experimental model, the intensification of the conditioning regimen by increasing the total body irradiation dose results in an increased graft-versus-host disease severity. Total body irradiation and allogeneic immune cells appear to act synergistically to damage the gastrointestinal tract, thereby permitting an increased translocation of bacterial endotoxin (lipopolysaccharide) into the systemic circula-

tion. As total body irradiation increases macrophage and endothelial cell priming to lipopolysaccharide resulting in higher systemic levels of inflammatory cytokines, adhesion molecules, and probably other mediators of inflammation, an increase in the severity of graft-versus-host-disease results.<sup>22, 50, 60, 69</sup>

### Conclusions

Although the interpretation of cytokine concentrations has to be made with caution with respect to the used method of analysis,<sup>98</sup> there is no doubt that cytokines are released in response to ionizing radiation and chemotherapy. They are involved in the development of side effects of these treatment modalities that, however, have a protective role in the organism and tissues.

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