NON-TARGETED BIOLOGICAL EFFECTS OF IONISING RADIATION

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Abstract:

The rupture of the DNA double helix, the genomic and chromosomal instability induced in the cell progeny of both irradiated and adjacent cells cause the appearance of non-targeted effects of ionizing radiation on tissues and organs. The mechanisms, by which cell damage is caused, have mainly been studied in cell-cultures in order to assess the radiation risk.

This review is referred to both target cells and the mechanisms of non-targeted effects.

Keywords: ionizing radiation, ARS, chromosomal instability, skin ulcerations.
1. **Introduction.**

Since 1895, when Wilhelm Conrad Röntgen described the discovery of penetrating radiation named x-rays, because of its mysterious nature, so far, science has clarified the nature and the biological effects of radiation.

Scientists such as Antoine Henri Becquerel, the Curie couple, Thomas Edison, Nicola Tesla etc., have “linked” their name with the first researches on radiation, named radioactivity by the Curie couple, and their scientific announcements have divided the scientific community.

Despite the fact that C. M. Dally death in 1904 was attributed to excessive exposure to radiation, the surgeon Dr. George Torney in about 1910 announced that exposure to natural radioactive hot springs, may alleviate cases of gout, rheumatisms, neuralgia, indigestion, diarrhea, etc. [1]. Radium was used in the industrial manufacturing of luminous paints [2] in the early 1900s with devastating effects on the workers’ health (bone cancer, leukemia, pernicious anemia, etc.) and up to 1931 people believed that moderate exposures to radiation had invigorating effects on their health. Dr. Knef first announced in 1922 that radium "while it was hailed as a boon to mankind in the treatment of cancer and other diseases, it became a subtle death-dealing menace" [3].

At present, the biological effects of radiation undoubtedly caused after exposure to radiation, are the subject of ongoing research in order to assess the radiation risk. These effects known as non-targeted or deterministic effects [4,5,6], have been clinically studied in radiation-exposed populations after nuclear accidents.

2. **Mechanisms of non-targeted effects.**
The DNA double-strand break is the primary lesion leading to chromosomal rearrangements. Alterations in gene expression disrupt cellular homeostasis and underlie the induced genomic instability [7]. This includes an increase in mutation rates, gene amplifications and cellular transformation, many generations after the initial insult. These delayed responses of the clonal descendants of the irradiated cells lead to chromosomal abnormalities which are the endpoint of radiation-induced genomic instability. Gene expression studies of the irradiated T cell clones, revealed subtle changes in the expression of many genes rather than significant changes in a few genes at a transcriptional level. A possible lack of chromosomal instability, naturally does not exclude the existence of an underlying genomic instability [8].

Recent studies have linked chromosomal instability after irradiation with oxidative stress-inducing agents. Since mitochondria are the natural source of reactive oxygen species (ROS), it was assumed that mitochondrial dysfunction may maintain elevated ROS levels in genetically unstable cells. Experimental studies demonstrated, that both succinate dehydrogenase mutations and respiratory chain hypofunction [9,10,11,12] are associated with a ROS/oxidative stress mechanism contributing to the radiation-induced instability.

Lesions have also been observed in non-irradiated bystander cells as a result of receiving signals from irradiated cells [13]. These include chromatid exchanges, micronucleus formation, gene mutations, chromosomal instability and cellular transformation. However, it has been observed that the bystander cells responses may include enhanced cell differentiation [14], secretion of growth inhibitory factors [15], or even development of radio-protective mechanisms [16,17]. The mechanisms involved in the bystander cells lesions, are associated with an increased oxidative metabolism and elevated ROS levels, as a result of transmembrane signaling and soluble factors-mediated intercellular communication damage. The substances production by the irradiated cells shifts the anti-oxidative balance in cells.
towards the oxidative state through the formation of lipid peroxidation products [18], inosine nucleotide [19] and cytotoxic cytokines [20].

The inflammatory processes that have been developed normally in order to fight potential tissue damage appear to be involved in the bystander cells lesions, in terms of the inherent immunological mechanisms aberration [21]. The increased incidence of the cardiovascular, gastrointestinal and respiratory diseases [22,23], to survivors in Japan after the dropping of the atomic bomb, seems that it may be associated with a chronic persistent inflammation [24,25]. The continued production of harmful inflammatory signals in the tissue micro-environment, probably by the tissues macrophages, may produce genetic damage in the adjacent cells [26].

3. **Non-targeted effects.**

The non-targeted effects are characterized by the fact that they are necessarily due to radiation exposure; there is a threshold of dose below which there are no consequences; and the magnitude of the effect increases by increasing the dose.

The radiosensitivity of a cell is determined by the Bergonie and Tribondeau law [27] practically summarized to the fact that the radiosensitivity of a cell type is proportional to the rate of cell division and inversely proportional to the degree of specialization. Thus, specialized and slowly or non-proliferating cells (CNS) appears to be radioresistant, whereas the rapidly proliferating progenitor cells (bone marrow) appear to be radiosensitive. The lethal dose of radiation for an organism (LD₅₀/30) is the one that will kill 50% of the cells within 30 days.

The death of an irradiated cell is due to the energy deposition in its nucleus and the subsequent DNA damage that may lead to mitotic failure and/or apoptosis. If the cell is able to survive, then the sustained genetic lesions are inherited by the progeny. It also indirectly
radiates bystander cells which sustain lesions as well, inherited by their progeny. These cell progeny constitute the explanatory basis of any significant health damage appearance in an irradiated organism - known as non-targeted effects - since they produce clonal progeny series which maintain the DNA damages.

3.1 Acute radiation syndrome (ARS).

It concerns a large exposure of the body to radiation. The direct clinical symptoms occurring within a few minutes or a few days after the exposure include nausea, vomiting, fatigue, diarrhea and in larger doses fever, respiratory distress, prostration. After an apparent recovery phase, that its duration depends on the uptake dose by the subject, the symptoms of the induced damage occur and they may lead to death in one or a few months or the subject will survive and recover after a period that may last years [28]. The non-targeted radiation damages are naturally directly dose-dependent and the affected systems follow the Bergonie - Tribondeau law.

3.1.1 Haemopoietic system damage.

The hematopoietic system cells in the bone marrow are the most radiosensitive. Progenitor cells damages and alterations in the peripheral blood, may occur in small doses of radiation. A sudden increase in granulocyte count is followed by a depression in leucocyte, red blood cell and platelet count. The subject usually recovers within one to two months.

3.1.2 Gastrointestinal system damage.

This damage requires higher doses of radiation and it concerns cells at the base of the intestinal villi, which are specialized but rapidly proliferating. The damage mainly occurs by the failure of cell division. The symptoms manifest at a second time, due to a reduction in these cells count by the loss of their mitotic activity. The patient exhibits severe fluid and
electrolyte disturbances. The survival chances, with medical intervention, are small but not nonexistent. The clinical picture of the patient is very serious if we also take into account the serious coexistent lesions of the haemopoietic system.

3.1.3 CNS (central nervous system) damage.

The CNS damage requires large doses of radiation, since the cells of the CNS are particularly radioresistant. These doses are incompatible with the survival probability of the subject, who exhibits instability, impaired orientation, apathy, convulsions, coma and leads to death within hours or one to two days.

3.2 Skin damage.

The skin as an organ exhibits median radiosensitivity but it absorbs most of the incident radiation. Its lesions are clearly dose-dependent, are manifested weeks or months after the exposure and vary from epilation and erythema at low doses, up to desquamation, phlyctenar eruption and necrosis at large doses. An early transient erythema due to damage of the skin capillaries may occur after large doses of radiation and it is unrelated to the erythema which will occur later because of the skin cells damage.

**Fig. 1.** Skin lesions on a worker's limbs, in Yanango of Peru, exposed to an unshied radiological Ir-192 source.

Source: International Atomic Energy Agency, Vienna, Austria, 2000 [29].

The real lesions appear after a latent, asymptomatic period, lasting days or even weeks after the exposure, when the basal layer is repopulated by the surviving clonogenic cells. After a period of three to four months erythema, edema, and severe pain appear. Late effects
may occur years later and they concern ulcers, lymphoedema, fibrosis, vasculitis, and subcutaneous sclerosis of the connective tissue. The recovery, if the subject survives, may last for many years.

3.3 Gametocytes’ damage.

Acute damage to the oocytes and spermatocytes after radiation exposure may result in temporary or permanent sterility, depending on the dose. Given the maturity of the oocytes in contrast to the continuously proliferating spermatocytes, it is clear that higher radiation doses are required in order to be manifested a permanent ovarian suppression compared with the appearance of permanent azoospermia. It is important to note that chromosome aberrations of the gametocytes, inherited to the subsequent generations, constitute a particularly important targeted effect of ionizing radiation and they does not concern the present review.


Ionizing radiation affects gene expression, intracellular communication and tissue micro-environment, causing serious disruption to the cell biology. The dose-dependent non-targeted effects are due to genetically unstable cell progeny with clonogenic features. The fact that they appear even in small radiation doses is of particular importance, in order that the aggressive medical intervention is able to save those who have been exposed to non-lethal doses. The study of the mechanisms at a molecular level, underlying the clinical manifestations, contributes to a most effective medical intervention. The nuclear accidents have provided considerable knowledge in this field and the ongoing experimental studies remains to help determine more precisely both the minimum dangerous levels of radiation and more effective treatment ways of the subjects exposed to radiation.
References


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