Int J Clin Exp Med 2019;12(8):10286-10293
www.ijcem.com /ISSN:1940-5901/IJCEM0095800

Original Article

Resveratrol inhibits IL-1β, IL-18, and ICAM-1 in a nasopharyngeal carcinoma model

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Received April 22, 2019; Accepted June 10, 2019; Epub August 15, 2019; Published August 30, 2019

Abstract: Objective: The current study aimed to examine the effects of resveratrol (RES) on interleukin-1β (L-1β), interleukin-1 (IL-18), and intercellular cell adhesion molecule-1 (ICAM-1) in a nasopharyngeal carcinoma nude mice model. Methods: Nasopharyngeal carcinoma was modeled in the experimental group. A total of 80 male nude mice were randomly divided into experimental group A, experimental group B, control group A, and control group B, with 20 in each group. RES injections were performed in experimental group A and control group A, respectively. The same amount of carboxymethyl cellulose sodium in saline was injected in experimental group B and control group B. Five nude mice in each of the 4 groups were killed by neck fractures at T1, 3 days (T2), 5 days (T3), and 7 days (T4) before injections, respectively. Blood and cancer tissues of the nude mice were obtained. Expression levels of ICAM-1 and IL-18 in cancer tissues, as well as serum IL-1β, were detected via enzyme-linked immunosorbent assays (ELISA). Results: There were no significant differences in IL-1β, IL-18, and ICAM-1 between control group A and control group B at T1, T2, T3, and T4 ($P > 0.050$). At T2, T3, and T4, serum IL-1β and IL-18 levels, as well as ICAM-1 expression levels, in cancer tissues of experimental group B were significantly lower than those in the experimental group A ($P < 0.050$). IL-1β, IL-18, and ICAM-1 in experimental group A increased with time ($P < 0.050$). IL-1β, IL-18, and ICAM-1 in the experimental group B decreased with time ($P < 0.050$). Conclusion: RES can inhibit levels of IL-1β, IL-18, and ICAM-1 in nasopharyngeal carcinoma.

Keywords: RES, nasopharyngeal carcinoma, nude mice, IL-1β, IL-18, ICAM-1

Introduction

Nasopharyngeal carcinoma is a very common malignant tumor in the nasopharynx. Incidence rates of the disease have great regional and ethnic differences. According to statistics, incidence of nasopharyngeal cancer is about 3.5~8.0 times higher than that of other regions [1-3] inhabited mainly by yellow races and countries with high population densities (such as China and India). Nasopharyngeal cancer is usually insidious, but deteriorates rapidly [4]. According to statistics, 5-year survival of nasopharyngeal cancer patients is less than 50.0% [5]. The main reason for poor prognosis of nasopharyngeal cancer patients is that nasopharyngeal cancer is extremely prone to distant metastasis. About 20.0%~40.0% of nasopharyngeal cancer patients have already experienced distant metastasis when diagnosed [6, 7]. Therefore, early diagnosis and treatment of nasopharyngeal cancer is particularly important in clinical practice. Radiotherapy is an effective treatment for most nasopharyngeal carcinomas. It is the main treatment for early nasopharyngeal carcinomas [8, 9]. However, for patients with nasopharyngeal carcinomas with high differentiation and late course of disease, chemotherapy is used in combination with chemotherapy during the course of radiotherapy [10] Therefore, it is necessary to find a drug that can effectively improve the radiotherapy effects of nasopharyngeal cancer, reducing toxic effects and side effects.

Resveratrol (RES) is a polyphenol compound. It is mainly extracted from the rhizome of polygonum cuspidatum [11]. RES is a pure natural antioxidant with low toxic and side effects. It has certain inhibitory effects on atherosclerosis, aging, and tumors [12]. At present, studies at home and abroad have proven that RES can

effectively inhibit the growth of nasopharyngeal cancer cells [13, 14]. However, the mechanisms of action are not yet clear. Therefore, the present nude mice model of nasopharyngeal carcinoma was established, aiming to detect the effects of L-1β, IL-18, and ICAM-1.

Materials and methods

Animal data

A total of 80 male nude mice, aged from 10 to 16 weeks, weighing 20 g to 30 g, were purchased from China Beijing Weitong Lihua Experimental Animal Technology CO., LTD (animal license SYXK (Beijing) 2012-0036, 102). There were only 5 nude mice per cage. Each cage had a temperature of 26°C ± 0.5°C and humidity of 35%~55%. They were normally lit and fed.

Methods

The 80 nude mice were randomly divided into the experimental group and control group, with 40 nude mice in each group. Nasopharyngeal carcinoma was modeled in the experimental group, as follows [15]: Before treatment, food was banned for 10 hours. After completion, the carcinogen dinitrosopiperazine (DNP, 15 mg/kg) and phorbol ester (TPA, 100 mg/kg) were injected, subcutaneously, 3 days/time, with continuous injections 28 times. Body weights of the nude mice were measured regularly every week. Injection volumes were adjusted accordingly. Continuous scratching, runny noses, and sneezing indicated successful modeling [16]. The experimental group and control group were then randomly divided into experimental group A, experimental group B, control group A, and control group B, with 20 nude mice in each group. RES injection intervention was performed in experimental group A and control group A, respectively. Intervention methods: RES (purchased from Shanghai Borman Biotechnology CO., LTD., D0051) was added to carboxymethyl cellulose sodium for solubility. Normal saline was used to dilute the melting concentration to 1%, then subcutaneous injections were performed. The dose was 1mL, once in the morning and once in the evening, for a total of 7 days [17]. Experimental group B and control group B were injected with the same amount of carboxymethyl cellulose sodium in saline at the same time. Five nude mice in each of the four groups were killed by neck fractures on the first day (T1), third day (T2), fifth day (T3), and seventh day (T4) before injections. Nude mice blood and cancer tissues were obtained. Expression levels of ICAM-1 in cancer tissues, as well as serum IL-1β and IL-18 levels, were detected by enzyme-linked immunosorbent assays (ELISA).

Five nude mice in each of the four groups were killed by neck fractures on the first day (T1), third day (T2), fifth day (T3), and seventh day (T4) before injections.

A total of 4 mL of blood from carotid arteries and tissue sections of nasopharyngeal carcinoma were obtained. The blood settled for 30 minutes. It was then centrifuged for 10 minutes (4,000 rpm/min) to obtain upper serum for testing. Cancer tissues were weighed after washing with PBS. Pre-cooled PBS was added at a ratio of 1:5 and fully grounded, obtaining a cancer tissue homogenate. The homogenate was centrifuged for 10 minutes (4,000 rpm/min), obtaining the supernatant liquid for testing.

The IL-1β kit was purchased from Wuhan Elabscience Biotechnology CO., LTD., E-EL-H0149c. The IL-18 kit was purchased from Shanghai Jingkang Bioengineering CO., LTD., JK-(a)-1443. The ICAM-1 kit was purchased from Shanghai Yubo Biotechnology CO., LTD., KT-1300. Assays were performed using duplicate sera, diluted at 1:2, according to manufacturer protocol.

Outcome measures

Expression levels of serum IL-1β and IL-18, as well as ICAM-1, in cancer tissues of the 4 groups were measured at T1, T2, T3, and T4. Changes in tumor volume sizes were calculated as follows: V (volume) = (0.5 × long diameter (L) × short diameter (S))^2.

Statistical methods

SPSS 24.0 statistical software (Shanghai Yuchuang Network Technology CO., LTD.) was used to analyze and process data. Results data are expressed in the form of mean +/- standard deviation. The mean between multiple groups was compared using one-way ANOVA, followed vby post-hoc Bonferroni's testing. $P < 0.001$ indicates statistical significance.

Table 1. Expression of serum IL-1β in nude mice at T1, T2, T3, and T4 (ng/L)

	Experiment A	Experiment B	Control A	Control B	F	P
T1	62.88 ± 6.84	62.05 ± 7.03	30.87 ± 2.95	31.04 ± 3.13	57.732	< 0.001
T2	55.72 ± 6.16	73.15 ± 6.86	31.12 ± 3.24	30.62 ± 3.36	79.824	< 0.001
T3	44.16 ± 2.85	86.54 ± 7.02	31.66 ± 3.69	31.15 ± 3.42	165.328	< 0.001
T4	36.73 ± 3.16	95.89 ± 7.22	31.16 ± 3.15	30.94 ± 3.08	221.424	< 0.001

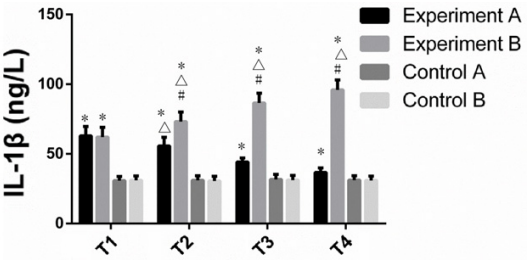

Figure 1. Serum IL-1β expression at T1, T2, T3, and T4. *represents levels of IL-1β in the experimental group, compared with the control group, at the same time, P < 0.05; #represents levels of IL-1β in experimental group A, compared with experiment group B, P < 0.05; △represents levels of IL-1β at time-dependent differences in the same group, P < 0.05.

Results

Modeling results

Of the 40 nude mice, 38 were successfully modeled, with a success rate of 95.0%. Therefore, there were 19 in experimental group A, 19 experimental in B group, 20 in control group A, and 20 in control group B. Five nude mice were killed in each group at T1, T2, and T3. There were 4 in experimental groups A and B and 5 in control groups A and B.

Expression of serum IL-1β at each time point (T1, T2, T3, and T4) in the four groups

In experimental groups A and B and in control groups A and B, IL-1β was (62.88 + 6.84) ng/L, (62.05 + 7.03) ng/L, (30.87 + 2.95) ng/L, and (31.04 + 3.13) ng/L at T1, respectively. In experimental groups A and B and in control groups A and B, IL-1β was (55.72 + 6.16) ng/L, (73.15 + 6.86) ng/L, (31.12 + 3.24) ng/L, and (30.62 + 3.36) ng/L at T2, respectively. In experimental groups A and B and in control groups A and B, IL-1β was (44.16 + 2.85) ng/L, (86.54 + 7.02) ng/L, (31.66 + 3.69) ng/L, and (31.15 + 3.42) ng/L at T3, respectively. In experimental groups A and B and in control groups A and B, IL-1β was 36.73 ± 3.16) ng/L, (95.89 ± 7.22) ng/L, (31.16 ± 3.15) ng/L, and (30.94 ± 3.08) ng/L at T4, respectively. There were no significant differences between experimental group A and experimental group B (P > 0.050). There were no significant differences between control group A and control group B (P > 0.050). IL-1β levels in experiment groups A and B were significantly higher than those in control groups A and B (P < 0.05). There were no significant differences between control groups A and B (P > 0.050) (**Table 1** and **Figure 1**).

Expression of serum IL-18 at T1, T2, T3, and T4 in the four groups

In experimental groups A and B and in the control group, IL-18 was (248.27 + 35.24) ng/L, (251.62 + 33.57) ng/L, (88.14 + 12.85) ng/L, and (87.92 + 12.43) ng/L at T1, respectively. In experimental groups A and B and in control groups A and B, IL-18 was (197.62 +/- 25.17) ng/L, (375.14 +/- 32.67) ng/L, (89.07 +/- 13.12) ng/L, and (88.57 +/- 13.05) ng/L at T2, respectively. In experimental groups A and B and in control groups A and B, IL-18 was (142.86 ± 14.3) ng/L, (298.63 ± 42.86) ng/L, (88.29 ± 11.68) ng/L, and (89.05 ± 12.28) ng/L at T3, respectively. In experimental groups A and B and in control groups A and B, IL-18 was (104.77 ± 7.64) ng/L, (331.76 ± 30.84) ng/L, (89.07 ± 13.05) ng/L, and (88.12 ± 12.59) ng/L at T4, respectively. There were no significant differences between control group A and control group B (P > 0.050). IL-18 levels in control experiment groups A and B were significantly higher than those in control groups A and B (P < 0.05). There were no significant differences between control groups A and B (P > 0.050). Levels in experiment A group were significantly lower than those in experiment group B (P < 0.05) (**Table 2** and **Figure 2**).

Expression of ICAM-1 in cancer tissues at T1, T2, T3, and T4 in the four groups

In experiment groups A and in control groups A and B, ICAM-1 at T1 was (92.87 + 10.57) ng/L, (92.68 + 9.79) ng/L, (23.24 + 4.54) ng/L, and

Table 2. Expression of serum IL-18 at T1, T2, T3, and T4 (ng/L)

	Experiment A	Experiment B	Control A	Control B	F	P
T1	248.27 ± 35.24	251.62 ± 33.57	88.14 ± 12.85	87.92 ± 12.43	65.023	< 0.001
T2	197.62 ± 25.17	275.14 ± 32.67	89.07 ± 13.12	88.57 ± 13.05	80.853	< 0.001
T3	142.86 ± 14.33	298.63 ± 42.86	88.29 ± 11.68	89.05 ± 12.28	84.640	< 0.001
T4	104.77 ± 7.64	331.76 ± 30.84	89.07 ± 13.05	88.12 ± 12.59	191.018	< 0.001

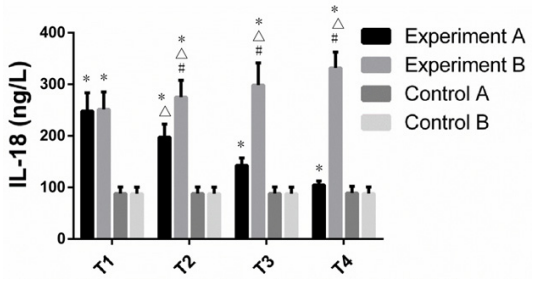

Figure 2. IL-18 expression at T1, T2, T3, and T4. A *represents levels of IL-18 in the experimental group, compared with the control group, at the same time, P < 0.05; #represents levels of IL-18 in experimental group A, compared with experimental group B, P < 0.05; Δrepresents levels of IL-18 at time-dependent differences in the same group, P < 0.05.

(22.84 + 4.62) ng/L, respectively. In experimental groups A and B and in control groups A and B, ICAM-1 was (67.43 ± 8.72) ng/L, (112.98 ± 10.05) ng/L, (24.05 ± 5.16) ng/L, and (23.15 ± 4.92) ng/L at T2, respectively. In experimental groups A and B and in control groups A and B, ICAM-1 was (51.99 ± 5.79) ng/L, (137.25 ± 15.86) ng/L, (24.86 ± 4.88) ng/L, and (24.33 ± 5.07) ng/L at T3, respectively. In experimental groups A and B and in control groups A and B, ICAM-1 was (31.77 ± 2.85) ng/L, (152.86 ± 10.24) ng/L, (23.76 ± 4.86) ng/L, and (22.57 ± 4.05) ng/L at T4, respectively. There were no significant differences between control groups A and B (P < 0.050). Levels were significantly lower than those between model groups A and B (P < 0.05). In the model group, ICAM-1 levels of the model A group were significantly lower than those of the model group B (P < 0.051) (**Table 3** and **Figure 3**).

Tumor growth at T1, T2, T3, and T4 in the four groups

There were no significant differences between control groups A and B (P < 0.05). Levels were significantly lower than those between model groups A and B (P < 0.05). In the model groups, tumor sizes in the A group were significantly lower than those of the B group (P < 0.05) (**Table 4** and **Figure 4**).

Discussion

Nasopharyngeal carcinoma is a relatively common malignant tumor in clinical practice, with high incidence rates and strong lethality [18]. At present, the main treatment method is radiotherapy. Prognosis of patients after radiotherapy has been significantly improved. However, some patients still have malignant development, such as tumor recurrence and metastasis [19]. Studies have shown that the main reasons for poor prognosis of patients with nasopharyngeal cancer are toxic effects and side effects during treatment [20]. Radiation therapy is a treatment method with great side effects. The combination of chemical drugs has great inhibitory effects on the ability of DNA replication. Damage to DNA bases, shedding, and DNA chain breaking are all key factors influencing changes in the biological functions of patient cells [21, 22]. Therefore, in the treatment of nasopharyngeal cancer, reducing toxic effects and side effects is important. RES, a pure natural active ingredient, has been proven to have antibacterial, anti-inflammatory, and other effects. In recent years, research at home and abroad has found that RES possesses strong anticancer activity [23]. However, current studies have been limited to the anticancer effects of RES. Few studies have focused on the application of RES in nasopharyngeal cancer. The impact of related RES on factors, such as IL-1β and IL-18, in nasopharyngeal carcinoma has not been proven. Therefore, in the current study, establishing a nude mice model of nasopharyngeal carcinoma, the effects of RES on IL-1β, IL-18, and ICAM-1 in nasopharyngeal carcinoma nude mice were explored. The current study aimed to analyze the significance of RES in the treatment of nasopharyngeal carcinoma.

Results of this experiment showed that expression levels of IL-1β, IL-18, and ICAM-1 at T, T3,

Table 3. Expression of ICAM-1 in cancer tissues at T1, T2, T3, and T4 (ng/L)

	Experiment A	Experiment B	Control A	Control B	F	P
T1	92.87 ± 10.57	92.68 ± 9.79	23.24 ± 4.54	22.84 ± 4.62	129.942	< 0.001
T2	67.43 ± 8.72	112.98 ± 10.05	24.05 ± 5.16	23.15 ± 4.92	160.144	< 0.001
T3	51.99 ± 5.79	137.25 ± 15.86	24.86 ± 4.88	24.33 ± 5.07	170.128	< 0.001
T4	31.77 ± 2.85	152.86 ± 10.24	23.76 ± 4.86	22.57 ± 4.05	473.043	< 0.001

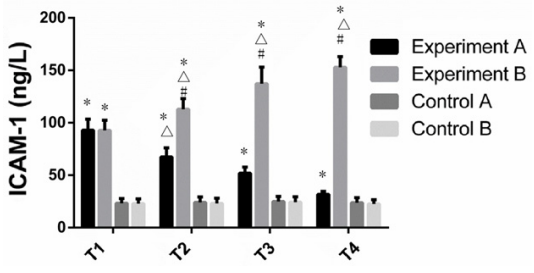

Figure 3. ICAM-1 expression at T1, T2, T3, and T4. *represents levels of ICAM-1 in the experimental group, compared with the control group, at the same time, P < 0.05; #represents levels of ICAM-1 in experimental group A, compared with experimental group B, P < 0.05; Δrepresents levels of ICAM-1 at time-dependent differences in the same group, P < 0.05.

and T4 of experimental group A with RES intervention were significantly lower than those of experimental group B without RES intervention. Results suggest that RES can effectively inhibit levels of inflammatory cytokines. Present results are consistent with the results of Moussa et al [24]. They studied RES intervention in Alzheimer's disease. IL-1β, a cytokine produced by monocytes, endothelial cells, and fibroblasts can bind to platelet growth factors and produce interleukin-2 to bind to T-cells, repairing tissues [25]. According to the results of this experiment, IL-1β levels of the experimental group were significantly higher than those of the normal control group. This is because elevated levels of IL-1β in the pathogenesis of nasopharyngeal carcinoma can greatly increase the production of eosinophils, accelerating the severity of patient conditions [26]. In experimental group A, IL-1β levels were significantly lower than those of the uninterrupted experimental group B. This suggests that RES can effectively inhibit the production of IL-1β, showing good effects on the disease control of nasopharyngeal carcinoma. The reasons may be related to the ability of RES to inhibit cell activity. RES greatly reduces levels of IL-1β by inhibiting specific receptors on the surface of vascular endothelial cells, reducing their ability to bind to other cytokines. IL-18 also belongs to the IL-1 ligand family. Its structure is similar to that of IL-1, mainly formed by the hydrolysis of cysteine aspartase at the N-terminus [27]. IL-18 is an extremely powerful pro-inflammatory cell. It has strong regulatory effects on cell development and secretion of cytokines. This can greatly promote the production of cytokines, such as IFN-γ and IL-2, by monocytes. It has strong toxic effects on NK cells [28]. In this study, IL-18 levels in the experimental group were significantly higher than those in control nude mice. Results suggest that toxic effects play an extremely important role in nasopharyngeal carcinoma. Through the intervention of RES, IL-18 levels of experimental group A were significantly reduced. This suggests that RES produces good effects in inhibiting IL-18 and reducing cytotoxicity. Some studies have reported that RES has the same inhibitory capacity for NK cells [29]. In nasopharyngeal carcinoma, RES inhibits the activity of NK cells. Proliferation of T-cells is reduced. This naturally leads to a decrease in levels of IL-18. However, the more precise mechanisms require further experimental confirmation. ICAM-1 is an extremely important adhesion molecule. It mediates adhesion reaction, promotes adhesion of inflammation sites, and controls tumor progression and metastasis [30]. In this experiment, ICAM-1 levels of the experimental group were significantly higher than those of the control group. High levels of ICAM-1 in the experimental group suggest that nasopharyngeal carcinoma has a strong metastatic rate. Levels of ICAM-1 in experimental group A after RES intervention were significantly decreased. This suggests that RES can effectively improve deterioration of nasopharyngeal carcinoma and reduce metastasis rates of nasopharyngeal carcinoma. The mechanisms by which RES reduces ICAM-1 levels are presumed to be related to the reduction of endothelial cell activation by RES. The ability of intercellular adhesion molecules on endothelial cells to mediate the contact and binding

Table 4. Tumor volume in nude mice at T1, T2, T3, and T4 (mm^3)

	Experiment A	Experiment B	Control A	Control B	F	P
T1	100.54 ± 2.04	98.65 ± 6.05	0	0	1634.512	< 0.001
T2	124.68 ± 6.21	163.54 ± 5.54	0	0	2334.414	< 0.001
T3	162.64 ± 4.54	229.82 ± 8.04	0	0	3372.541	< 0.001
T4	207.64 ± 5.14	324.86 ± 6.54	0	0	8452.610	< 0.001

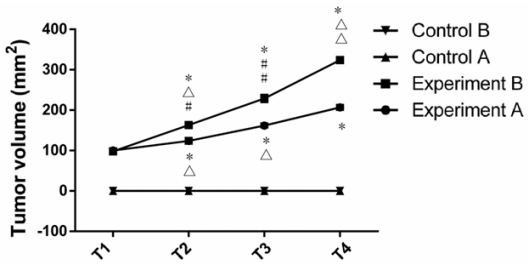

Figure 4. Growth curves of tumors. The *x*-axis represents time after nasopharyngeal carcinoma cells injection. The *y*-axis represents volume of tumors ($V = L \times (W)^2/2$).

between cells and between cells or between cells and matrix is reduced. As a result, signal transduction and activation, cell tissue growth, and differentiation involved in the cells are greatly inhibited. The process of tumor metastasis and development naturally decreases. There were no significant differences in IL-1β, IL-18, and ICAM-1 expression levels between control group A and control group B without RES intervention at each time point. Results suggest that RES has no toxic side effects for nasopharyngeal carcinoma.

In this experiment, a nude mice model of nasopharyngeal carcinoma was established, examining the effects of RES on IL-1β, IL-18, and ICAM-1 in nasopharyngeal carcinoma. There were some limitations to the current study. These limitations were due to limited experimental conditions, such as a lack of analysis concerning cytokines that RES may affect in nasopharyngeal carcinoma. Since the current pathogenesis and drug use mechanisms of nasopharyngeal carcinoma and RES have not yet been fully clarified, it is impossible to confirm the effects of RES on abnormalities of the above factors. Moreover, there are differences between animal models and the human body. Thus, the effects of RES on nasopharyngeal cancer may be different in human experiments. Present researchers will continue to explore the mechanisms of RES in nasopharyngeal cancer, aiming to verify present conclusions.

In summary, RES can inhibit levels of IL-1β, IL-18, and ICAM-1 in nasopharyngeal carcinoma nude mice. Therefore, this method may become a new direction for clinical treatment of nasopharyngeal carcinoma.

Acknowledgements

This work was supported by Grants from National Natural Science Foundation of China (Grant No. 81402502), Innovation Project in Hunan Province (Grant No. 2016zzts142).

Disclosure of conflict of interest

None.

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