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Low Doses of Gamma Radiation Induce Cellular Stress Associated with Hsp70 Expression in HaCat Cells

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Abstract

Ionizing radiation is widely used in the diagnosis and treatment of diseases; however, cumulative exposure, even within doses considered permissible, can induce cellular damage, particularly in the skin, as it is the first organ exposed. In this context, the present study aimed to evaluate changes in the expression of the Hsp70 protein as a bioindicator of cellular stress in HaCaT epithelial cells exposed to low doses of gamma radiation. To this end, HaCaT cells cultured *in vitro* were irradiated using a ^{137}Cs source, and Hsp70 expression was subsequently analyzed by SDS-PAGE, Western blotting, and immunodetection. Basal Hsp70 expression was detected in non-irradiated cells, as well as an increase in expression under heat stress conditions. Following exposure to the radiation field, an increase in Hsp70 expression was observed at a dose of 73.7 μGy, followed by a slight decrease as the dose increased. These findings suggest a dose-dependent response in Hsp70 expression to gamma radiation and demonstrate that exposure to low doses induces cellular stress in HaCaT cells, as reflected by changes in the expression of this protein. Taken together, these results support the potential use of Hsp70 as an early biomarker of cellular stress and may contribute to the development of more effective radiological protection and safety strategies for low-dose radiation exposures.

Keywords

Hsp70, Cellular Stress, Gamma Radiation, Ionizing Radiation, HaCaT Cells

1. Introduction

Biological organisms are increasingly exposed to low or high doses of gamma radiation, particularly humans, through clinical diagnostic procedures, the application of nuclear analytical techniques, and radiological accidents. Low levels of gamma radiation pose a stochastic health risk, defined as the probability of inducing genetic damage and cancer, whereas high doses produce deterministic effects, meaning the severity of acute tissue damage that will occur with certainty. Acute exposure to high doses rapidly leads to significant injury, and the long-term effects of exposure include health problems ranging from fibrosis to cancer [1] [2].

The interaction of gamma rays with cells and the damage they cause is a function of probability [3] [4]. Since cellular repair usually occurs, damage to living tissue is not necessarily permanent, considering that energy deposition within a cell occurs very rapidly, approximately within 10^{-18} seconds, and randomly. These interactions and the resulting cellular damage may affect organs and the organism as a whole; however, it should be noted that there is no single specific type of cellular damage uniquely associated with radiation. The action of radiation on the cell can be classified as either direct or indirect, depending on the medium in which energy transfer occurs [5] [6]. In direct interactions, the entire cell is affected because its macromolecules (proteins or DNA) are damaged to an extent that results in cell death or DNA mutations [7]. One of the main causes of this type of cell death is DNA double-strand breaks (DSBs), since if they are not repaired or are repaired incorrectly, DSBs can lead to chromosomal aberrations and human diseases, including cancer [5] [8]. Indirect action occurs when radiation energy is deposited in the cell and interacts with water rather than with macromolecules [9]. Since most living organisms are composed largely of water, the probability of an event occurring in a water molecule is very high. This interaction causes radiolysis of the water molecule, resulting in the formation of highly reactive free radicals (reactive oxygen species and reactive nitrogen species) that are potentially toxic to the cell [5].

These biological effects or damages in molecules and cellular structures activate intracellular mechanisms that attempt to maintain homeostasis and cell survival; one such mechanism involves the expression of heat shock protein 70 (Hsp70) [10]-[14]. In 1962, Ritossa discovered a group of proteins known as heat shock proteins (Hsps) [15]. Most function as molecular chaperones, possessing the ability to bind to other proteins and mediate their folding, transport, and interactions with other proteins. They comprise a family of highly conserved proteins classified according to their molecular weight. Their expression is induced in both prokaryotic and eukaryotic cells in response to various physiological and environmental

stressors, such as heat shock, inflammation, infections, environmental contaminants, ultraviolet radiation, low-frequency radiation, and gamma radiation fields. They are also expressed in malignant neoplasms, contributing to tumor growth, differentiation, invasion, and metastasis; in tumor cells, they play an important role in tumorigenesis by inhibiting apoptosis and senescence [16].

The induction of Hsps in response to stress protects against the initial insult and generates a state of stress resistance within the cell. This protective role has been attributed to several functional properties, including the prevention of protein aggregation and the promotion of protein disaggregation through the catalysis of refolding of damaged or denatured proteins [17]. Therefore, heat shock proteins are essential for survival under adverse environmental conditions [18].

Hsp70 is the most evolutionarily conserved member of this family, existing in constitutive and inducible forms and being localized in different intracellular organelles. Under normal conditions, its primary function is to mediate the folding and transport of newly synthesized proteins. Additionally, it restores proteome homeostasis by assisting in the refolding or elimination of denatured proteins through its ATPase activity. During cellular stress processes that result in protein damage or abnormal folding, Hsp70 processes these molecules by either refolding or degrading them. It has been demonstrated that following heat shock, Hsp70 accumulates within the nucleolus, the cellular structure responsible for ribosome production. It also provides protection to the centrosome and intermediate filaments [19].

In its constitutive form, Hsp70 is expressed at low levels in healthy, unstressed cells, whereas its heat-inducible form is rapidly expressed during cellular stress and throughout cell-cycle progression. This process begins with signaling cascades involving extracellular signal-regulated mitogen-activated protein kinase (MAPK/ERK) and stress-activated protein kinase (SAPK), which activate heat shock factors [20].

Several recent studies have demonstrated that Hsp70 modulates the progression of apoptosis induced by a wide variety of stimuli [17]. During apoptotic signaling, high Hsp70 expression interferes with multiple steps, including cytochrome c release, caspase activation, accumulation of misfolded proteins, generation of reactive oxygen species, and DNA fragmentation. Inhibition of Hsp70 increases cellular sensitivity to apoptosis. Therefore, Hsp70 directly or indirectly modulates both intrinsic and extrinsic apoptotic pathways [21].

The skin is the first biological barrier exposed to radiation, and its outermost layer is composed of cells known as keratinocytes. The biological model used in this study consisted of HaCaT cells, an immortalized human keratinocyte cell line [22] [23], which were exposed to low gamma-radiation fields to subsequently evaluate the potential damage generated by this factor.

One of the most extensively investigated biological mechanisms used by both prokaryotic and eukaryotic cells to cope with potential damage generated by gamma-radiation exposure is the activation of heat shock protein (Hsp) expression [19].

Among this family of proteins, Hsp70 is considered a bioindicator used to assess cellular damage resulting from exposure to ionizing radiation [11] [13] [14].

Considering the above, the objective of this study was to evaluate changes in Hsp70 protein expression as a biomarker of cellular stress in HaCaT cells exposed to low doses of gamma radiation. This work contributes to a deeper understanding of the biological effects triggered by exposure to low-dose gamma radiation.

2. Materials and Methods

2.1. Study Model

Human keratinocytes from the HaCaT cell line were used as the experimental model.

2.2. Cell Culture

HaCaT cells were obtained from the American Type Culture Collection and cultured at 36.5˚C in disposable plastic culture flasks (Costar 3151, Cambridge, MA) under a controlled atmosphere of 95% air and 5% carbon dioxide (SteriCult 200, Forma Scientific, Ohio). Cells were maintained in 20 mL of Dulbecco's Modified Eagle Medium (cDMEM; D1152, Sigma Chemical Co., St. Louis, MO) supplemented with penicillin (100 U/mL), streptomycin (100 μg/mL; In Vitro, Mexico), insulin (0.08 U/mL; Eli Lilly, Mexico), and 10% certified fetal bovine serum (FBS) (Gibco BRL, 16000-028, Grand Island, NY).

For cell detachment, trypsin combined with EDTA (In Vitro, Mexico) was used to promote cell dissociation through calcium chelation and disruption of substrate adhesion interactions. Cells were subsequently seeded in polystyrene culture dishes (Costar) until reaching a confluence of 5×10^6 cells/mL, using a total of 15 culture dishes.

Of the total dishes, three were exposed to 40˚C for 40 minutes and used as positive controls to induce Hsp70 expression; three were maintained without heat or radiation exposure and used as negative controls; and the remaining nine were exposed to a ^{137}Cs radioactive source. Overall, the experimental design included three biological replicates for each exposure condition.

2.3. HaCaT Cells Exposed to Gamma Radiation

The samples were irradiated by placing each cell culture (contained in a Petri dish) on a plastic platform positioned 10 cm from a ^{137}Cs source emitting 0.662 MeV gamma rays, located at the Academic Unit of Nuclear Studies (UAEN), Autonomous University of Zacatecas (UAZ). The radioactive source was positioned at the center of the experimental setup (**Figure 1**), and the experimental samples were arranged around it at a distance of 10 cm.

All procedures were carried out inside an incubator to maintain the temperature at 37˚C, and the exposure process was performed in accordance with the regulatory radiological protection measures established for sealed radioactive sources. During exposure to the ^{137}Cs source, the absorbed doses were calculated.

Following irradiation, the cultures were incubated for 45 minutes at 37˚C to allow the cells to activate their homeostatic mechanisms involved in nuclear and protein repair.

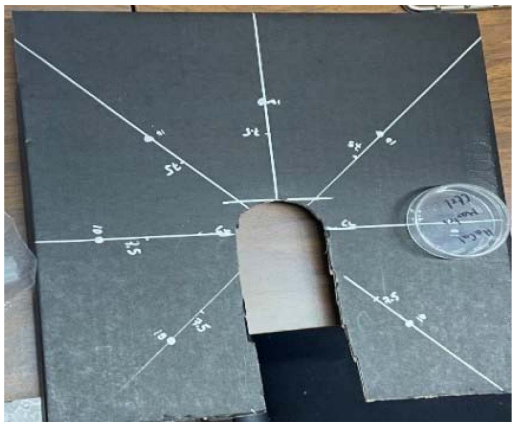

Figure 1. Experimental setup used for irradiation of HaCaT cells with gamma radiation from a ^{137}Cs source.

2.4. Absorbed Dose Analysis Using TLD-100 Dosimeters (Calibration)

Thermoluminescent dosimeters (TLDs) type 100 (lithium fluoride, natural Li), Harshaw ribbon-type dosimeters measuring 3.2 × 3.2 × 0.89 mm, were used. TLD-100 dosimeters are widely employed for X-ray and gamma-ray dosimetry in the range of 10 pGy to 10 Gy. Prior to use, the TLDs were annealed at 400˚C for 1 hour to erase any residual signal.

During exposure, groups of four TLDs were placed in Eppendorf tubes. The TLD-100 groups were exposed for 0, 60, 90, and 150 seconds at a distance of 10 cm from the ^{137}Cs source and the samples. One group of TLD-100 dosimeters was used to measure background radiation (0 exposures).

The same procedure was repeated using a RaySafe ThinX RAD solid-state monitor, which was activated during sample exposure to the ^{137}Cs source. The same number of exposure times used for the thermoluminescent dosimeters was employed with the RaySafe equipment.

2.5. Absorbed Dose Calculation

During gamma-ray exposure, TLDs were used to calculate the absorbed dose. Their response was measured using a Harshaw 3500 reader by heating the dosimeters in a nitrogen atmosphere from 50˚C to 350˚C at a rate of 10˚C/s.

The responses from each exposed TLD group were averaged and corrected using the mean response of the TLDs employed for background measurements. These values were correlated with the readings obtained from the RaySafe monitor, resulting in a strong correlation ($r^2 = 0.9987$) between the TLD response, expressed in nanocoulombs, and the number of exposures of cells subjected to the ^{137}Cs source.

2.6. Cell Lysis

Following irradiation, cells were washed with 3 mL of cold phosphate buffer (pH 7.2; Gibco BRL, Grand Island, NY, USA, 21300-58) and subsequently lysed with 500 µL of lysis buffer containing 1% Triton X-100, 140 mM NaCl, 1 mM EDTA, 10 mM Tris-HCl (pH 7.6), and a protease inhibitor cocktail (11697498001, Roche Diagnostics).

Using a cell culture scraper, the bottom surface of each Petri dish was scraped to obtain the cellular extract. Cell extracts were collected, homogenized, and centrifuged at 14,000 rpm for 10 min at 4˚C to obtain the soluble protein fraction present in the supernatants.

2.7. Protein Quantification

Protein quantification was performed using the soluble fraction obtained after cell lysis according to the method described by Bradford (1976) [24].

2.8. Determination of Hsp70 and Tubulin Expression by SDS-PAGE and Western Blot-ECL

Hsp70 and Tubulin (constitutive control) protein expression was analyzed for each experimental unit. Twenty micrograms (20 µg) of total protein were separated on 7.5% SDS-polyacrylamide gels according to the method described by Laemmli (1970) [25].

Following electrophoresis, proteins contained in the polyacrylamide gels were transferred onto nitrocellulose membranes (Hybond-C RPN 303 C, Amersham, Little Chalfont, Buckinghamshire) using the method described by Towbin *et al.* (1979) [26].

2.9. Immunodetection

The proteins retained on the nitrocellulose membranes were subjected to immunodetection. Non-specific binding sites were blocked overnight at 4˚C with a 3% casein-PBS solution.

After blocking, the membranes were incubated with the primary monoclonal antibody against Hsp70 (SC-24, Santa Cruz Biotechnology®, USA) and anti-β Tubulin (T-5293, SigmaAldrich®, USA) at a dilution of 1:1000 for 1 hour at room temperature under gentle agitation (25 rpm). Membranes were then washed seven times alternately with PBS and PBS-Tween solutions (5 min per wash, 45 rpm agitation).

Subsequently, the peroxidase-conjugated secondary antibody against mouse IgG (anti-mouse IgG-HRP conjugate, SC-2005, Lot F0412, Santa Cruz Biotechnology®, USA) was added and incubated for 1 hour, followed by eight additional washes.

For signal detection, an enhanced chemiluminescence (ECL) solution (GERPN-2232-ECL™ Prime Western Blotting System) was applied to the membranes. This reagent interacted with the HRP-conjugated antibody and generated a photolu-

minescent signal. Signal intensity was analyzed using the Image Lab imaging system (Bio-Rad® Laboratories) to perform optical densitometric analysis and determine the level of Hsp70 and Tubulin (constitutive control) protein expression [27].

2.10. Statistical Analysis

Three biological replicates were performed for each gamma-irradiation condition and control group. Statistical analyses were conducted using Microsoft Excel® and GraphPad Prism version 8.0.1.

Hsp70 expression was quantified by densitometric analysis of the protein bands obtained from Western blots and expressed as arbitrary optical density units. Calculations were performed using Image Lab software version 2.0.1 build 18 (Bio-Rad® Laboratories, Copyright © 2009).

Differences among experimental groups were evaluated using one-way analysis of variance (ANOVA), followed by Dunnett's post hoc test to compare each experimental condition with the control group. Results were graphically represented using GraphPad Prism and expressed as mean ± standard error of the mean (SEM). A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Cell Culture, Irradiation, and Absorbed Doses

Confluent HaCaT cell cultures were irradiated using a ^{137}Cs source that emits gamma radiation. The irradiation periods were 1, 1.5, and 2.5 minutes. During this process, the absorbed doses received by the cell cultures were calculated.

Thermoluminescent dosimeters (TLDs) were used, and the average response of each dosimeter group was determined and corrected using the mean response of the TLDs employed for background measurements. The absorbed doses corresponded to 73.7 μGy after 1 minute of exposure, 110.5 μGy after 1.5 minutes, and 184.3 μGy after 2.5 minutes (Table 1).

Table 1. Absorbed dose in each of the samples as a function of exposure time.

Sample	Irradiation time	Dose (μGy)
1	Control, not irradiated	0.0
2	Exposure to 40˚C for 40 minutes	0.0
3	1 minute	73.5
4	1.5 minutes	110.5
5	2.5 minutes	184.3

3.2. Hsp70 Protein Expression

Following the irradiation of HaCaT cells, Hsp70 protein expression was evaluated in each experimental unit using Western blot-ECL analysis (Figure 2). Densitometric analysis of the Hsp70 and Tubulin bands obtained was subsequently per-

formed.

The mean optical densities obtained from the immunodetections showed significant differences compared with the basal control. As expected, the positive control subjected to heat treatment at 40˚C exhibited the highest Hsp70 expression. This was followed by the 1-minute exposure group corresponding to a dose of 73.7 μGy, then the 1.5-minute exposure group receiving 110.5 μGy, and finally the 2.5-minute exposure group receiving 184.3 μGy.

Analysis of the optical density values revealed an increase in Hsp70 expression at 73.7 μGy. Subsequently, as the radiation dose increased, Hsp70 expression progressively decreased (Figure 3).

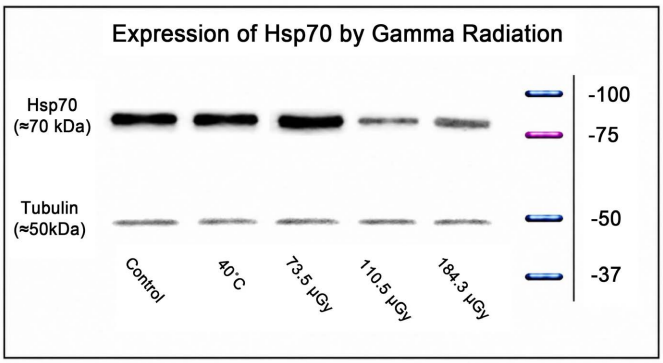

Figure 2. Expression of Hsp70 and Tubulin in HaCaT cells exposed to low doses of gamma radiation. Western Blot-ECL technique.

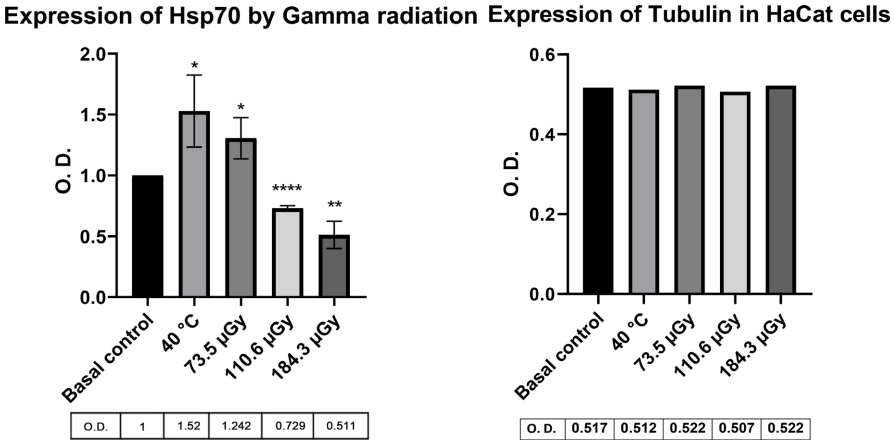

Figure 3. Optical density measurements of Hsp70 expression (±S.E.) and Tubulin in HaCaT cells exposed to low doses of gamma radiation (73.7 μGy, 110.5 μGy and 184.3 μGy).

4. Discussion

In the present study, the expression of a biomarker of cellular stress induced by low doses of gamma radiation was evaluated. The results showed the presence of Hsp70 protein in the control samples analyzed. These findings are consistent with previous studies demonstrating that Hsp70 is constitutively and ubiquitously ex-

pressed in eukaryotic cells, where it plays an essential role in maintaining cellular function [12]-[14] [28]-[31].

Likewise, analysis of Hsp70 expression in cells exposed to low doses of gamma radiation revealed an increase compared with the control group, with the first dose (73.7 μGy) producing the most significant quantitative increase ($p < 0.05$). It is noteworthy that the heat-induced expression of Hsp70 was very similar to that observed during the first minute of exposure to gamma radiation. These findings are consistent with reports from different experimental models exposed to gamma rays. For example, irradiated C3H 10T1/2 and NIH3T3 mouse cells exhibited increased Hsp70 expression following irradiation [32]. Similar observations have been reported in cells recovered from the salivary glands of one of the most radioresistant organisms known, Chironomus ramosus [33]. In human leukocytes exposed to low gamma-radiation fields, Hsp70 overexpression has also been documented [14].

In a study reported by Murakami *et al.* [34], the expression of several proteins involved in apoptosis was analyzed in irradiated cells, leading to the conclusion that Hsp70 plays an important role in cellular recovery under stress conditions. Furthermore, low doses of gamma radiation have been shown to accelerate the differentiation process in keratinocytes (HaCaT cells), accompanied by the expression of involving and p21 proteins, both associated with cellular differentiation [35].

It is also known that Hsp70 expression promotes adaptive responses to various stressors, including heat, ionizing radiation, and reactive oxygen species. Radioadaptive effects induced by low doses of gamma radiation have been demonstrated in acinar cells of the parotid salivary gland of Rattus norvegicus [36]. In myeloid leukemia cells, improvements in colony-forming capacity and increased Hsp70 mRNA expression have been reported, although no changes in Hsp70 protein levels were observed [37]. Collectively, these findings suggest that low-dose radiation-induced cellular stress modulates Hsp70 expression and may contribute to the development of radioadaptive responses. However, although radioadaptation may occur, it is also important to consider that repeated exposure to low-dose radiation fields may generate stochastic risks due to cumulative dose effects.

The analysis of Hsp70 expression also reflects the degree of stress imposed by the low-intensity gamma-radiation field to which keratinocytes are exposed. From a dosimetric perspective, it is important to consider any specific quantity or unit of natural or artificial radiation to which the human body is exposed, since the present study demonstrates that even low-dose exposures can elicit a cellular stress response, evidenced by increased Hsp70 expression. These observations highlight the importance of establishing more precise radiation-protection standards and occupational exposure limits for ionizing radiation [38] [39].

Taken together, the results of the present study suggest that exposure to low doses of gamma radiation induces a cellular stress response, as evidenced by increased Hsp70 expression in HaCaT keratinocytes. However, these findings should be in-

terpreted with caution and do not allow a direct conclusion that HaCaT cells exhibit radiosensitivity or that the low doses evaluated necessarily lead to progressive accumulation of cellular damage over time. This study did not assess direct indicators of biological injury, such as DNA damage, cell survival, proliferative capacity, apoptosis, senescence, or mechanisms of sustained cellular adaptation.

Therefore, the observed overexpression of Hsp70 should primarily be regarded as a marker of stress-response activation under the experimental conditions evaluated. Future studies incorporating genotoxicity biomarkers, functional survival assays, and repeated-exposure or longitudinal assessments will be necessary to determine whether this response is associated with radioadaptive processes, maintenance of cellular homeostasis, or, alternatively, cumulative effects resulting from exposure to low doses of ionizing radiation.

5. Conclusion

Exposure of HaCaT cells to low doses of gamma radiation from a ^{137}Cs source induced cellular stress, as evidenced by the expression of the Hsp70 biomarker. The data generated suggest that the early expression of Hsp70 may serve as valuable information for the implementation of safer radiological protection measures, not only in the context of high-dose radiation exposure but also for low-dose exposures. This is particularly relevant because the effects of low-dose radiation may accumulate over time, potentially leading to significant biological alterations in the future, especially among occupationally exposed personnel.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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