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ARTICLE

Structural and functional changes of cell junctions on effect of ionizing radiation

Zoltan Somosy[1]*, Gyozo Horvath[2], Gabriella Bognar[1], Gyorgy Koteles[1]

[1]Fodor József National Public Health Center, Frédéric Joliot-Curie National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary, [2]Institute of Health Protection of Hungarian Defence Forces, Budapest, Hungary

ABSTRACT Cell junctions are specialized regions of the cell membrane that are responsible for the formation of physical connections among the cells. They are also playing a role in cell communication and in the signal transduction processes of the plasma membrane. Following ionizing irradiations, their structural as well as functional changes are clearly detectable. They are generally able to modify the overall cell responses to various agents, whereas in some cases their functional changes can also be brought into relation with some end-points, such as apoptosis or tumor formation. According to experimental data, biologically active molecules (free radicals, signal transfer molecules) formed on the effect of radiation can get across into neighboring cells through the gap junctions that are responsible for intercellular chemical communication, and may there bring about changes characteristic to radiation injury (bystander effect) and they are also involved in/contribute to the so-called radio-adaptation of the cells. The permeability changes in the tight junctions caused by irradiation can be detected by EM and also by biochemical methods. Using morphometric analysis of EM specimens made by freeze-fracture technique, or by immunohistochemical detection of proteins derived specifically from tight junctions, it can be established that there are structural modifications occurring due to irradiation by X-rays. Using tissue culture model systems, radiation induced redistribution of cadherin and ß-catenin, two characteristic structural proteins of adherent junctions, is also detectable. Other molecules are also affected. Their expression or changes could play an important role in the development of acute or delayed injuries, including inflammatory processes occurring in the tissue - either as a cause or as an effect.
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Animal cells in tissue organization are establishing and maintaining connections with each other as well as with the intercellular matrix. The build-up scheme thereof is a rather simple one. They possess one or more coupling protein(s) embedded in the plasma membrane, bearing extracellular side chains, which are linked to proteins of the neighboring cells or of intercellular matrix having the same function or structure. These proteins are also linked to a membrane-integrated protein, whose side chain is building up connections to cytoskeletal elements at the inner (cytoplasmatic) side of the cell membrane. From chemical point of view, these proteins establishing direct links between cells or cell-to-matrix connections can be of various kinds (Hynes 1999; Lodish et al. 2000). In tight junctions (TJs) this linking function is provided by JAM, occludin and claudins (Mitic and Anderson 1998; Stevenson and Keon 1998) while in the adherens type junctions the same function is attributed to cadherins (Takeichi 2000). In addition, such coupling proteins may originate from the family of immunoglobulins, some mucine-like proteins, integrins, lectins (p-selectin) (Hynes 1999; Lodish et al. 2000; Gottardi and Gumbiner 2001).

The coupling proteins that are establishing links to cytoskeleton are also dependent on the type of cell junction; these are the ZO proteins in case of tight junctions, while at adherent junctions the same role is played by the α- and β-catenins (Mitic and Anderson 1998; Hynes 1999). The various types of cell junctions regularly form cell coupling complexes in the epithelial cells by ordering themselves in a particular array matrix (Lodish et al. 2000).

The cell contacts, for example the tight junction or some adherent junctions, possess a variety of functions. They play a role in developing and maintaining the mechanical stability of the tissues, are regulating the paracellular transport of molecules, and are fundamental in the development and maintenance of the polarity of the plasma membrane (Nusrat et al. 2000). Their change, *i.e.*, development, modification, or even cease of linkages in which they are involved, will provide a distinct signal to the cell which may – through various kinds of signal transduction mechanisms – then affect a number of cell functions (growth, development, protein

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*Corresponding author. E-mail: somosy@hp.osski.hu

synthesis, mitosis (Stevenson and Keon1998; Christofori and Semb 1999; Lodish et al. 2000; Tsukita and Furuse 2002).

The formation and change of cell junctions is fundamentally significant in tissue development, and is frequently related to their function. Their alterations may either initiate pathological processes or can play a pathophysiological role in their course thereof (Albelda and Buck 1990; Karczewski and Groot 1999; Nusrat et al. 2000).

Co-ordination of cell couplings (maintaining their structure and function) is realized via difficult, multi-level regulation systems, the particular details of which are not yet exactly known. Structural and functional alterations are controlled by regulatory processes representing at least three different levels of biological organizations, *i.e.*, physiological, cellular and molecular (Denker and Nigam 1998; Matter and Balda 2003). Regulation at the physiological level manifests itself as a joint resulting effect of many hormones, neurotransmitters, cytokines and growth factors. At cellular and molecular levels, tight junctions are regulated by different important signal transduction systems, such as phospholipase C, protein kinases, tyrosin kinase, phosphatase, Rho-GTP-ase. Signal transfer molecules (secondary messengers; cAMP, cGMP and NO) seem to play decisive role in this regulation both in coordinating as well as in subordinating relations.

As far as the structure and function of cell couplings are regarded, some other regulatory options also exist, namely: directly through the change of the internal relationship among cell coupling proteins, via modification of the intensity of molecular connections within the junctional complex, by the enzymatic degradation of structural proteins, and by changing the strength and the extent of the links attaching them to the cytoskeleton. Indirect regulation is presumably occurring via the change of the half-lives of some constituting proteins of the given cell coupling, or by alterations in the transcription or synthesis thereof.

Structural and functional changes of cell couplings following ionizing radiation exposures

Following exposures to ionizing radiation a number of reversible and irreversible responses on cellular, tissue, and organ levels can be detected. There is a sequence of events spread in space and time and the resulting physical, chemical, and biological changes effected by the absorbed radiation energy that can be observed. Should the energy absorption occur at different macromolecules of vital importance, this may then cause a direct break in the DNA molecule (Lett 1992). Breaks to macromolecules may also be affected indirectly via the mediatory effects of radiolytic products of water and of several reactive free radicals (Livesey et al. 1985). Impairments of the macromolecules due to direct and indirect effects may lead to cell death, to an irreversible impairment of the genetic matter, including tumorous transformation and to a number of other pathologic changes, *e.g.* giving rise to an inflammation. Pursuant to experimental data available the change in cell couplings is in direct or indirect way – often involved in developing radiation injuries. Based on some observations, the communication via gap junctions, or eventually a particular change in it after irradiation, is influencing some end-points (tumorous transformation, cell death) of the radiation effect (Trosko and Inoue 1997; Wilson et al. 2000). The radiation impairment of the tight junctions and the epithelial junctional complex may play role in the pathogenesis of inflammatory processes.

The role of gap junctions in developing radiation injuries / impairments

The gap junctions can be regarded as the organelles of intercellular chemical communication. Its coupling proteins, the connexins, are forming channels between the cells, through which different ions and small molecules get across under regulated conditions (Lodish et al. 2000; Skerret 2002). Irradiation induces the connexin expression in the skin of mice (Liu et al. 1997) and in alveolar cells *(*Kasper and Traub 1996*).*

The radiation susceptibility of cells grown in suspension or in two-dimensional cultures has proved to be greater than that of spheroids or tissues made up from the same cells. (Durand and Sutherland 1972; Dertinger et al. 1993; Green et al. 2002*).* In general, it can be stated that the presence of gap junctions, the increase of the amount of their proteins is accompanied by the lowering of radiation susceptibility of the cells (Lin et al. 2003). These experimental data, suggest that the expression of connexin, beyond its radioprotective effect, has a certain protective role of rather general character against different harmful effects. The metabolic coupling and metabolic cooperation bound to cell couplings may result in both radio-protective as well as radio-sensitizing effects. Thus the gap junctional communication has a proven role in the radio adaptation of cells (Ojima et al. 2001*).* The role/ contribution of gap junctions is also significant in the observed so-called bystander effect within the domain of biological effects of ionizing radiation (Azzam et al. 2001; Little et al. 2002; Lorimore and Wright 2003*).* The biologically active molecules (free radicals, signal transmitter molecules, etc.) produced in the respective cells on effect of radiation get across via the gap junctions to the neighboring cells, directly not hit by radiation injury, where they can cause death or impairment of that cells, too.

Functional and structural changes of tight junctions following ionizing radiation exposures

The tight junction is a sophisticated molecular complex establishing multifunctional connections among epithelial

cells. This cell coupling stabilizes the neighbouring cells, regulates the intercellular transport of ions and of paracellular matter, inhibits lateral shift of membrane proteins; its signal transmitter and signal generating function is also well known (Mitic and Anderson 1998; Stevenson, and Keon 1998).

In tissues covered by different epithelial cells (kidney, small intestine, brain capillaries, etc.), the radiation injuries of the cell couplings play an important role-either as a cause or as an effect-in the pathogenesis of acute or delayed pathologic processes (alterations in permeability barriers, inflammatory processes) occurring in the tissue on effect of radiation (Robbins and Bonsib 1995; Somosy 2000; Dör and Hendry 2001; Robbins et al. 2002; Somosy et al. 2003, 2002).

The early increase of permeability of the intestinal wall and the subsequent progression of it, associated with inflammation, is well known. This functional change is the basis of evolution of the gastrointestinal syndrome on effect of irradiations with high-dose which may cause death of the organism *(*Young 1987). Permeability changes and accompanying acute and chronic pathologic processes can be detected also in the case of smaller, therapeutic dosages. Thus, applying ruthenium-red technique, it has been demonstrated in mice that following application of relatively low doses (3, 5 Gy) during whole-body irradiation experiments, presence of the tracer ruthenium-red, characteristic to the enhanced paracellular permeability can be detected among the epithelial cells covering the intestinal mucosa (Somosy et al. 1993).

Parallel to the functional changes there are data available from direct electron microscopic and immunohistochemical investigations, that point to the structural damages of cell couplings due to irradiation. Morphometric analysis of freeze-fracture specimens from small intestine epithelial cells of X-ray irradiated mice reveals that irradiation causes a reversible loosening of the molecular structure of tight junctions *(*Porvaznik 1979; Somosy 2000; Páfia et al. 2001; Somosy et al. 2002*).* By immunohistochemical investigation of distribution of occludin, one of the main structural proteins of the tight junctions in MDCK- and in HT-29 cell lines, we demonstrated the dose- and time-dependent nature of changes brought about by X-ray irradiation (Somosy et al. 2002; Somosy et al. 2003). In unexposed MDCK cells occludin was detected in a circumcellular distribution at the cell periphery and showed characteristic honeycomb-like pattern indicating the tight junctional zone (Fig 1). The x-ray caused a time- and dose-dependent reduction in the staining intensity of occludin as well as breaks in the mainly continuous lines of stain (Fig. 1). The extent and distribution of staining of occludin are dependent on its structural organization and on the barrier function *(*Balda and Matter 1998*).*

As it was mentioned earlier cAMP and cGMP have an important contribution to the regulation of permeability of endothelial cells and to the determinination of the structural integrity of cell couplings (Dye et al. 2001; Wan et al. 2001). A high level of cAMP stabilizes the structure of the cell couplings, diminishes the permeability, while an elevated level of cGMP impairs the structure of the cell couplings, and an increases the paracellular permeability. These data indicate that the equlibrium of the local concentrations of these signal transmitters, and the regulatory processes influenced by them, determine the maintenance of the structural and functional integrity of cell couplings. According to our recent data (Somosy et al. 2003), treatment with dibutyryl-cAMP (db-cAMP), increases the cAMP level, and the disorganization of the tight junctions caused by X-ray irradiation can be prevented. At the same time, no considerable irradiation damage of tight junctions was observed, by inhibiting the enzymes responsible for the production of NO, the NO-synthases (NOSs), either. To the contrary, a treatment with db-cGMP, known to increase the cGMP level, was able in itself to induce such damages similar to those brought about by irradiation Based on these experimental results, it can reasonably be supposed that the NO-cGMP-cAMP-system might be a regulating element of essential significance in the development of permeability changes following exposures to ionizing radiations.

It is to be noted that the role of the NO-mediated system plays in the pathomechanism of inflammations following irradiation appears to be significant, and is thus consequently important in the permeability increase associated with the late occurring inflammation.

The permeability increase within the therapeutic dose range of the permeability barrier found in the brain capillaries, *i.e.* of the blood-brain-barrier (BBB), due to irradiation is also known (van Vulpen and al. 2002; Yuan et al. 2003*).* The same phenomenon has been described in the literature (Diserbo et al. 2002*)* after a smaller, single dose in whole-body irradiation experiments, too. This phenomenon is also correlated with the radiation impairment of the endothelial cells covering the surfaces of the brain capillaries. The regulation of permeability of the BBB is a complex, multi-level system. There are no experimental data available in details regarding the possible mechanism of the radiation effect. It should be noted that the permeability increase of the BBB following irradiation is being employed in the combined therapy of certain brain tumours.

Changes of adherens type junctions following irradiation

The adherens type junctions constitute a considerable group of cell couplings in which the binding protein is cadherin, whereas the catenins are responsible for establishing cytoskeletal links. They participate in the formation of the cell coupling complex of epithelial and of endothelial cells. Two different cell couplings of the complex, namely the adherens

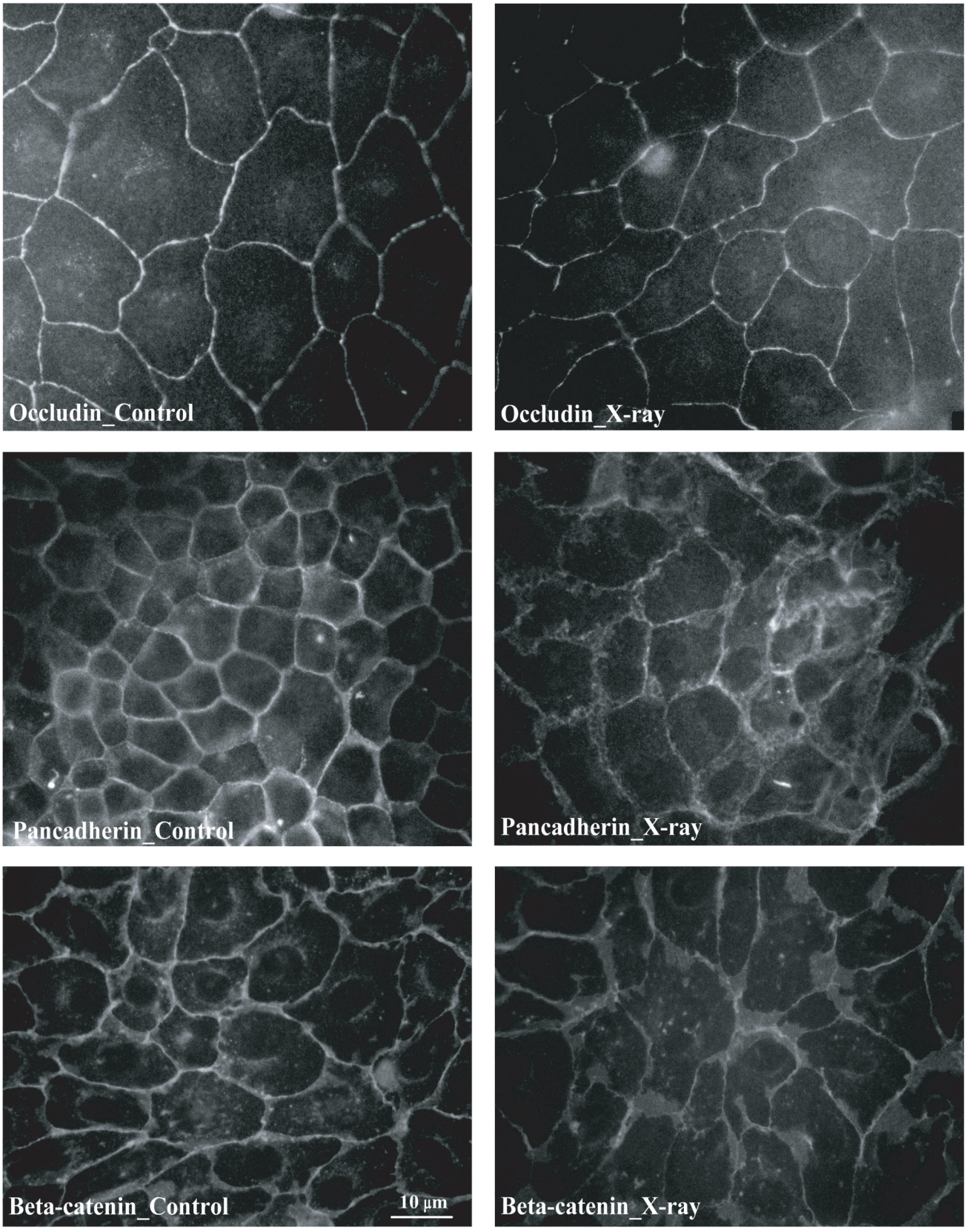

Figure 1. Binding characteristics of anti-occludin, pancatherin and beta-catenin antibodies to Madin-Darby Kidney cells.

junctions and the desmosomes belong to this group (Hynes 1999). In the cell coupling complex they are arranged behind the tight junction to which they are functionally and structurally closely connected. There are evidences concerning their involvement in determining the extent of permeability, and in addition, in the signal transmission processes. Adherens type junctions are essential in cell-to-basement links, too. In this case the protein embedded in the membrane, belonging to the cadherin group, is attached by heterofolic adhesion to some particular proteins of the matrix, like integrin and fibronectin; the cytoskeletal linker proteins could be vinculin, tropomyosin, and α-actinin. (Gottardi and Gumbiner 2000; Lodish et al. 2000; Blaschuk and Rowlands 2002). These connections are fundamental in determining cell shape and in the maintenance/stabilization of it, as well as the moving of cells (Hynes 1999; Lodish et al. 2000).

Irradiation and the adherens junctions in junctional complex

On effect of ionizing radiation (^{60}Co γ-radiation, whole-body) a quick, reversible loss of cadherins (E and OB) was found in rat colon crypt cells and in pericryptal myofibroblasts as well (Thiagarajah et al. 2000). This loss is also coincides with the enhanced permeability of the colon mucosa, which allows to conclude to a direct, cause-and-effect type link between the two phenomena. The amount of β-catenin, being the cytoskeleton linker protein of cadherin, also decreases following irradiation (Fig. 1). Our experiments carried out *in vitro* on MDCK-cells have led to similar result. We used pan-cadherin antibody which was able to detect cadherins both in basal and in lateral positions. X-ray irradiation affected the lateral marking giving rise to its significant decrease, while the basal marking did not change in an appreciable manner. We have also experienced the loss of β-catenin in our experiments.

The reason for the detected structural changes could not yet be elucidated, and the eventually accompanying, irradiation-caused functional modifications are not yet known in details. Pursuant to the view of Thiagarajah et al. (2000) an indirect process could be behind, which is triggered by caspase 3, having been induced by the irradiation. According to their hypothesis the observed loss of E-cadherin in crypts is in correlation with that of the water addsorption of the colon. In addition, the observed changes in the pericryptal myofibroblasts could give an explanation to the disintegration of the pericryptal sheet(s).

Hardy et al. (2002) showed that a considerable expression of P-cadherin, a kind of cadherins normally not present in colon, occurs parallel to translocation of E-cadherin and catenin associated thereto, from the membrane. Pursuant to their view, this cell coupling protein, *de novo* synthetized in that particular tissue, may promote/facilitate the regeneration of the tissue in a way. On the other hand many researchers (Akimoto et al. 1998; Ebara et al.1998) working on tumour cell lines (lung carcinoma, A549 and thyroid gland carcinoma T-SCC) have observed a time- and dose-dependent increase of E-cadherin and of α-catenin, and have described a fall in cell migration.

Changes in the cell-matrix and cell-substrate connections

Irradiation could change cell shape. This phenomenon was observed on irradiated primary human fibroblasts (Somosy 2000), lung artery endothelial cell cultures (Friedman et al. 1986) and neuroblastoma cells. The ruffling activity on fibroblasts and on neuroblastoma cells increases and characteristic to the moving cell forms. The stuck cell surfaces are partly splitting off, ruffles, microspikes and blebs are going to occur (Hamberg et al. 1978; Somosy 2000). Ionizing radiation modifies the expression of various integrines on cell surface (Meineke et al. 2002), as the cell-matrix connections may be subject of modification. In some cases an increase in cell migration has been found (Wick et al. 2002) while in others the irradiation brings about an enhancement of adhesion (Cordes et al. 2002). It is also known that irradiation modifies the composition of the extracellular matrix. Giannopoulou et al. (2001) reports that 6 hours following an exposure to X-ray the irradiation has diminished both the amount and the expression of the relevant genes of fibronectin and laminin. Changes in cell-matrix connections after irradiation are dependent of the alterations in the binding proteins, both on the cell surface and in the matrix as well.

Quantitative and distribution changes of adhesion molecules that play role in the pathomechanism of inflammation development following irradiation

Ionizing radiation is known to evoke both acute and chronic inflammatory reactions in several organs and tissues, such as skin, intestinal system, lungs and kidneys. The development of inflammatory response is a finely regulated process that involves sequential lecocyte-endothelial or epithelial interactions designed as rolling, activation, adhesion, and emigration. By changing the connections between these two cell types, in relation to this phenomenon, changes in the expression of various cell coupling molecules, such as selectines, integrins, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) can be observed (William 2002).

After giving higher doses (2 to 20 Gy) in a number of *in vivo* and *in vitro* experimental setups of endothelial cell systems, dose- and time-determined quantitative changes of the E-selectin, P-selectin, ICAM-1, VCAM-1 have been described (Hallahan and Virudachalam 1999, 1997; Molla et al. 2001*).* According to these data the up-regulation of these

adhesion molecules is in correlation with the enhanced concentration of various intercellular mediators occurring upon effect of radiation (Barcellos-Hoff 1998; Gorbunov et al. 2000; Köteles és Somosy 2001). It is also probable that hydroxi radicals, appearing as an early effect of radiation, have an essential role in the development and course of inflammation diseases. NO is involved in the pathomechanism of the development of inflammations (Freeman and MacNaughton 2000; Leach et al. 2002).

It is of considerable interest that low-dose irradiations (0.3-0.7 Gy) have an anti-inflammatory effect, contrary to that of higher doses. Hypothetically, it may be assumed that in the course of development of this antiphlogistic effect, these doses are diminishing the expression of L-selectin that is fundamental in the initial steps of the inflammatory process (Roedal et al. 2002).

Conclusions and Perspectives

It is evident from the brief summary above that structural and functional alterations of cell couplings are of essential significance from the point of view of development of changes following the radiation-organ and radiation-tissue interactions. Thus the early change in permeability of the endothelium or of the epithelium covering different hollow organs, the inflammatory processes, and the accumulation of connective tissue appearing as a late effect, can play a role in the alterations of the cell couplings both as a cause and as an effect. Changes in cell-to-cell communication occurring on effect of radiation, in the evolution of which many types of cell couplings (gap junction, adherens junction, integrin mediated connections) are involved, are of significance also in development of both the early and the late effects of radiation. From these important roles of cell couplings it is to be concluded that those regulating processes, and those biologically active compounds which influence the alterations of the cell couplings, contribute to the modification of the effect of radiation, too, and thus it is conceivable that they can have a role in radioprotection or in enhancing the effectivity of radiotherapy by making the cells more sensitive to radiation. It is therefore comprehensible that the antiphlogistic treatment based on the modification of connections of the cells is effective in radiotherapy, or the NO inhibitors having a stabilizing effect on the tight junctions, possess a radioprotective effect. It can be predicted that results of these research will help in preventing radiation injuries/damages associated with irradiations of therapeutic purpose or those deriving from accidental irradiation exposures.

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