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GADD45A gene expression applied to biodosimetry for radiological accidents

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1. Introduction

Electromagnetic radiation (gamma and X rays) are defined as high energy waves, capable of causing a series of ionizations, which, when interacting with matter, transfer energy to atoms and molecules, causing intracellular physicochemical disturbances, and post-exposure biological effect [1].
These consequences can vary from a small molecular modification, without great relevance, death of one or more cells, organic dysfunctions and even the death of the exposed individual. These effects occur according to the sensitivity of living organisms to ionizing radiation (IR), varying depending on the type of radiation, the absorbed dose and the area of the organism that was affected [2].
IR induces changes in the expression of some specific genes, which can be used as new molecular biomarkers to estimate the exposure dose of cells [3].
Human health effects at low doses of radiation are expected to be small but the uncertainties associated with current best estimates of risks are considerable. Nevertheless, exposures at low doses are of primary interest for setting standards to protect individuals against the adverse effects of ionizing radiation. The main health effect associated with exposure to low doses of ionizing radiation is cancer [4].
The analysis of gene expression profiles in individuals with different radiation toxicity will probably assistance to identify relevant candidate genes to predict these adverse side effects. In this sense, a better knowledge of these factors should lead to the development of in vitro predictive assays to identify radiosensitive individuals and, as a result, to establish individualized radiation therapy protocols [5].
Rapid and accurate evaluation of exposure dose plays an important role in early triage, diagnosis and medical treatment of the victims during emergency response efforts in nuclear and radiological accidents [6].

2. Methodology

The methodological strategy addressed was a systematic literature review with purpose of contributing to knowledge, developed in six stages: (1) elaboration of the leading question; (2) literature search; (3) data extraction; (4) evaluation of the studies found; (5) analysis and synthesis of the results and (6) finally the presentation of the final work.

The following research question "How *GADD45A* expressed under IR dose of 4, 5, 6 and 8 Gy?" The search was carried out between April and June 2021 on databases: Library Online (SciELO) and Latin American and Caribbean Literature on Health Sciences Information (LILACS). It was considered as

inclusion criteria articles that answer the guiding question in Portuguese and English in a timeless manner due to the scarcity of theme. The search was carried out by crossing the following Health Sciences Descriptors (DeCS): gamma rays, *GADD45A* gene and absorbed dose of 4, 5, 6, 8 Gy.

Eleven titles and the abstract articles were read, evaluating their adequacy to the inclusion and exclusion criteria. Inclusion criteria were: ionizing radiation, *GADD45* and *GADD45A* gene, doses between 4 and 8 Gy, biomarker, humans, mice, gamma rays and x-rays. Exclusion criteria were: doses lower than 4 Gy or higher than 8 Gy, ultraviolet radiation and gene inactivation. After that, the results were obtained containing the objective, method, result and conclusion of each author. Title of the article, authors and year of publication were found in the references and the discussion of results organized in narrative form, describing common findings among the studies. Due to the scarcity in the literature on the *GADD45A* gene induced by IR at 4, 5, 6 and 8 Gy, five articles were selected between the years 2004 to 2011 that meet the research objective.

3. Results and Discussion

When DNA is damaged by radiation, the expression of *GADD45* is increased. The biological function of *GADD45* closely related to radiation damage from DNA makes it a focus of research in molecular radiation biology and is best suited for development as a molecular biological dosimeter for people exposed to nuclear accidents. The expression of the *GADD45* and *p21* genes in human peripheral blood lymphocytes is dose-dependent when exposed to medium and low doses and is exponentially correlated in the 1-5 Gy radiation dose range. In 24 hours after X-ray irradiation, *GADD45* gene expression in human peripheral blood lymphocytes increased with increasing radiation dose [3].

To provide accurate detection of exposures to radioisotope, Joiner *et al.* [7], provided data from human blood leukocytes irradiated *in vitro* at doses between 0 and 10 Gy. *GADD45A* also showed substantial increases in expression because of exposure, maintaining its maximum expression out to 24 h. While not as large an increase as observed with these other genes, *GADD45A* showed a 6-fold increase in expression that is coupled with a relatively stable expression with time over the 48 h examined. In that study, *GADD45A* was also identified among the four genes from our initial sets of data as having the most robust responses, and that quantitative PCR can be used to accurately analyze the expression of a panel of genes induced by exposure to radiation doses of 0.5–10 Gy.

Li *et al*. [6], used the peripheral blood of mice and irradiated at doses of 4, 6 and 8 Gy with gamma rays. Table I shows highlights the expression values of the *GADD45A* gene found at 24 and 48 hours. *GADD45A* is largely involved in DNA repair or cell cycle regulation associated with DNA repair. *GADD45A* expression was up-regulated approximately 2–3-fold only at the 48 h post-irradiation time-point within all exposure dose ranges, and no significant changes were found at other time-points. Recent reports have shown that gene expression signatures induced by IR are specific, durable and accurate in prediction of exposure doses in both mice and humans.

Table I: Relative Expression Values Of *GADD45A*. Values in parentheses represent relative expression levels compared to the control group [6].

Time (hours)	4 Gy	6 Gy	8 Gy
24	(2.01)	(1.70)	(1.38)
48	(2.25)	(1.89)	(1.57)

Turtoi *et al*.[8], aimed at identification of specific proteins and genes as candidate biomarkers for the development of a novel biodosimeter. Human peripheral blood lymphocytes were exposed to

clinically relevant doses (1, 2 and 4 Gy) of radioisotope *ex-vivo*. *GADD45A*, is a gene whose expression is reported to increase following treatment with DNA damaging agents, including IR. In addition, concluded to have value as a potential biodosimetric marker of acute exposure to clinical levels of IR.

Zhang *et al.*[9], investigated the expression of exposed *GADD45A* at up to 10 Gy in human tongue squamous cell carcinoma cell lines. They stated that after 24 h, IR induced up-regulation of gene mRNA and increased apoptosis of Tca8113 cells compared to baseline levels. These results implied that the induction of *GADD45A* by IR in Tca8113 cells was specific and long lasting. *GADD45A* over-expression could increase the radiosensitivity of Tca8113 cells. Therefore, the high level *GADD45A* expression induced by IR might contribute to apoptosis of oral cancer cells. The gene therapy targeting *GADD45A* in tumor cells could have important implications for the development of novel strategies in radiotherapy.

Therefore, the use of real-time quantitative fluorescence RT-PCR technology to detect changes in the expression of specific target genes as a molecular biological dosimeter can compensate for the shortcomings of commonly used detection methods such as the CB micronucleus method and chromosomal aberration method of analysis for more time, complicated operation, among others, in good application perspectives [3].

4. Conclusions

From the assessments made in this research section, it can be ascertained that the *GADD45A* gene was up-regulated, showing large and persistent responses after exposure IR.
Therefore, the gene expression of *GADD45A* has useful and potential values for application as biomarker systems for human exposure to IR.
The definition of the dose-response calibration curve using gene expression in the Laboratory of Biological Dosimetry (LDB) of the Regional Center for Nuclear Sciences of the Northeast, will bring another reliable method of evaluating absorbed dose to be used in the provision of biological dosimetry services, and it is expected to apply it in future research with gene expression.

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