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Review Article

Aspects of Radiotherapy and its Impact on Radio Resistance and Cellular Metabolic Activity

Muhammad Torequl Islam*

Department of Pharmacy, Life Science Faculty, Bangabondhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj-8100, Bangladesh

***Corresponding Author**: Muhammad Torequl Islam, Department of Pharmacy, Life Science Faculty, Bangabondhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj-8100, Bangladesh.

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Abstract

Purpose: Metabolic diseases or disorders are widespread, and the causes are numerous. Radiation therapy is one of the popular modalities in current cancer treatment. Although, radiation has some beneficial effects in biological systems, but scientific evidence suggesting that it has a number of harmful effects in our body. The aim of this review is to sketch a current scenario on radio resistance and the effects on radio therapy on metabolic activity.

Materials and Methods: Evidence from the databases PUBMED and SCIENCE DIRECT were considered.

Results: Findings suggest that radiation has a dose-dependent effect in our body. Abnormal ROS effects, diverse cellular metabolic activity, apoptosis suppression, alteration of the DNA damage response, and adaptation to hypoxic stress are the most common causes of radio resistance in our body. At high dose radiation can induce excessive ROS and inflammatory phenomena. Moreover, radiation has direct or indirect effects on biological regulators such as signaling proteins, enzymes, hormones, which might be the consequences of radiation-induce harmful effects on the cellular metabolic activities.

Conclusion: Radio resistance is a prominent case in radiotherapy. Radiation has beneficial as well as harmful impacts on biological systems.

Keywords: *Radiotherapy; Cancer; Combination Therapy; Metabolic Effects*

Abbreviations

ABL1: Abelson Murine Leukemia Viral Oncogene Homolog 1; AMPK: AMP-Activated Kinase; CSF1: Colony Stimulating Factor 1; DSBs: Double-Strand Breaks; GSH: Reduced Glutathione; HIF-1: Hypoxia-Inducible Factor 1; iNOS: Inducible Nitric Oxide Synthase; IR: Ionizing Radiation; MAPK: Mitogen-Activated Protein Kinase; NF-κB: Nuclear Factor Kappa B; NO: Nitric Oxide; $O_2^{\bullet}$: Superoxide Radical; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; TBI: Total-Body Irradiation; TIGAR: TP53 Induced Glycolysis and Apoptosis Regulator; VEGF: Vascular Endothelial Growth Factor.

Introduction

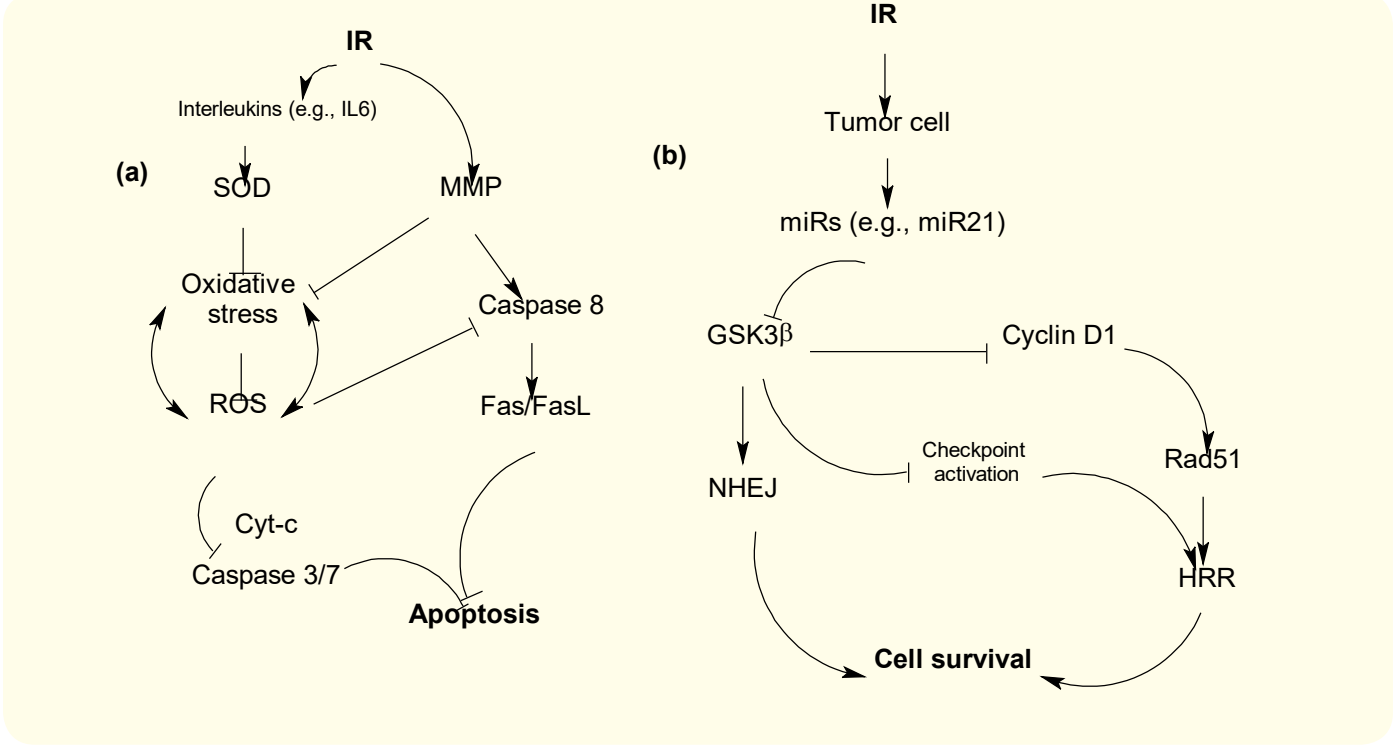
Radiotherapy is one of the common strategies of cancer management. Now-a-days, more than 50% of the cancer patients have undergone radiation treatment. However, anatomical changes and tumor regression during radiotherapy may affect in the tumor therapy [1], this leading the understanding of this treatment modality.

Radiation source is a kind of physical stress which may cause environmental pollution, increases the oxidative pressure and induces further damages such as DNA lesions, cell death, cancer and other diseases [2]. Therefore, radioprotective agents are administered either before or after radiation exposure to minimize radiotoxicity [3]. However, radiation affects biological system within a narrow range. For an example, in a recent study, the TBI at 6 Gy reduced signs of radiation sickness and improved survival rates, while TBI at 7 Gy decreased the rate of survival of the experimental animals [4]. 5,7-bis(methylaminosulfonyl)-8HQ and 8-methoxyquinoline derivatives were evident to show low cytotoxic activity against MOLT-4 cells [5], while some aminothiol derivatives were found to exert systemic toxicities [6]. On the other hand, radioiodine 131 is associated with side effects such as salivary gland dysfunction and an increased risk of leukemia [7].

Radiotherapy, depending upon the dose, has been reported to have different effects on tumor infiltrating myelomonocytic cells [8,9]. Ionizing radiation (IR) at high dose may cause elicit regenerative responses, thus the tumor regrowth. The CXCR4-CXCL12 chemokine axis has been implicated in the recruitment of tumor promoting myeloid cells after local irradiation [10]. Irradiation caused nuclear translocation of the damage-activated kinase Abelson murine leukemia viral oncogene homolog 1 (ABL1), which enhanced colony stimulating factor 1 (CSF1) gene transcription [11]. This review focuses on the occurrence of radioresistance and its impacts on metabolic activity.

Radiotherapy and radio resistance

Radiotherapy is also evident to activate new subnetworks, resulting in network flexibility [12]. IR exerts effects on whole cell components [13], thus, a dilution effect of the non-hub elements by IR. Chronic exposure to this low level of IR may cause greater damage [14]. Hubs that remain undamaged could eventually activate other radiation-responsive signaling networks, reintegrate network topologies and establish networks more resistant to radioresistance [15]. Irradiation-induced reactive oxygen species (ROS) can upregulate nuclear factor kappa B (NF-κB)-mediated inflammatory signaling cascade in cancer cells [16]. Possible pathways of the occurrence of radioresistance have been shown in figure 1. Moreover, activated inflammatory network (e.g. chemokines and cytokines) may result cancer cells survival by overcoming IR-induced inflammatory stress. It may result in acquired radioresistance and consequently reduced efficacy of radiotherapy in patients. However, radioresistance is more prominent in older patients than the youngs [17]. It may be due to higher ROS (e.g. NO and $O_2^{\bullet}$) production rate in the former category patients.



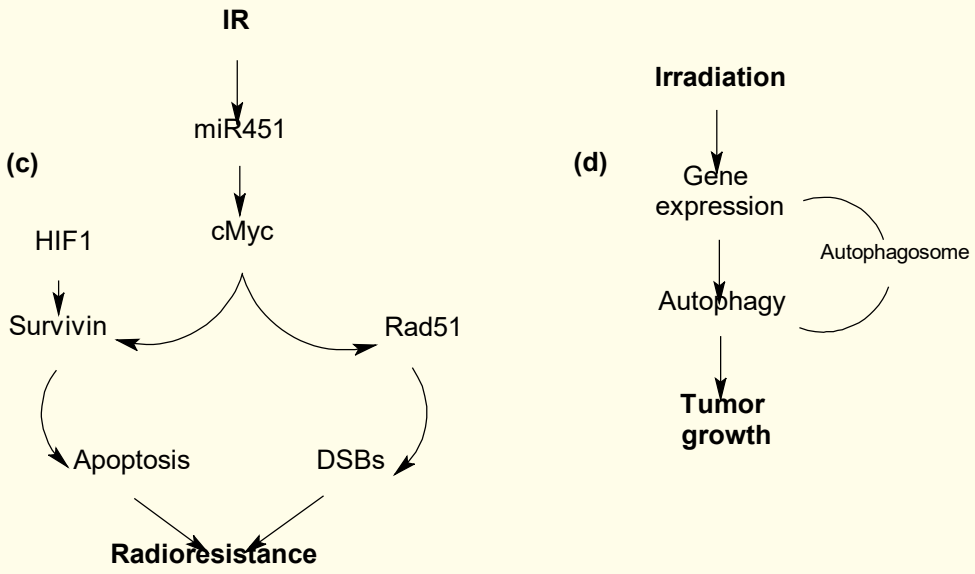


Figure 1: *Mechanism of radioresistance in mammalian cells. [(a) Ionizing radiation (IR)-induced reactive oxygen species (ROS) and mitochondrial membrane potential (MMP) dependent radioresistance pathway. (b) IR-induced miRs, especially miR21 and cyclin D1 dependent cell survival. (c) IR-induced hypoxia inducible factor 1 and miR451 dependent radioresistance. (d) Irradiation effects in tumor cell growth. Other abbreviations → SOD: superoxide dismutase; Cyt-c: Cytochrome c; GSK3β: Glycogen Synthase Kinase 3 Beta; NHEJ: Non-Homologous End Joining; HRR: Homologous End Joining; DSBs: Double Strand Breaks.*

Conventional radiotherapy doses up to 70 Gy is evident to show biochemical failure rates of 30% or more in localized disease [18]. In a recent study, resveratrol (an antioxidant) was founded to promote IR effects in prostate cancer (PrCa) cells, possibly *via* mitogen-activated protein kinase (MAPK)-Akt-dependent pathway [19]. Antioxidants such as polyphenol chemical class, xanthine derivatives, tocopherol, sucralfate, and ascorbate have been evident to alter cytokine release affecting cutaneous and systemic changes in experimental animals [20]. In a recent study, it has been demonstrated that medicinal plants and their active constituents, especially plant-derived antioxidants may alleviate radiation-induced damage through antioxidant, anti-inflammatory, wound healing and immunostimulatory properties [21].

Certain chemical can cause mutation which is one of the major consequences of radioresistance. For an example, in a study trichloroethylene was found to cause mutation in P81S VHL, thus leading to diversify metabolic activity, apoptosis suppression, and alteration of the DNA damage response by IR therapy [22]. Moreover, exposure of tumor cells to radiation could impact a large number of proteins simultaneously, leading to modify chemotherapeutic agent's action [23].

In the development of tumor cancer cells partially undergo a hypoxic condition due to insufficient vasculature systems. These cells show hyper-activation of hypoxic-inducible factor (HIF)-1 network for adaptation to hypoxic stress. This also leads an IR resistance [24], possibly *via* increasing in vascular endothelial growth factor (VEGF) expression [25]. Early reports suggest that bevacizumab, one of the best-known VEGF inhibitor can normalize tumor vasculature, overcome resistance to radiation, inhibit repopulation after radiation and blockade of radiation-induced increased VEGF expression [26], therefore should be effective with an acceptable toxicity profile [27]. However, autophagy activation can promote bevacizumab resistance in some cancer cells [28].

Moreover, protected tumor vasculature can supply required oxygen and nutrients to the tumor cells, which may lead to grow tumor radioresistance and tumor growth progression. However, Sharma and Jain [29] suggested that radioresistance of hypoxic cells can be overcome by the combined therapy with the radio modifiers such as hematoporphyrin derivative (Hpd) and 2-deoxy-D-glucose (2-DG).

Radiation impacts on metabolic activity

Exposure of IR has some beneficial impacts, especially in the synthesis of vitamin D_3 and its various biological roles in our body [30] (Figure 2).

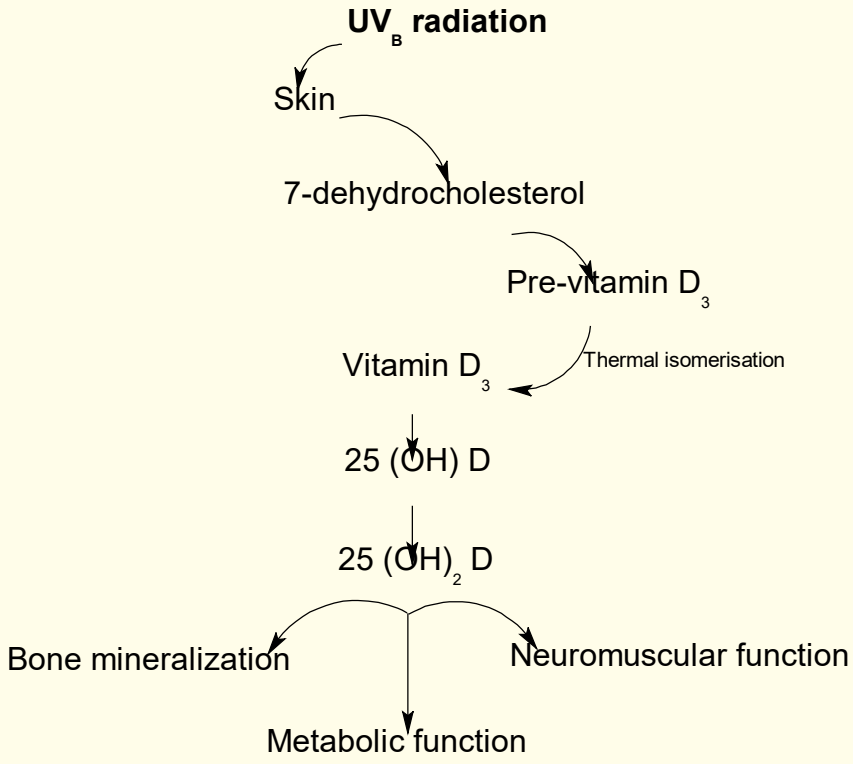


Figure 2: *Beneficial effects of UV in human. [Our skin produces vitamin D3 in the presence of UVB ray, which is helpful for bone mineralization, neuromuscular function and varieties of metabolic activities.*

However, it is also evident that IR has a variety of adverse effects on the immune system as it can affect the key metabolic processes such as glucose uptake, glycolysis, and energy metabolism [31]. Uptake of the radiopharmaceuticals is increased by the tumor cells than the normal cells [32], which may be a reason of effectivity of iodine-125 and IR combination therapy of certain malignant diseases [33].

At low doses (≤ 1.25 Gy) IR inhibits the inducible nitric oxide synthase (iNOS) pathways (e.g. translational and post-translational). However, an increased degradation of heme is essential for iNOS activity, which demonstrating other post-translational modifications may be involved in the proteasome degradation pathway [34]. However, Hildebrandt., *et al.* [35] reported that IR up to 10 Gy did not stimulate macrophages, changes metabolic activity, cell proliferation, and reproductive integrity other than an increased in nitric oxide (NO) pro-

duction. Furthermore, irradiation of autologous blood by UV rays in 81 patients with proinflammatory diseases is evident to modulate indices of antimicrobial protection, increase in the intensity of the histochemical reaction to peroxidase, reduction of pH in the neutrophil phagosomes, restore the serotonin, increased of the intensity of metabolic processes, changes in membrane phospholipid composition, and juvenile platelet forms [36]. Low dose irradiation (0.5-6 Gy) was also found to reprogram macrophage function, normalization of the tumor vasculature and more efficient recruitment of specific antitumor T cells, possibly *via* endothelial cell activation and down-regulation of immunosuppressive tumor promoting functions [37].

On the other hand, IR at high dose (4-8 Gy) induces cell impairment. Irradiation within a short period may upregulate TP53 induced glycolysis and apoptosis regulator (TIGAR) that lowers fructose-2,6-bisphosphate levels in cells, consequently decreases glycolysis and lead to the scavenge of ROS. The ultimate result is the highest resistance to cell death [38]. Generally, the high glycolytic rate protects cancer cells from ROS-induced DNA damage by supplying large amounts of reducing equivalents such as pyruvate, lactate, glutathione, and NADPH that scavenge ROS [39]. Ketone bodies and fatty acids may inhibit glycolysis [40]. An impairment of glycolysis causes mitochondrial dysfunction, which increases excessive ROS production, thus leading cell death [41]. Moreover, oxidation of ketone bodies in peripheral tissue decreases the $NADP^+$/NADPH ratio, thus increases the levels of the important physiological antioxidant enzyme, reduced glutathione (GSH) [42]. Vlashi., *et al.* [43] suggests that cancer stem cells possess high metabolic flexibility, which is the major cause of radioresistance in these types of cells. Effects of various doses of radiation in test systems have been shown in table 1.

Doses	Test systems	Health effects	Mechanisms	References
100 mGy	Mice	Brain damage and impaired cognition	DNA damage, inflammation, vascular damage, white matter injury and coagulation necrosis	Lowe and Wyrobek [44]
0-0.20 Gy	Human	Breast cancer	DNA damage, oxidative stress, chromosomal aberrations	Ozasa., *et al*. [45]
50 mGy	Huamn	Leukemia	DNA damage	Pearce., *et al*. [46]
0.05 or 0.30 Gy	Mice	Malformation	DNA damage, global genome DNA methylation, chromosomal aberrations	Wang., *et al*. [47]
> 2 Gy	Human	Cataracts	DNA damage, inflammation	Fujimichi and Hamada [48]
1 - 3 Gy	Rats	CVD	Endothelial dysfunction, inflammation, oxidative stress, alterations in coagulation and platelet activity, DNA damage, senescence and cell death	Baselet., *et al*. [49]
60 mGy	Huaman	Brain tumors	DNA damage, chromosomal aberrations	Kutanzi., *et al*. [50]
-	Human	Thyroid cancer	DNA damage, chromosomal aberrations	Philchenkov and Balcer-Kubiczek [51]

Table 1: *Effects of radiation in some test systems.*

IR at 0 to 8 Gy is evident to phosphorylate and activate the metabolic sensor and tumor suppressor AMP-activated kinase (AMPK), possibly *via* p53 and cyclin-dependent kinase inhibitors $p21^{cip1}$ and $p27^{kip1}$ inhibit induction of nuclear fragmentation and cleavage of caspase 3 [52]. On the other hand, IR at 50 to 70 Gy may cause acute and late grade > or = 2 xerostomia and mucositis. In a study, amifostine (WR-2721), a cytoprotective agent was found to show protective effects of advanced ovarian cancer cells by conversion and uptake of the active metabolite, WR-1065 [53]. Effects of chronic and/or high IR dose in biological system has been shown in figure 3.

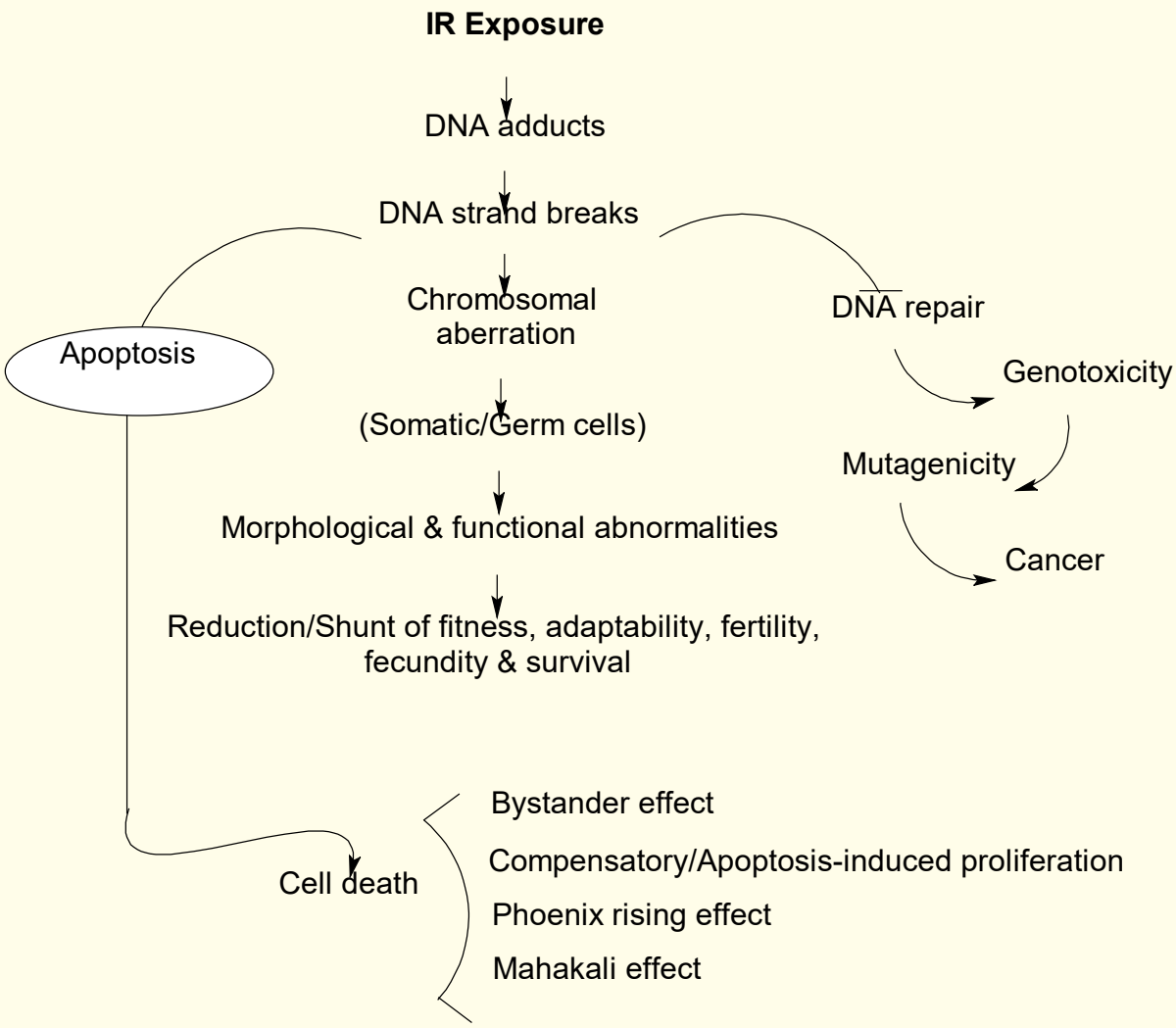


Figure 3: *Effects of chronic/high dose IR in human. [IR at high dose causes DNA adducts and DNA breaks, leading to apoptotic cell death. If the damage remains un-repaired, it may turn into the cancer. Chronic and high IR exposure are evident to cause morphological and functional abnormalities such as reduction of cell function and body fitness, changes or reduction of adaptability and even survival.*

Total-body irradiation (TBI) is evident to cause morphological changes in different organs in rats with differential expression of 53% (765 genes) that were mainly involved in a total of 21 pathways, including metabolic, cancer, and MAPK pathways [4].

IR generates intermediate free radicals and ROS leading to DNA double-strand breaks (DSBs) [54]. Delay or an impairment of the cellular repair system of this type of injury directly or indirectly causes mutation or even cell death. Furthermore, tumor cells can survive through activation of the DSB repair pathway, including homologous recombination and nonhomologous endjoining [55,56], this may lead to growing radioresistance [57]. Mainly the exposure of IR modulates numerous cellular networks, including DNA repair, survival, apoptosis, cell cycle, cell migration, protein localization, RNA processing, antioxidant defense, inflammation and cell proliferation, and so on. For example, p53-related genes and DNA-damage response genes are generally activated by irradiation in lung cancer cells [58].

In a study, a significant reduction of Cho/Cr and NAA/Cr ratios was observed with gamma knife radiosurgery performed in 18 metastatic brain tumor patients [59]. A decrease in Cho/Cr ratio reflects inhibition of proliferative activity and early apoptotic cell loss, while the reduction of NAA/Cr is associated with the radiation-induced modulation of neuronal activity. Petersen., *et al.* [60] suggests that cyclo-oxygenase-2 and its products may act as protectors against cell damage by ionizing radiation. In another study, IR at 25 cGy was found to modulate neurotransmission processes *via* metabotropic muscarinic ChR and gamma amino butyric acid receptor pathways [61]. Radio-immunotherapy using 131I-UJ13A or 131I-3F8 monoclonal antibodies have been evident to show moderate response and considerable side effects in IV neuroblastoma patients, probably *via* enhancing tumor uptake by modulation of antigen expression or by increasing the tumor perfusion/vascularity/permeability [62]. IR-induced damaging effects on our body have been shown in figure 4.

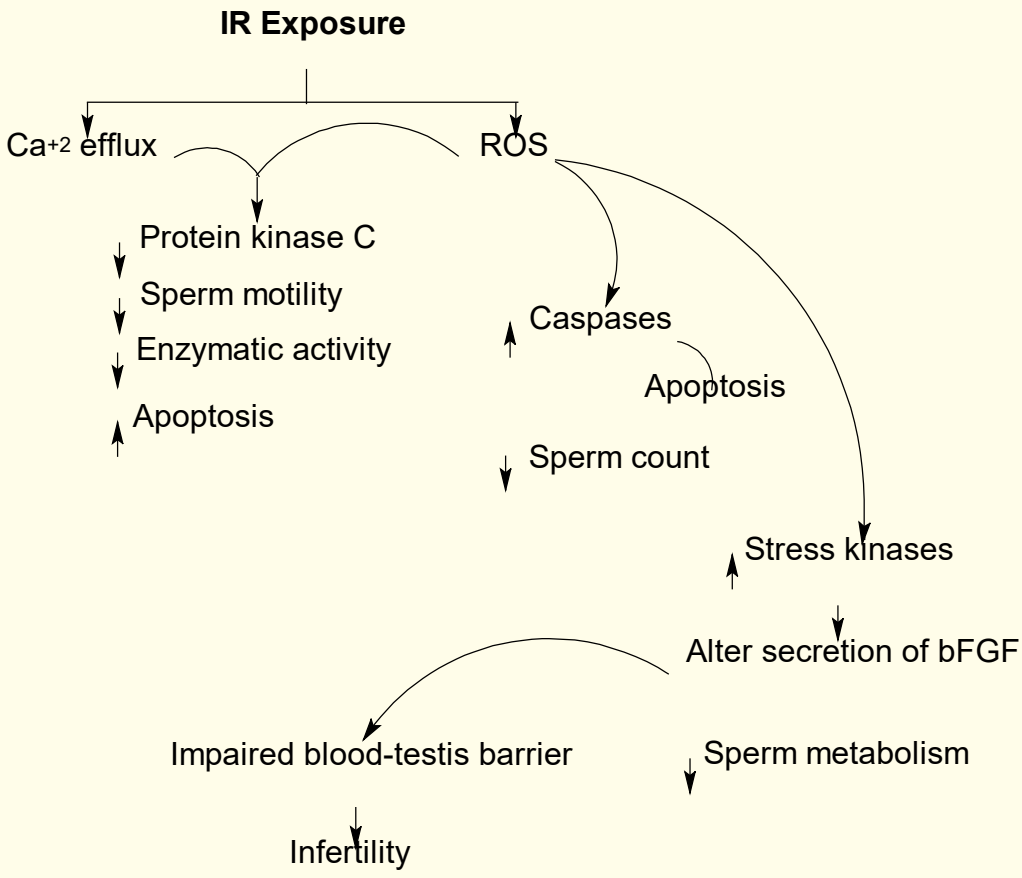


Figure 4: *IR exposure and changes of biological phenomena. [IR-induced Ca=2 efflux and excessive production of reactive oxygen species (ROS) alters normal biological activities. ROS increased stress kinases alters the secretion of basic fibroblast growth factor (bFGF), which causes infertility in male by the destruction of blood-testis barrier.*

Conclusion

The biological effects of radiation are dose-dependent. At low dose it is beneficial for us, however, chronic exposure to radiation at any dose is evident to produce various abnormalities in our body. Metabolic abnormalities are one of them. Radiation can act by the induction of ROS, inflammatory phenomena, regulation of cell signalling cascades, and so on. Radioresistance is evident through a number of ways, including alteration of cellular metabolic activities, suppression of apoptosis, alteration of the DNA damage response, and adaptation of the hypoxic stress. Chronic and at high IR doses directly and/or indirectly can induce oxidative stress and inflammatory responses. Furthermore, radiation can alter cell signalling cascades and other biochemical activities, thus the harmful effects of it on the metabolic activities in a biological system.

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