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Gamma radiation in association with moderate training reduce the effects of asthma in mice

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ABSTRACT

Ionizing radiation has been used for the treatment of various diseases for over a century, including chronic inflammatory diseases and cancer. The relationship between radiation and asthma are contradictory; while some authors associate radiation exposure with the development of the disease, others report an attenuation of asthma in response to radiation. Asthma is a chronic inflammatory disease and represents a worldwide public health problem with a high number of deaths. In the present study, we have conducted an investigation of the effects of radiation with 10 doses of 0.5Gy of Co^{60} and/or moderate lung training of mice with ovalbumin-induced asthma. For this purpose, we have compared six experimental groups of mice: 1-Saline (non-irradiated, sedentary and saline); 2- IR (irradiated and sedentary); 3- OVA (non-irradiated, sedentary and asthma); 4- OVA+IR (irradiated, asthma and sedentary); 5- OVA+IR+MT (irradiated, asthma and moderate training -TM); 6- OVA+MT (asthma and moderate training). The results indicate that radiation and moderate training reduced inflammatory parameters significantly both in BALF cells and in mucus production, thus attenuating the asthma symptoms.

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1. INTRODUCTION

Radiation therapy is one of the most important treatments for cancer, having been applied to more than 50% of patients, and clinically for over 100 years [1]. Radiation therapy uses radiation to kill cancer cells. It can be used before or after surgery and its mechanism of action is linked to its cytocidal effects, mainly through damage to the DNA of tumor cells [2]. Recent studies have suggested that radiotherapy may also generate antitumor immunity in the treatment of cancer, and when used as an immune system stimulating agent, may elicit immunological responses to negative or positive modulation [3, 4, 5, 6, 7].

The response of the tissues and the immune system to ionizing radiation depends on factors such as: radiation quality, dose and total exposure time, oxygen concentration and tissue water, in addition to factors such as absence or presence of diseases associated with the target tissue [2, 5, 8]. While high doses of radiation have been reported to have proinflammatory properties, studies have shown that exposure to low-dose radiation promotes anti-inflammatory effects [9, 10, 11]. Modulatory effects of low radiation doses have been confirmed in the treatment of various human diseases such as: skin infections, arthritis, pneumonia and asthma [12, 13, 14].

The relationship between the effects of ionizing radiation and asthma is contradictory. While studies associate radiotherapy with the development and worsening of asthma symptoms [15], other studies report an attenuation of the disease by exposure to radiation [16]. Asthma is a heterogeneous disease, usually characterized by chronic inflammation of the air passages where many cells of the innate and adaptive immune system act in conjunction with epithelial cells, causing remodeling of the air passage walls, air passage hyper reactivity and mucus hyper secretion [18,19]. This pathology has genetic and environmental determinants and is frequently associated with the genetic predisposition presented by some individuals to develop responses to common aeroallergens mediated by Immunoglobulin E (IgE) [20, 21, 22]. According to the World Health Organization, 235 million people worldwide are affected by this disease, reaching 250,000 deaths a year. The main cause of death from asphyxiation of asthma is due to obstruction of the intraluminal air passages by mucus buffers [23, 24].

In recent years, a growing number of studies have shown that regular physical exercise (depending on type, intensity, frequency and duration) can provide important health benefits [25]. Physical exercise provides a change in the state of homeostasis in the organism, leading to the reorganization of the response of several systems, including the immune system, thus causing an important modulating effect on the function of its cells. Regular physical exercise is associated with protecting the body from infectious diseases, as well as implications for prevention and treatment of various diseases, including diabetes, primary hypertension, cancer, cardiovascular and pulmonary diseases, including asthma [26, 27, 28, 29, 30].

Therefore, in the present work we have evaluated the relationship of the effects caused by 10 fractionated doses of 0.5Gy of Co^{60} on the lungs of BALB/c mice after the challenge with ovalbumin in association with moderate physical exercise seeking to clarify certain questions about lungs to asthmatic patients in need of such treatment. In addition, several studies both with animal models and humans, affirm that moderate physical exercise can minimize the symptoms of asthma. However, research with moderate exercise in association with gamma radiation is non-existent in literature.

2. MATERIALS AND METHODS

2.1. Animal testing

We have used thirty female mice (n=30), all 8-12 weeks old and from the BALB/c strain. These were kept at the UFMG's Federal University of Minas Gerais (UFMG), under preparation and rationing standards according to the Ethics Committee on Animal Experimentation (CETEA/UFMG No. 167/2010). A combination of 10% ketamine hydrochloride (100mg/kg) and 2% xylazine hydrochloride (50mg.kg^{-1}) diluted in 1% sterile saline solution were used both in OVA immunization and in sacrifice procedures. Proportions (v/v/v) 1 ketamine/1 xylazine/4 saline. Anesthesia time was set to 60-100 minutes. On the twenty-seventh day, euthanasia was performed to extract BALF and lungs.

The animals were divided into 6 experimental groups (n=6), named, (1) Saline: non-irradiated, sedentary and exposed to aerosol saline solution; (2) IR: irradiated, submitted to 10 doses of 0.5Gy

of Co^{60} and sedentary; (3) OVA: non-irradiated, sedentary and induced to experimental asthma (immunization and challenge with ovalbumin solution); (4) OVA+IR: irradiated, induced to experimental and sedentary asthma; (5) OVA+IR+MT: irradiated, induced to experimental asthma and moderate training; (6) OVA+MT induced to experimental asthma and moderate training.

2.2. Irradiation

Irradiation of the animals was performed using the Gamma-Cell irradiator from the Center for the Development of Nuclear Techniques (CDTN). This irradiator has a source for Co^{60} (E=1.25 MeV) of initial activity of 13.98 $Gy.h^{-1}$ and updated dose rate of 9.347 $Gy.h^{-1}$ calculated from the equation $D=Do.e^{-\lambda t}$. The animals underwent full body irradiation every other day, with 10 fractionated doses of 0.5Gy for a time calculated by means of the dose/day rate of 3 minutes and 13 seconds.

2.3. Sensitization with ovalbumin and challenge

The experimental model of asthma used in mice was induced by sensitization with ovalbumin (OVA, Grade V; Sigma, St. Louis, MO). Four experimental groups have been sensitized with ovalbumin, namely groups C: (OVA), D: (OVA+IR), E: (OVA+IR) and F (OVA+MT). All animals from these groups were immunized on day 1 via subcutaneous injection containing 0.2ml of saline solution containing 1mg of $Al(OH)_3$ (Sigma) and 10μg of OVA. We have performed the second immunization procedure on day 14, via subcutaneous injection but with 10μg of OVA in the absence of aluminum hydroxide. From the 21st on to the 26th day, the animals were challenged with aerosol by means of a nebulizer (1% OVA saline solution) and no longer subjected to irradiation and to the training. On day 1, we have submitted groups A: Saline and B: IR to subcutaneous injection with 0.2ml of saline solution containing 1 mg of aluminum hydroxide; on the 14th day, they were submitted to the second immunization via subcutaneous saline solution only. The aerosol challenge of these two groups happened in parallel to the other groups from the 21st to the 26th day, however these animals were nebulized with saline aerosol [31].

2.4. Moderate Training (MT)

Groups: E (OVA+IR+MT) and F (OVA+MT) were submitted to Moderate Training according to the protocol of Meneguello and Rosa [32]. We have used individual pools of 5 liters each, equipped with a heating system (30°C). The groups were initially adapted to the liquid medium through 05 sessions performed during the first week: a 15 min session on the 1st day, 20 min on the 2nd day, 25 min on the 3rd day, 30 min on the 4th day and 40 min on the 5th day. After the adaptation period, in the second week, we have initiated the moderate training MT, initially composed of two sessions of 40 min each, two sessions of 50 min, and one of 60 min. During the 2nd week, the first day of irradiation and immunization of the animals started in association with MT. In the following three weeks, the 05 sessions were all performed with a duration of 60 min. At this time, the animals would swim with a weight equivalent to 5% of their body weight attached to the tail to avoid flotation.

2.5. Collection of bronchoalveolar fluid (BALF) and serum

After peripheral blood collection, the animals were submitted to tracheostomy and a cannula was inserted into their trachea to collect the bronchoalveolar fluid (BALF). One mL of sterile, ice-cold PBS was injected into the lungs of the animals via the trachea. Immediately after the injection, the wash was recovered, returning 800μL of fluid and then stored on ice. The BALF was centrifuged at 1800rpm for 10 minutes at 4°C, and the supernatant was stored at approximately -4°C. At the time of counting, the cell buttons were resuspended with 1mL of saline solution and 20μL was collected for total cell count using the Neubauer chamber under an OLYMPUS B12 microscope with a 40X objective lens.

2.6. Histological Analysis and cell counting

After blood and BALF collection, the animals were sacrificed by anesthetic overdose for extraction of the lungs. This was hyper fused with 5ml of saline solution to remove all blood, aiming to analyze structures through different procedures and staining techniques: Toluidine Blue for the counting of mast cells (n=5slide/group) and visualized by means of a light microscope (BX40, Leica DMI 3000B, Leica); Alcian Blue for identification of goblet cells in which the images (n=8slide/group) were captured under light microscopy (Leica MDI 3000B) and finally

Hematoxylin and eosin (HE) for the counting of eosinophil in which the slides (n=5slide/group) were examined under an optical microscope (Olympus B201) for the analysis of structures and lung cells.

2.7. Statistical Analysis

Results are presented as averages ± SEM. Statistical analysis have been performed using Graph Pad Prism, version 6.0 (Graph Pad Software). The results were submitted to the Bartlett test to define the type of test (parametric or nonparametric). To conduct the analysis of the possible differences between the studied groups, we have used the analysis of variance (ANOVA), followed by the Tukey's test of multiple comparisons. The level of significance was considered when $P < 0.05$.

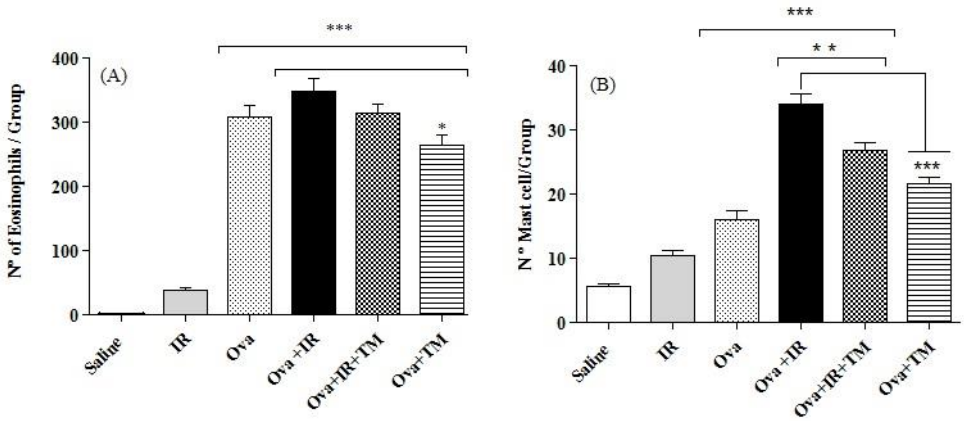
3. RESULTS AND DISCUSSION

3.1. Effects of Radiation and Moderate Training on the Migration of Eosinophils and Mast Cells in Pulmonary Tissue

The inflammatory response with eosinophil infiltrates is one of the main features of the asthma pathology. In order to analyze the effects of 10 doses of 0.5Gy gamma radiation on eosinophilia in the experimental asthma model, we have performed specific cell counting in the lungs and made a comparison between the experimental groups. Animals from the Saline and IR groups had a significantly lower number of cells ($p < 0.0001$) when compared to the other groups which had been sensitized and challenged with ovalbumin (Figure 1A). OVA+IR+MT and OVA+MT had a reduction in the number of esophagophiles compared to the groups irradiated and challenged with ovalbumin (OVA+IR) but this reduction was only statistically significant for the OVA+MT ($p > 0.05$) (Figure 1A). In order to verify the effects of radiation and moderate training on the number of mast cells in BALB/c lungs, we performed the histological analysis with 5μm lung cuts and Toluidine Blue staining. It is possible to observe, in the infiltrated mast cell counting in the alveolar parenchyma and in the peribronchial regions, that the Saline, IR and OVA groups had lower mast cell numbers than the other groups. Animals sensitized and challenged with ovalbumin and

submitted to radiation doses (OVA+IR) presented an expressive increase in the number of mast cells in comparison to IR and OVA groups ($p<0.0001$). Comparing the OVA+IR group with the OVA+IR+MT and OVA+MT groups, there was a significant reduction in the number of mast cells in the groups that underwent moderate training, ($p<0.01$) and ($p<0,0001$) respectively (Figure1B).

Figure 1: *(A) Quantification of eosinophils and (B) mast cells in lung tissue of mice submitted to different treatments*



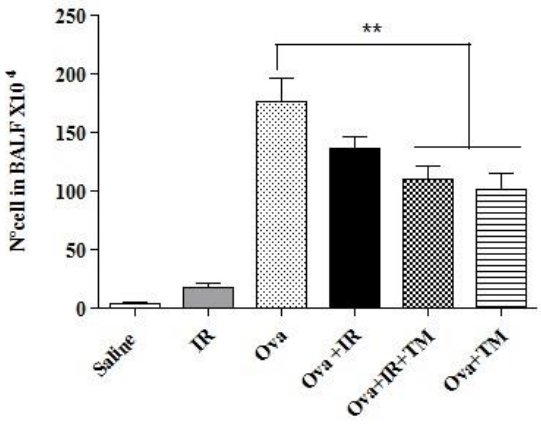
These figures show the results: Saline - exposed to saline solution and sedentary; IR: submitted to radiation and sedentary; OVA: non-irradiated, sedentary induced and challenge with ovalbumin solution; OVA+IR: irradiated, induced to experimental and sedentary asthma; OVA+IR+MT: irradiated, induced to experimental asthma and moderate training; OVA+MT induced asthma experimental and moderate training. Values represent the average of 5 animals in each group. Level of statistical significance of 5%, *($p <0.05$), **($p <0.01$) and ***($p <0.0001$).

3.2. Gamma Radiation and Moderate Training reduce Inflammation of Inflammatory Cells in Lung Tissue

The total number of inflammatory cells in the BALF is higher in OVA mice when compared to the other treatments. However, a significant reduction in the total number of these cells ($p <0.01$) occurs when compared to OVA+IR+MT and OVA+MT groups (Figure 2). The total cell results in

the BALF coincided with the pathological changes in the lung tissue of the animals submitted to the different treatments (Figure 3). Observed that the animals challenged only with Ovalbumin (Figure 3C) showed an intense inflammatory infiltrate, specifically in the peribronchial and perivascular region, when compared to animals administered with saline solution (Figure 3A) and animals that received only doses of IR radiation (Figure 3B). Animals challenged with OVA and exposed to radiation and/or submitted to MT also showed a significant reduction in inflammatory cell infiltrate (Figures 3E and F). These results demonstrated that radiation and/or moderate training and the association of both were able to reduce air passage inflammation in an animal model with experimental asthma induced by ovalbumin.

Figure 2: *Quantification of the BALF cells in mice submitted to different treatments*

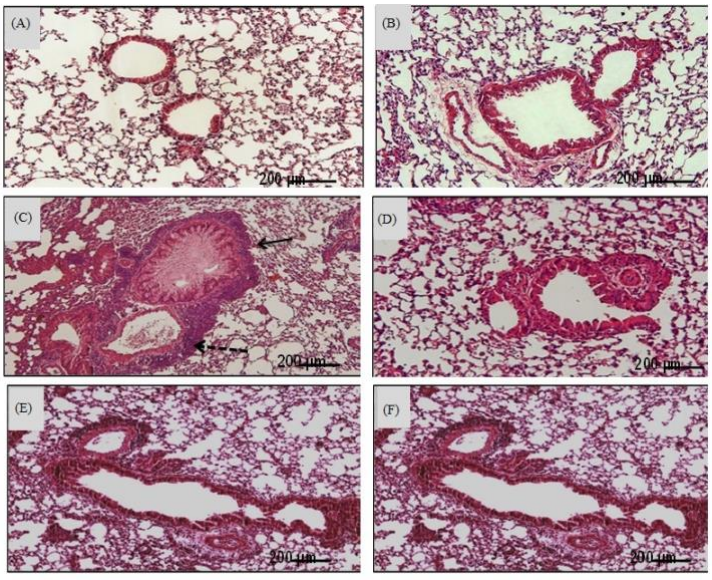


This figure shows the results: Saline - exposed to saline solution and sedentary; IR: submitted to radiation and sedentary; OVA: non-irradiated, sedentary induced and challenge with ovalbumin solution; OVA+IR: irradiated, induced to experimental and sedentary asthma; OVA+IR+MT: irradiated, induced to experimental asthma and moderate training; OVA+MT induced asthma experimental and moderate training. Values represent the average of 5 animals in each group. Statistical significance level of **($p < 0.01$). These images show part of the pulmonary parenchyma, the peribronchial region (full arrow) and perivascular (dotted arrow). (Microscope Leica, Bar 200μm).

3.3. Gamma Radiation and Moderate Training reduce Mucus Production by Goblet Cells in Lungs with Experimental Asthma.

Mucus is produced and secreted by goblet cells, which are specific to the epithelium and react as the first line of defense of the mucosa. The histology of the epithelium was analyzed in order to identify whether radiation and/or moderate training have an influence on goblet cell hyperplasia and mucus production (Figure 4) and mucus quantification was performed in the experimental groups (Figure 5). Histological analysis of the BALB/c pulmonary epithelium revealed that the animals in the Saline groups did not present mucus production, whereas in the irradiated group (IR) this production was rather discrete (Figures 4A and B). In the epithelium of animals challenged with ovalbumin, the goblet cell hyperplasia was intense (Figure 4C). Interestingly, the groups challenged with ovalbumin and subjected to irradiation and/or MT significantly reduced goblet cell hyperplasia when compared to the OVA group (Figures 4D, E and F).

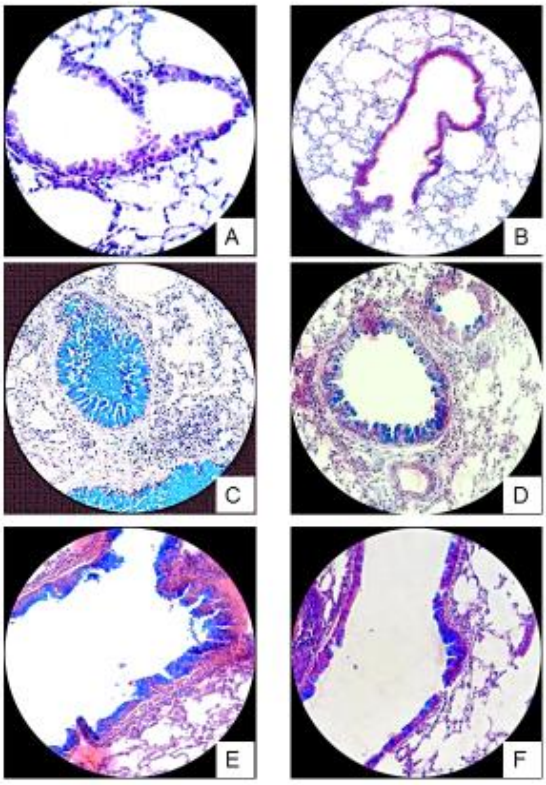
Figure 3*: Photomicrography of histological sections of the lungs of mice. 5µm sections stained with HE. In (A) Saline, (B) IR, (C) OVA, (D) OVA+IR, (E) OVA+IR+MT, (F) OVA+MT*



The results presented in Figure 4 corroborate with the quantification of mucus performed through the histological analysis of goblet cells (Figure 5). There was no mucus production in animals of the Saline groups and there was a discrete production in the irradiated group (IR).

However, when comparing the IR group with the other groups sensitized with ovavalbumin (OVA, OVA+IR, OVA+IR+MT and OVA+MT), we have observed a significant increase ($p < 0.0001$) in mucus production. Mucus production in the OVA+IR and OVA+IR+MT groups presented a significant reduction ($p < 0.05$) of about 40% when compared to the OVA group, whereas for the OVA+MT group, this reduction in mucus production was even higher, namely of about 78% ($p < 0.0001$) (Figure 5). These data suggest that radiation and/or moderate training either alone or in combination can reduce goblet cell hyperplasia and the production of lung mucus in BALB/c with experimental asthma.

Figure 4*: Photomicrography of histological sections of the BALB/c lung epithelium submitted to the treatments*



The images show the results of the analysis of goblet cells in 5μm-sections stained with Alcian Blue (A): Saline, (B): IR, (C): OVA, (D): OVA+IR, (E): OVA+IR+MT and (F): OVA+MT. Morphometry performed under light microscope (Leica MD3000). Bar 100μm.

Figure 5: *Quantification of mucus production.*

4. DISCUSSION

Were analyzed 08 epithelia/slide, small caliber (less than 2mm) and medium (between 4mm to 6mm), total=40/group, using a Leica microscope (DMI 3000B) with a 20X objective and then analyzed in Image J software. The histological analysis of the mucus was calculated by the percentage of filled mucus in the reticulum (area 126nm^2)/number of total epithelia counted in each section of tissue. Values represent the average of 5 animals in each group. Level of statistical significance of 5%, *($p < 0.05$), **($p < 0.01$) and ***($p < 0.0001$).

Asthma is a chronic respiratory disease that occurs in the air passages due to the combined responses of structural cells and immune cells after exposure to allergens, viruses or other

environmental challenges. These combinatorial responses result in the production of a series of inflammatory mediators that drive the disease process characterized by inflammation, hyper responsiveness and remodeling of the air passages in addition to hyper secretion of mucus [33].

This inflammatory process can be clearly observed in the present study. Animals sensitized and challenged with ovalbumin had increased eosinophil and mast cell infiltration when compared to saline and irradiated (Figure 1A and B). The number of eosinophils increased about tenfold among the groups challenged with OVA. The inflammatory response with an excessive presence of eosinophils is one of the main characteristics of the asthma pathology [34]. Cottin et al. [35] described the occurrence of eosinophilic pneumonia in patients after being submitted to radiotherapy. The interaction of the allergen with the organism leads to the recognition of antigens by antigen-presenting cells (APCs). These antigens, in turn trigger a series of responses in which activation of proinflammatory cytokines such as interleukins (IL) and tumor necrosis factor (TNF-α), as well as the activation of T helper 2 (Th2) cells and IgE synthesis. Th2 cells produce IL4 and IL13 which induce proliferation and differentiation of the eosinophils. Recently, it has been suggested that eosinophils may play a role in airway remodeling because they have the ability to synthesize and release fibrogenic cytokines. Together, these cytokines associated with eosinophils are responsible for the destructive potency of the tissues of this proinflammatory cell [36, 37, 38]. Kim et al. [39] reported a noticeable reduction in the number of eosinophils and other inflammatory cells in the BALF of induced and sensitized OVA mice submitted and exposed to low doses of continuous irradiation (0.3 and 1.0Gy) for 24 days after initial sensitization. This decrease was concomitant with the reduction in IL-4, IL-5 and OVA-specific IgE levels.

The number of mast cells found in our study was significantly higher in the group of animals sensitized and challenged with ovalbumin. The animals in group OVA+IR presented considerably higher numbers than the other treatments (Figure 1B). This number was reduced with the combined application of radiation and/or moderate training (OVA+IR+MT, $p < 0.01$ and OVA+MT, $p < 0.0001$). Mast cells are implicated in allergic reactions such as asthma [40], in addition to inflammatory disorders and radiation-induced injuries, and are found in large numbers in skin and lung irradiation lesions [41]. Mast cells can produce several mediators that decrease inflammation and influence tissue remodeling and function; this occurs in response to IgE activation through FcεRI receptors and specific antigens [42]. Joo et al. [43] have reported in their works that low

doses of radiation inhibit the activation of mast cells by means of FcεRI suppression. Low-dose ionizing radiation significantly suppressed the release of mediators.

Some of these mediators are responsible for the influx of eosinophils to the inflammatory site, triggering physiological and pathological reactions linked to immediate hypersensitivity, such as in allergic processes which increase vascular permeability, bronchoconstriction and mucus secretion [18, 42, 44]. These pathological changes are characteristic of the inflammatory process and can also be observed in the increase in the total number of bronchoalveolar fluid inflammatory cells (BALF) (Figure 2), as well as in mucus production by goblet cells (Figures 4 and 5) in mice of the groups challenged with ovalbumin. However, when observing the animals challenged with OVA and exposed to radiation and/or submitted to MT, it is possible to observe a reduction in the infiltration of inflammatory cells in relation to the OVA group (Figure 2). Similar results have also been found in the numbers of eosinophils and mast cells, as well as in the mucus area (Figures 1A and B, 2, 4 and 5) in which the inflammatory process triggered by experimental asthma was reduced in the OVA+IR+BALB/c mice groups MT and OVA+MT culminating in a lower production of mucus.

The pathological development of mucus is the main cause of morbidity and `mortality associated with asthma where the formation of mucus buffers leads to obstruction of the intraluminal air passage [18]. Mucus is produced and secreted by goblet cells. In chronic asthma, the metaplasia of these cells leads to secretion of mucin in greater proportions, mainly mucin 5AC and 5B, which constitute the main forming element of the gel component conferring viscoelastic characteristics to the produced mucus [45]. Eosinophils induce MUC5AC mucin expression in air passage epithelial cells. The increase in the expression of mucin genes generated by epidermal growth factors due to epithelial damage and the interleukins IL-4 and IL-13 originated from the TH2-mediated inflammatory response, explain the increase in the number of goblet cells in the epithelium of severe asthma disease [18]. In this way the reduction of eosinophilia, as occurred in the OVA+IR+MT and OVA+MT groups results in a lower production of mucus by the goblet cells.

The mechanisms by which moderate training and radiation minimize the inflammatory effects are complex, and especially those regarding radiation are still not fully understood. Reductions in mucus production and expression of the MUCIN-5 gene in the lung tissue of induced and sensitized OVA mice have been observed with the use of low radiation doses [39].

Studies have shown that physical activity, especially moderate physical activities that are practiced regularly, can provide considerable health benefits by modulating positive cells involved in innate and adaptive immunity [25, 46, 47, 48] and has been used as a tool to decrease the incidence and even aid in the treatment of cardiovascular diseases, obesity, diabetes, respiratory diseases, among others [28, 49, 50]. Specific physical exercises have been used to assist cancer patients both during and after radiotherapy [29, 51, 52, 53].

In the present study, physical exercise of moderate intensity alone or in association with radiation was able to reduce the inflammatory process in OVA-induced mice. Regular moderate physical activity has an immunomodulatory effect and is related to reduced production of proinflammatory cytokines such as TNF-α, IL-1β, IL-4, macrophage inflammatory protein beta (MIP-1β) [47, 54].

The type of study we have proposed to conduct used whole body irradiation in mice with 10 doses of 0.5Gy gamma rays using CO^{60} and demonstrated that although the number of eosinophils and mast cells have been increased in the induced and irradiated asthma group (OVA+IR), in relation to the induced asthma group (OVA) the number of BALF cells, goblet cells and consequently the mucus area were all reduced in animals with induced asthma associated with irradiation and moderate training (Figures 1, 2, 4, 5), thus evidencing an anti-inflammatory effect. High doses of radiotherapy (single dose ≥ 2Gy total doses ≥ 40Gy) induce an inflammatory effect (production of proinflammatory cytokines). However, in studies using low doses of radiation (single ≤ 1.0Gy total doses ≥ 12Gy) *in vivo* and *in vitro*, anti-inflammatory effects have been observed [9, 11, 55].

Radiation can be considered an "unconventional" treatment in asthma therapy, compared to other clinical treatments. In the last decades of the 20th century, concerns about possible increased risks of cancer possibly caused the rejection of irradiation by populations of children and young people affected by asthma [14] The recent nuclear accident in Japan has increased public concern about the critical effects of radiation exposure. High-dose and high-dose-rate radiation have been shown to induce detrimental effects in various organisms, thereby causing cell death, in contrast, low-dose radiation has been reported to exert various beneficial effects [39,61]. Defining the health effects of low-dose (<100 mGy) ionizing photon radiation (LDR) on health, the relationship between LDR and human cancer risk remains elusive, the big question is in the low dose of

radiation and its fractionation [55, 59, 60, 61]. Several studies point to the prospects of low-dose anti-inflammatory radiation treatments associated with post-Covid-19 lung diseases, stating that although radiotherapy has been more widely used to control malignant tumors, it has also been used for the treatment of non-malignant diseases, including acute and chronic inflammation in situations where anti-inflammatory drugs may be ineffective or contraindicated [59].

Stimulation of the immune system through low doses of radiation is a complex process. Studies have shown that low doses of radiation exert anti-inflammatory effects, thus inhibiting leukocyte-endothelium interactions, modulating the immune system by reducing the recruitment of inflammatory cells, which reduces the secretion of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α); increases to the synthesis of anti-inflammatory cytokines such as transforming growth factor (TGF-β1), decreased NO, increased apoptosis and activation of the NF-κB transcription factor [11, 55, 56, 57, 58]

5. CONCLUSION

It has been shown that chronic changes in severe/refractory asthma are quite different from mild or moderate asthma, there is evidence of bronchial remodeling caused by the use of inhaled corticosteroids, used for eosinophil apoptosis, but in the opposite direction, increase neutrophils. The question is: if the use of medication does not meet the treatment needs for patients with severe asthma, and in a situation of risk of death, could the use of low-dose radiotherapy be indicated as a last option?

This research showed that the effects of the association between gamma radiation and moderate training in an experimental murine model of asthma, performed in an unprecedented way, significantly reduced inflammatory parameters and mucus production, factors that cause complications and high numbers of deaths in asthmatic patients and /or in radiotherapy. However, further experimental studies are needed for the use of gamma radiation in asthma therapy.

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