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Journal of Clinical & Experimental Dermatology Research

Short Communication

Effect of Melatonin on Radiosensitivity of Human Keloid Fibroblasts and Preliminary Mechanism Study

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DESCRIPTION

Keloid is a special type of pathological scar [1], it grows extensively outside the boundaries of the original wound invasive to the surrounding skin. It doesn't spontaneously fade over time and it is very likely to recur after surgical resection. Its impact is not only aesthetic but also causes pain itching and other discomfort. Scar contracture leads to dysfunction reduces the quality of life of patients [2] and causes psychological and physiological damage to patients its treatment is still a huge challenge. Surgical resection combined with radiation therapy is currently considered to be the most effective treatment for keloids. Keloid has certain characteristics of radiotherapy resistance. Although high dose radiation can achieve the purpose of treating keloid [3,4]. But it will also bring related radiation side effects. In order to achieve satisfactory therapeutic effect with low dose radiation [5], it is necessary to improve the radio sensitivity of keloid. Melatonin (MLT) is a neuronatural hormone produced in the pineal gland of the brain it has anti-oxidation, anti-aging, diurnal regulation, anti-inflammatory and other effects. Numerous studies have reported that melatonin has radio sensitization and melatonin combined with radiation therapy can increase the effect of radiation therapy and reduce the side effects of radiation therapy in many tumor treatments [6,7]. At present there is a lack of relevant literature on melatonin and keloid fibroblasts in the world. Therefore, this study aims to study the effect of melatonin on the radio sensitivity of human keloid fibroblasts and preliminarily explore the related mechanism. The purpose of this study was to investigate the effect of melatonin on the radio sensitivity of human keloid fibroblasts and explore its mechanism, so as to lay a theoretical foundation for the role of melatonin combined with radiotherapy in the treatment of keloid and provide a new idea for the treatment of keloid.

Human keloid fibroblasts were cultured *in vitro* and the effects of different concentrations of melatonin on the proliferation of human keloid fibroblasts were detected by CCK-8 assay and the appropriate experimental concentration and action time of melatonin were screened. The effect of each treatment group on the proliferation of human keloid fibroblasts was detected by CCK-8 assay and the radio sensitizing effect of melatonin was proved. The appropriate experimental radiation dose and time were selected. The effect of each treatment group on apoptosis was detected by flow cytometry. The effects of each treatment group on cell migration and invasion were examined by scratch test and transwell migration and invasion test. The effect of each treatment group on cell cycle distribution was detected by flow cytometry. Western Blot analysis was performed to determine the effects of treatment groups on γH2AX and DNA-PKcs protein expression.

The results of CCK-8 experiment showed that melatonin within a certain concentration range could inhibit the proliferation of human keloid fibroblasts in a concentration and time dependent manner. The IC_{20} concentration for 24 hours was 1.586 m mol/L, and 1 m mol/L was selected for 24 hours as the drug concentration and action time for subsequent experiments. And it also showed that radiation inhibited cell proliferation in a time and dose-dependent manner. 1m mol/L melatonin combined with different radiation doses (MLT+2Gy, MLT +6Gy, MLT+10Gy group) can significantly inhibit cell proliferation. Its inhibitory effect was significantly stronger than that of radiation alone group (2Gy, 6Gy, 10Gy) and 1 m mol/L Melatonin group (MLT group), and the inhibitory ability of cell proliferation in MLT+2Gy group was higher than that in 6Gy group, similarly, the inhibitory ability of cell proliferation in MLT+6Gy group was higher than that in 10Gy group. The results showed that melatonin could improve the radio sensitivity of human keloid fibroblasts. The radiation dose of 10Gy and treatment for 24h were selected as the subsequent experimental conditions. Flow cytometry was used to detect

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Received: 01-Dec-2023, Manuscript No. JCEDR-23-28365; **Editor assigned:** 04-Dec-2023, PreQC No. JCEDR-23-28365 (PQ); **Reviewed:** 18-Dec-2023, QC No. JCEDR-23-28365; **Revised:** 25-Dec-2023, Manuscript No. JCEDR-23-28365 (R); **Published:** 02-Jan-2024, DOI: 10.35841/2329-9509.23.14.652.

Citation: Cate D (2023) Effect of Melatonin on Radiosensitivity of Human Keloid Fibroblasts and Preliminary Mechanism Study. J Clin Exp Dermatol Res. 14:652.

apoptosis. The results showed that compared with the Control group, the apoptosis of cells in 1m mol/L melatonin group (MLT group) was slightly increased, and the apoptosis of cells in 10Gy radiation group (IR group) was significantly induced. 1 m mol/L melatonin+10Gy radiation group (MLT+IR group) can significantly promote apoptosis compared with IR (Ischemia-Reperfused) and MLT groups. The results of scratch test and transwell migration test showed that compared with the Control group, the cell migration ability of all intervention groups was inhibited, and the cell migration ability of MLT+IR group was significantly weaker than that of IR and MLT group, and the healing was slower as time went on. The results of transwell invasion experiment showed that the cell invasion in the Control group was inhibited under different intervention conditions, and the number of cell invasion in the MLT+IR group was significantly lower than that in the IR and MLT groups. Flow cytometry cell cycle assay showed that compared with Control group, the proportion of G0/G1 phase cells in MLT group, IR group and MLT+IR group was reduced, and the proportion of G2/M phase cells was increased. The proportion of G2/M stage cells in MLT group was slightly increased, G2/M stage cell arrest was obvious in IR group, and G2/M stage cell arrest was further increased in MLT+IR group. Compared with IR group and MLT group, the proportion of G2/M phase cells in MLT+IR group was significantly increased, and the proportion of G0/G1 phase cells was significantly decreased. Western Blot test results showed that compared with the control group there was no significant difference in the expression of γH2AX protein in MLT group, while the expression of γH2AX protein in IR group and MLT+IR group was significantly increased. The expression of γH2AX protein in MLT+IR group was significantly higher than that in MLT and IR groups. Compared with the Control group, the expression of DNA-PKcs protein in MLT group and IR group was significantly up-regulated, but there was no significant difference in DNA-PKcs protein expression in MLT+IR group. The expression of DNA-PKcs protein in MLT+IR group was significantly lower than that in MLT group and IR group.

CONCLUSION

Melatonin inhibited the proliferation of human keloid fibroblasts in a concentration and time-dependent manner. Melatonin can enhance the radio sensitivity of human keloid fibroblasts, enhance the ability of radio inhibition of cell proliferation, promote radiation-induced apoptosis, and enhance the ability of radio inhibition of cell migration and invasion. The radio sensitization mechanism of melatonin on human keloid fibroblasts may be related to blocking the cell cycle in G2/M phase, promoting DNA damage and inhibiting DNA damage repair

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