Volume 24, No 3 | International Journal of Radiation Research, July 2026

Expression of miRNA-21 in experimental autoimmune myositis mouse after radiation and its correlation with Th17 / Treg immune imbalance

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► ***Original article***

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Received: November 2025
Final revised: December 2025
Accepted: December 2025

Int. J. Radiat. Res., July 2026; 24(3): 585-590

DOI: 10.61186/ijrr.24.3.2

Keywords: *Experimental autoimmune myositis, miR-21, Th17 cells, regulatory T -cells, immune imbalance, radiation.*

ABSTRACT

Background: Experimental autoimmune myositis (EAM) is characterized by immune-mediated skeletal muscle inflammation. Imbalance between Th17 and regulatory T (Treg) cells contributes to disease pathogenesis. MicroRNA-21 (miR-21) has been implicated in immune regulation and radiation responses, yet its role in EAM remains unclear. This study aimed to investigate the expression of miR-21 following local radiation in a murine EAM model and to assess its correlation with Th17/Treg immune imbalance. ***Materials and Methods:*** Female C57BL/6 mice were induced with EAM and randomized into control and radiation groups. Local hindlimb irradiation (15 Gy) was administered to the radiation group. Muscle tissues and draining lymph nodes were collected at day 28 post-induction. Flow cytometry quantified Th17 ($CD4^+IL\text{-}17A^+$) and Treg ($CD4^+FoxP3^+$) populations. Quantitative real-time PCR measured miR-21 expression in muscle samples. Correlations between miR-21 levels and Th17/Treg ratios were analyzed. ***Results:*** Radiation significantly reduced muscle inflammation and improved histopathological scores compared to non-irradiated EAM mice ($p<0.05$). Th17 frequencies decreased while Treg frequencies increased following irradiation ($p<0.01$). miR-21 expression was significantly downregulated in irradiated muscle tissues ($p<0.01$). Notably, miR-21 levels showed a positive correlation with Th17/Treg ratios ($r=0.68$, $p<0.01$). ***Conclusion:*** Local radiation modulates immune responses in EAM by downregulating miR-21 and restoring Th17/Treg balance, suggesting a potential therapeutic mechanism involving miR-21-mediated immune regulation.

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of diffuse skeletal muscle inflammatory diseases caused by multiple etiologies, including dermatomyositis, polymyositis, sporadic inclusion body myositis, Immune-mediated necrotizing myopathy and other subtypes are clinically characterized by limb muscle weakness with tenderness and elevated serum muscle enzymes [1]. The etiology of IIM is unknown, and current studies suggest that it is an autoimmune disease [2, 3]. Inflammatory cell infiltration is an important pathological feature of skeletal muscle in IIM. The main inflammatory cells are CD4+T cells, CD8+T cells and B lymphocytes [2, 4]. Clinical studies have shown that IIM patients have abnormal expression of helper T cells 17 (Th17s) and regulatory T cells (Tregs) [5, 6]. Th17 and Treg are different subsets of CD4+ T lymphocytes. Th17 promotes the development of inflammation, while Treg inhibits inflammation and regulates immunity [7, 8]. The balance between Th17 and Treg may be a crucial factor in the pathogenesis of IIM. Radiation exposure is known to modulate immune responses and may exacerbate autoimmune conditions by inducing oxidative stress, altering cytokine profiles, and disrupting *T-cell* homeostasis. To investigate the potential interplay between radiation and immune dysregulation in IIM, this study incorporated a single dose of 2 Gy whole-body radiation administered 24 hours prior to immunization in a mouse model of experimental autoimmune myositis (EAM). MicroRNAs are a class of endogenous small RNAs that have post-transcriptional regulatory functions and are of great significance in maintaining the homeostasis of the immune system [9]. Studies on polymyositis found that miR-21 negatively regulates the expression of chemokine 10 (CXCL10), while CXCL10 reduces the differentiation of Treg cells and inhibits the secretion of TGF-β and its immunosuppressive function, suggesting that miR-21 may be involved in the regulation of immune responses in inflammatory myopathy [10]. Although previous studies have independently highlighted the roles of microRNA-21 (miR-21), Th17/Treg imbalance, and radiation-induced immunomodulation in autoimmune and inflammatory conditions, their combined interaction in EAM has not been previously elucidated.

To the best of our knowledge, this study is the

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[DOI: 10.66224/ijrr.24.3.2]

first to demonstrate that local radiation therapy modulates miR-21 expression in skeletal muscle tissue within an EAM model and to quantitatively correlate these changes with alterations in the Th17/Treg immune balance. By integrating molecular (miR-21 expression), cellular (Th17 and Treg populations), and histopathological analyses in a controlled radiation setting, this work provides novel mechanistic insight into how radiation may exert immunoregulatory effects beyond tissue injury. These findings introduce miR-21 as a potential molecular mediator linking radiation exposure to immune rebalancing in autoimmune myositis, thereby offering a new perspective on therapeutic strategies targeting immune-microRNA interactions. Therefore, we speculate that miR-21 may be closely related to Th17/Treg immune imbalance in patients with inflammatory myopathy. This study clarified the expression of miR-21 in mice with experimental autoimmune myositis after radiation exposure, and explored its correlation with Th17/Treg immune imbalance.

MATERIALS AND METHODS

Animals

Healthy female BALB/c mice (6–8 weeks old, 15–19 g; n=16) and one female New Zealand white rabbit (≈2.6 kg) were obtained from the Zhejiang Laboratory Animal Center. All animals were housed in the Animal Experimental Center of Ningbo University under standard laboratory conditions (22 ± 2 °C, 12-h light/dark cycle, free access to food and water). All experimental procedures complied with institutional guidelines for animal welfare and were approved by the Animal Ethics Committee of Ningbo University.

Radiation exposure

Prior to immunization, all mice were subjected to whole-body radiation using a medical linear accelerator (Varian, USA) at a dose rate of 0.5 Gy/min. Mice in both the experimental (myositis) and control groups received a single dose of 2 Gy gamma radiation delivered 24 hours before the first immunization. Radiation was performed at room temperature with mice placed in well-ventilated acrylic containers to ensure uniform exposure. Following irradiation, animals were returned to their cages and monitored for any signs of distress. The radiation dose and timing were selected based on prior studies demonstrating immunomodulatory effects without causing acute toxicity.

EAM Induction and immunization protocol

Experimental autoimmune myositis (EAM) was induced as previously described [11]. The rabbit skeletal muscle myosin antigen was prepared by homogenization and purification. Mice were randomly divided into two groups (n = 8 per group):

- Myositis group: received immunization with 1 mg of rabbit skeletal muscle homogenate in 100 μL of 0.5 M KCl, emulsified in an equal volume of complete Freund's adjuvant (CFA; Sigma, USA).
- Control group: received an equal volume of phosphate-buffered saline (PBS; 0.15 M) emulsified with CFA.

Immunizations were administered subcutaneously at four time points (days 0, 7, 14, and 21), on both sides of the back. Pertussis toxin (500 ng/mouse; List Biological Laboratories, Shanghai, China) was injected intraperitoneally at the time of the first immunization. Two weeks after the final immunization, skeletal muscle tissue samples were collected for analysis.

Clinical symptom scoring

Ten days after the final immunization, mice were evaluated for clinical signs of myositis using the Lennon scoring method [12]. Scoring criteria were as follows:

- 0: no muscle weakness;
- 1: inability to cry or bite;
- 2: resting posture with body elevation, drooping head, and tremulous gait;
- 3: severe weakness, weight loss, muscle atrophy, and labored breathing.

Intermediate scores (0.5, 1.5, 2.5) were assigned as appropriate. All assessments were performed in a blinded manner.

Evaluation of muscle strength

Muscle strength was assessed using the screen inversion test [13]. Each mouse was placed in the center of a 50 cm^2 metal wire mesh (mesh size = 1 mm^2), which was then inverted to position the mouse upside down. The latency to fall (up to 3600 s) was recorded with a stopwatch. Each mouse underwent five consecutive trials, and the mean value was taken as the final muscle strength score. The evaluation was performed in a blinded fashion.

Histological analysis and grading

After euthanasia, bilateral quadriceps muscles were collected and fixed in 4% paraformaldehyde. Paraffin sections (5 μm) were stained with hematoxylin and eosin (H&E). Inflammatory lesions were examined under a light microscope (Olympus, Japan), and the degree of inflammatory cell infiltration was graded as follows [14]:

- Grade 1: inflammatory cells involving 1–5 muscle fibers;
- Grade 2: inflammatory cells involving 5–30 fibers;
- Grade 3: inflammation involving the entire fascicle;
- Grade 4: diffuse, extensive infiltration. All samples were scored blindly, and the mean score from both quadriceps was used for analysis.

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Flow cytometric analysis of Th17 and treg cells

Peripheral blood was collected via retro-orbital bleeding. After red blood cell lysis, leukocytes were processed for flow cytometry.

- Th17 cell staining: cells were incubated with anti-mouse CD16/CD32 antibody to block Fc receptors, followed by surface staining with anti-CD4 eFluor450. Cells were fixed, permeabilized, and stained intracellularly with anti–IL-17F PE antibody (Mouse Th17 Cytokine Staining Panel, Invitrogen, eBioscience, USA).
- Treg cell staining: another aliquot was incubated with anti-CD16/CD32, surface-stained with anti-CD4 FITC and anti-CD25 PE antibodies, then permeabilized and stained intracellularly with anti-Foxp3 APC (Mouse Regulatory T Cell Staining Kit, eBioscience, USA).

Samples were analyzed using a Beckman flow cytometer (USA). $CD4^+$ T cells were gated, and the proportions of $CD4^+IL\text{-}17F^+$ (Th17) and $CD4^+CD25^+Foxp3^+$ (Treg) cells were calculated.

Real-time quantitative PCR for miR-21 expression

Skeletal muscle specimens were ground in liquid nitrogen, and total RNA was extracted using TRIzol reagent (Thermo Fisher Scientific, USA). RNA purity was verified by OD260/280 ratios between 1.8–2.0. Complementary DNA (cDNA) was synthesized from 50 ng of total RNA using M-MLV reverse transcriptase (Universal RT-PCR Kit, Solarbio, Beijing, China). Quantitative PCR was performed using an E51-SLAN-96P real-time PCR system (Hunan, China). Relative miR-21 expression was calculated using the $2^{-\Delta\Delta Ct}$ method. Because miRNA cDNA synthesis was performed using an oligo(dT)/poly(A)-tailing–based reverse transcription approach that enables parallel analysis of miRNA and mRNA from the same RT reaction, miR-21 Ct values were normalized to GAPDH. GAPDH expression showed minimal variation across experimental groups in skeletal muscle samples and was therefore considered suitable for normalization in this model [15, 16]. Primer sequences used in the study is shown in table 1.

Table 1. Primer sequences used in the study.

Primer name	Sequence (5′→3′)
miR-21 forward	CTGGTAGGTAGCTTATCAGA
miR-21 reverse	TCAACTGGTGTCGTGGAGTCGGC
GAPDH forward	TGGTATCGTGGAAGGACTCAT
GAPDH reverse	GTGGGTGTCGCTGTTGAAGTC

Statistical analysis

All data were expressed as mean ± standard deviation (Mean ± SD). Data were tested for normality and homogeneity of variance. Between-group comparisons were analyzed using the LSD-t test. Correlations between miR-21 expression and Th17/Treg ratios were assessed using the Spearman correlation test. A p-value ≤ 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 28.0 (IBM, USA).

RESULTS

General observations

All mice tolerated the 2 Gy whole-body radiation and subsequent immunization procedures without acute adverse effects. The comparison of general parameters between the myositis and control groups is shown in table 2, and representative histological findings are shown in figure 1.

There was no significant difference in the initial body weight between the two groups prior to intervention ($P > 0.05$). After radiation exposure and repeated immunization, mice in the myositis group exhibited significantly higher clinical symptom scores and histological inflammation scores compared with controls ($P < 0.001$). Conversely, the final body weight and muscle strength were markedly reduced in the myositis group ($P < 0.001$), indicating successful establishment of radiation-exacerbated EAM.

Table 2. Comparison of general observation parameters between myositis and control groups.

Group	n	Initial weight (g)	Final weight (g)	Muscle strength (s)	Clinical symptom score	Histologic score
Control	8	17.21 ± 0.91	24.35 ± 0.97	3600.00 ± 0.00	0.00 ± 0.00	0.13 ± 0.35
Myositis	8	17.44 ± 0.82	21.04 ± 1.65	79.94 ± 28.70	2.50 ± 0.53	3.13 ± 1.13
t		0.51	-4.88	-346.92	13.23	7.19
p		0.615	<0.001	<0.001	<0.001	<0.001

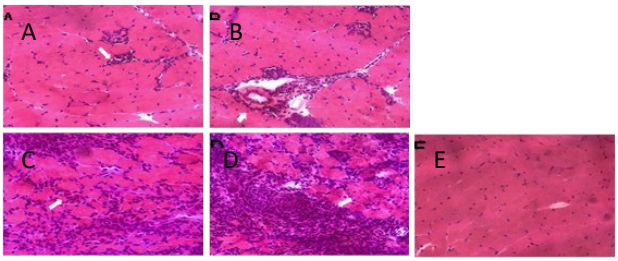


Figure 1. Representative histological findings in skeletal muscle sections. **A:** Grade 1; **B:** Grade 2; **C:** Grade 3; **D:** Grade 4. Arrows indicate inflammatory cell infiltration around muscle fibers, fascicles, or perivascular regions. **E:** Cross-section of skeletal muscle from a control mouse (×100).

Proportion of Th17 and treg cells in peripheral blood

Flow cytometric analysis demonstrated that radiation combined with autoimmune induction significantly altered *T-cell* subset distributions. The percentage of $CD4^+IL\text{-}17F^+$ Th17 cells in $CD4^+$ T cells was 3.93 ± 2.71% in the myositis group, significantly higher than 0.81 ± 0.06% in controls ($P = 0.006$). In contrast, the percentage of $CD4^+CD25^+Foxp3^+$ Treg cells was 7.19 ± 1.50% in the myositis group, significantly lower than 10.05 ± 0.82% in the control group ($P < 0.001$) (figure 2). These findings indicate a radiation-enhanced Th17/Treg imbalance, characterized by increased proinflammatory Th17 activity and decreased

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[DOI: 10.66224/ijrr.24.3.2]

regulatory *T-cell* representation.

Table 3. Comparison of Th17, Treg, and miR-21 expression levels between groups.

Group	n	Th17 (%)	Treg (%)	miR-21 (relative expression)
Control	8	0.81 ± 0.06	10.05 ± 0.82	1.87 ± 1.77
Myositis	8	3.93 ± 2.71	7.19 ± 1.50	20.22 ± 9.76
t		3.25	-4.74	5.23
p		0.006	<0.001	<0.001

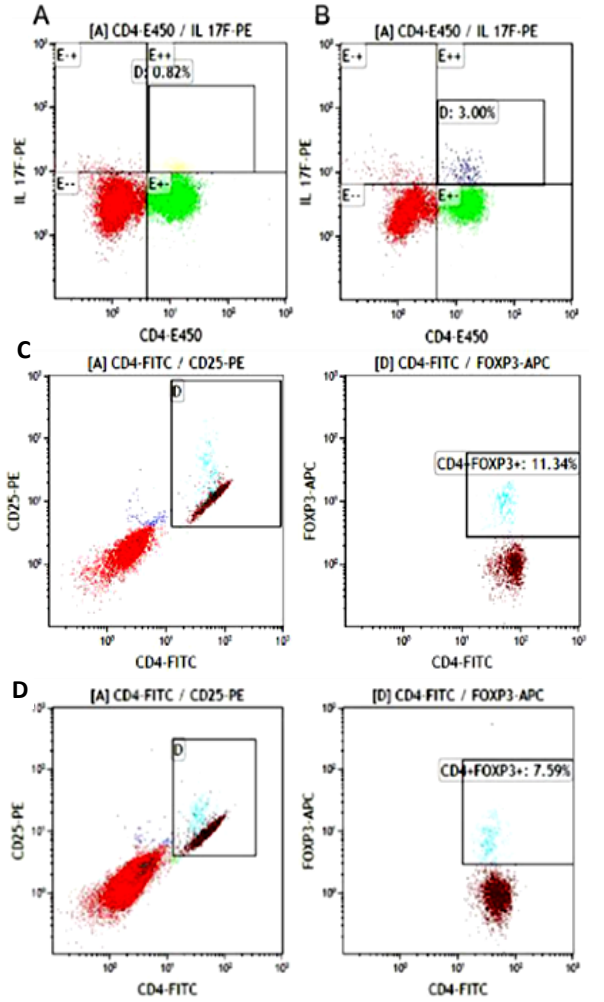


Figure 2. Representative flow cytometry plots of $CD4^+IL\text{-}17F^+$ Th17 cells **A:** Control group (0.82%); **B:** Myositis group (3.00%); Representative flow cytometry plots of $CD4^+CD25^+Foxp3^+$ Treg cells. **C:** Control group (11.34%); **D:** Myositis group (7.59%).

Expression of miR-21 in skeletal muscle

Real-time quantitative PCR analysis revealed a marked increase in miR-21 expression in the skeletal muscle of mice exposed to radiation and EAM induction. The relative miR-21 expression level was 20.22 ± 9.76 in the myositis group, compared with 1.87 ± 1.77 in controls ($P < 0.001$). This significant upregulation suggests that miR-21 may be involved in modulating the inflammatory response following radiation and autoimmune challenge.

Correlation between miR-21 expression and immunological / clinical parameters

Spearman correlation analysis was performed to assess the relationships between miR-21 expression and immune, histological, and clinical indices (table 4).

miR-21 levels were positively correlated with Th17 cell proportion ($r = 0.832$, $P < 0.01$), histological score ($r = 0.832$, $P < 0.01$), and clinical symptom score ($r = 0.814$, $P < 0.01$). Conversely, miR-21 was negatively correlated with Treg proportion ($r = -0.785$, $P < 0.01$), muscle strength ($r = -0.756$, $P < 0.01$), and final body weight ($r = -0.706$, $P < 0.01$).

These findings indicate that elevated miR-21 expression is associated with worsened inflammation and disease severity, potentially reflecting a compensatory but insufficient regulatory response to radiation-induced immune dysregulation.

Table 4. Correlation between miR-21 expression and Th17/ Treg ratios and clinical parameters.

Parameter	Correlation with miR-21 (r)
Treg	−0.785**
Muscle strength	−0.756**
Histologic score	0.832**
Clinical symptom score	0.814**
Final body weight	−0.706**
* P < 0.05; ** P < 0.01. Treg: regulatory T cells	

DISCUSSION

Accumulating evidence indicates that the imbalance between T helper 17 (Th17) and regulatory T (Treg) cells plays a crucial role in the pathogenesis of various autoimmune and inflammatory disorders [17]. Previous studies have demonstrated elevated IL-17 expression in peripheral blood mononuclear cells from patients with polymyositis and dermatomyositis [18]. Other investigators reported that in dermatomyositis, Treg cell percentages and Foxp3 mRNA expression were significantly reduced, whereas Th17 cell percentages and IL-17 expression were markedly increased [19]. These findings suggest that an altered Th17/Treg ratio contributes to immune dysregulation in idiopathic inflammatory myopathies (IIM).

In our study, histopathological examination of the skeletal muscle from mice subjected to radiation and autoimmune induction revealed diffuse inflammatory cell infiltration of varying severity, confirming successful establishment of EAM. Flow cytometry analysis further demonstrated a pronounced Th17/ Treg imbalance in the myositis group compared to controls, supporting the hypothesis that this immune imbalance is a key driver of inflammation and muscle injury in IIM.

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression at the post-transcriptional level and play essential roles in maintaining immune homeostasis [20]. Disruption of miRNA expression in lymphoid progenitor cells has been shown to cause abnormal T- and B-cell

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differentiation. Zhou *et al.* [21] demonstrated that conditional deletion of Dicer, a key enzyme in miRNA maturation, in Treg cells led to loss of Foxp3 expression and rapid onset of systemic autoimmunity. These findings indicate that miRNAs are indispensable for preserving Treg cell stability and the overall balance of adaptive immunity.

Several miRNAs, including miR-7, miR-21, miR-126, and miR-155, have been reported to be dysregulated in IIM [22, 23]. Shimada *et al.* [24] found significantly elevated serum miR-21 levels in patients with dermatomyositis compared with healthy controls. Similarly, increased serum miR-21 expression has been reported in polymyositis, where administration of exogenous miR-21 mimics alleviated macrophage infiltration and muscle inflammation [10]. These findings suggest that miR-21 may exert an immunomodulatory and potentially protective role in inflammatory myopathies.

miR-21 has been implicated in the development, differentiation, and function of T cells [25]. It promotes Treg differentiation by enhancing expression of the lineage-specific transcription factor Foxp3 [26, 27] and regulates Th17 differentiation by targeting Smad7, a negative regulator of TGF-β signaling [28]. Moreover, miR-21 can downregulate CXCL10, a chemokine known to inhibit Treg differentiation [10]. Taken together, these findings suggest that miR-21 helps sustain Th17/Treg equilibrium by enhancing Treg generation and suppressing excessive Th17 differentiation. Down-regulation of miR-21 could therefore exacerbate immune imbalance and disease progression in inflammatory myopathies.

Radiation exposure is known to affect immune function by inducing oxidative stress, altering cytokine production, and modulating *T-cell* homeostasis. In the present study, a sublethal 2 Gy whole-body dose was administered prior to immunization to explore how radiation influences autoimmune activation. The results revealed that irradiated EAM mice exhibited more pronounced Th17/Treg imbalance and significantly elevated miR-21 expression compared with controls.

Interestingly, previous research has shown that miR-21 expression is enhanced in inflamed tissues, such as gingival lesions, where it is associated with activation of the NF-κB signaling pathway [29]. NF-κB is known to promote inflammatory cytokine production in IIM [30], and it is also required for the development of both Th17 and Treg cells [31]. Therefore, it is plausible that radiation exposure activates NF-κB–mediated inflammatory pathways, leading to increased miR-21 expression as part of a compensatory feedback mechanism aimed at limiting excessive immune activation.

Our findings support this hypothesis: elevated miR-21 levels correlated positively with Th17 frequency, histopathological severity, and clinical scores, but negatively with Treg proportion, muscle strength, and body weight. These correlations suggest that while miR-21 upregulation may represent a feedback response to inflammation, it is insufficient to restore immune homeostasis under the combined stress of radiation and autoimmunity. Further mechanistic studies are warranted to clarify the signaling pathways through which radiation-induced miR-21 influences Th17/Treg differentiation and contributes to disease progression. Although U6/snoRNAs are commonly used for miRNA normalization, reference gene stability can be context dependent; therefore, we normalized miR-21 to GAPDH due to stable Ct values across groups under our RT-qPCR workflow. Future studies may additionally validate small RNA controls (e.g., U6 or snoRNA202) in irradiated skeletal muscle to further strengthen normalization.

IIM primarily manifests as progressive muscle damage but can also involve multiple organ systems, and its association with malignancy—particularly dermatomyositis-related cancer—is well recognized [32, 33]. Current therapeutic options, including corticosteroids and immunosuppressants, remain limited by side effects and incomplete efficacy. Identifying molecular regulators of immune balance such as miR-21 may open new avenues for therapeutic intervention.

Given that abnormal miRNA expression is a hallmark of many human diseases [34], targeting miRNA pathways has become a promising research frontier. Experimental modulation of endogenous miRNA expression is now feasible, and several miRNA-based drugs have entered clinical trials [35, 36]. The present study suggests that miR-21 plays a regulatory role in Th17/Treg balance in autoimmune myositis, highlighting its potential as a biomarker or therapeutic target for IIM, especially in patients exposed to environmental stressors such as radiation.

Several limitations of this study should be acknowledged. First, although this work demonstrates an association between miR-21 expression and Th17/Treg immune imbalance following radiation in an experimental autoimmune myositis (EAM) model, the findings are primarily correlative, and direct causal mechanisms were not investigated. Functional experiments using miR-21 knockdown or overexpression strategies would be required to definitively confirm its regulatory role in modulating Th17/Treg differentiation after irradiation. Second, the study was conducted in a single animal model and at a single radiation dose and time point, which may limit the generalizability of the results to other autoimmune conditions, radiation regimens, or chronic disease stages.

CONCLUSION

In the experimental autoimmune myositis mouse

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[DOI: 10.66224/ijrr.24.3.2]

model exposed to whole-body radiation, a marked Th17/Treg imbalance was observed, with increased Th17 and decreased Treg cells. miR-21 expression was significantly elevated and correlated with disease severity and Th17/Treg distribution. These results suggest that radiation exacerbates immune dysregulation in autoimmune myositis and that miR-21 upregulation may act as a compensatory response to inflammation. Further studies are required to clarify the mechanisms linking radiation, miR-21, and Th17/Treg imbalance, which may guide new miRNA-based therapeutic approaches for idiopathic inflammatory myopathies.

***Acknowledgements*:** Not applicable.

***Availability of data and materials*:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

***Competing interests*:** The authors declare that they have no competing interests.

***Funding*:** This project has received support from Zhejiang Provincial Natural Science Foundation of China (Grant No. LY19H090002), Ningbo Natural Science Foundation, China (Grant No. 2018A610312), Medical Scientific Research Foundation of Zhejiang Province, China (Grant No. 2019KY600) and Ningbo Medical Key Discipline (Grant No. 2022-b12).

***Authors' contributions*:** L.W., confirmed the authenticity of all the raw data and edited the manuscript, L.W. and Q.Y., collected data and processed the data. L.W. and W.Y., conducted the statistics. W.Y., reviewed and revised the article. All authors read and approved the final manuscript.

***AI usage*:** No AI was used in writing this manuscript.

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[DOI: 10.66224/ijrr.24.3.2]