Research Article

Influence of Dehydroxymethylepoxyquinomicin on Radiosensitivity of Thyroid Carcinoma TPC-1 Cells

Jie Liu,1 Hu Cai,2 Heqing Yi,1 Xin Li,1 Yunsong Peng,3 and Linfa Li1

1Department of Nuclear Medicine, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer Chinese, Hangzhou, Zhejiang 310022, China
2Department of Integrated Traditional Chinese and Western Medicine, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer Chinese, Hangzhou, Zhejiang 310022, China
3Department of Pharmacy, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer Chinese, Hangzhou, Zhejiang 310022, China

Correspondence should be addressed to Linfa Li; pet-ct001@163.com

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Objective. To investigate the influence of dehydroxymethylepoxyquinomicin (DHMEQ), an NF-κB inhibitor, on radiosensitivity of thyroid carcinoma (TC) TPC-1 cells. Methods. The isolation of CD133 positive cells (CD133+ TPC-1) and negative cells (CD133− TPC-1) from TPC-1 cells used immunomagnetic bead sorting. After verification of the toxicity of DHMEQ to cells by MTT and cell cloning assays, the cells were divided into four groups, of which three groups were intervened by DHMEQ, 131I radiation, and DHMEQ + 131I radiation, respectively, while the fourth group was used as a control without treatment. Alterations in cell growth, apoptosis, and cell cycle were observed. Results. DHMEQ had certain toxic effects on TPC-1 cells, with an IC50 of 38.57 μg/mL (P < 0.05). DHMEQ inhibited CD133+ and CD133− TPC-1 proliferation and their clonogenesis after irradiation. DHMEQ + radiation contributed to a growth inhibition rate and an apoptosis rate higher than either or them alone (P < 0.05), with a more significant effect on CD133− TPC-1 than CD133+ TPC-1 under the same treatment conditions (P < 0.05). Conclusion. DHMEQ can increase the radiosensitivity of TC cells to 131I, inhibit tumor cell growth, and promote apoptosis. However, its effect is less significant on CD133+ TPC-1 compared with CD133− TPC-1, which may be related to the stem cell-like properties of CD133+ cells. In the future, the application of DHMEQ in TC 131I radiotherapy will effectively improve the clinical effect of patients.

1. Introduction

Recent years have witnessed the rising incidence of thyroid carcinoma (TC), the most prevalent malignancy of the endocrine system [1]. As indicated by a survey, the global incidence of TC has increased by about 5 times over the past two decades, with a younger age at onset [2]. At present, the accepted standard treatment principle for TC in clinic is the comprehensive therapy based on surgery, supplemented by 131I radionuclide therapy and thyrotropin inhibitors [3]. The ten-year survival rate of most TC patients can be as high as 90%-95%, but some still relapse or metastasize after routine treatment, accompanied by radioactive iodine treatment tolerance and reduced 131I radiosensitivity, which is called radio-iodine refractory differentiated TC (RR-DTC) [4]. For such patients with a five-year survival rate less than 20%, the treatment difficulty is substantially increased, posing a huge challenge to current TC treatment [5]. Therefore, the clinic is eager to find a new treatment for RR-DTC to improve patients’ outcomes.

Nuclear factor-kappa B (NF-κB) is an eukaryotic transcription factor and a highly active molecule that, by binding to DNA, participates in regulating the expression of nearly 400 different genes, realizing the transcription regulation of various genes, cell proliferation, apoptosis, invasion, metastasis, immunity, and other processes [6]. Currently, NF-κB has been confirmed to be activated in many kinds of head and neck tumors including TC, for example, NF-κB-
activated miR-574 promotes multiple malignant and metastatic phenotypes by targeting BNIP3 in TC [7]. Whole-genome profiling of nasopharyngeal carcinosarcoma reveals viral-host co-operation in inflammatory NF-κB activation and immune escape [8]. Thus, NF-κB is also considered a breakthrough in future cancer treatment. Dehydroxymethyllepiperoxiquinomicin (DHMEQ) is a novel NF-κB inhibitor developed in recent years and synthesized from quinomycin C, a weak antibiotic [9]. DHMEQ has been shown to suppress NF-κB activity stimulated by bacterial lipopolysaccharide, chemotherapy, radiotherapy, and other stimulating factors. In mice, it inhibited hormone-depleted prostate cancer growth in vivo without side effects [10]. At present, DHMEQ has been found to effectively kill myeloma cells [11] and at the same time reverse the resistance of non-Hodgkin’s lymphoma cells to chemotherapy [12], which fully demonstrates the excellent role of DHMEQ in anti-tumor therapy in the future. Furthermore, the research of Pushkarev and Ukaji found that the combined use of paclitaxel and DHMEQ could inhibit the chemotherapy resistance of undifferentiated TC cells to paclitaxel; moreover, compared with common tumor cells, DHMEQ, as an NF-κB inhibitor, is more active in tumor stem cells [13, 14]. All these suggest the potential of DHMEQ to improve the treatment status of RR-DTC in the future. However, there is a group of cells with stem cell properties in tumor cells, which has the potential of self-renewal and multidirectional differentiation, which is the basis for tumor occurrence, development, metastasis, recurrence, and anti-radiotherapy and chemotherapy [15]. At present, researchers have found in TC that cancer stem cells are the key cells that cause tumor cell self-renewal and immune escape and reduce the sensitivity of TC cells to chemotherapy or 131I [16, 17]. It can be seen that in the research on drug resistance of tumor cells, tumor stem cells are one of the focuses that must be paid attention to. However, although a number of studies have shown the effect of DHMEQ on TC cells and the drug resistance of TC cells [18, 19], no study has yet confirmed whether DHMEQ has the same excellent effect in TC cancer stem cells.

Accordingly, in this experiment, DHMEQ + 131I radiation was applied to human papillary TC TPC-1 cells cultured in vitro and isolated its tumor stem cells to observe the changes in their biological behavior, so as to provide new ideas for future treatment of TC and a more reliable guarantee for the prognosis of patients.

2. Materials and Methods

2.1. Cell Culture. TPC-1 cells of the human papillary TC cell line (purchased from ATCC) were cultured at 37°C with 95% oxygen and 5% carbon dioxide in 10% fetal bovine serum and 1% penicillin/streptomycin-supplemented DMEM (Gibco BRL, Life Technologies, NY, USA). Cells at logarithmic (log) phase were selected for subsequent experiments.

2.2. Cell Isolation and Identification. After digestion, log-phase TPC-1 cells (1×10⁷) were centrifuged (1000 r/min, 5 min), washed twice with magnetic bead separation buffer, and added with 10μL CD133 antibody (designed and constructed by Suzhou Beike Zhenze Biotechnology) with magnetic beads to incubate at 4°C for 15 min. After being cleaned twice with 5 mL buffer, they were immersed in 3 mL buffer and slowly pipetted to form a single-cell suspension, which was then slowly dripped into a CD133 positive separation column placed in a magnetic field in advance, waiting for the natural flow. This was followed by two slow rinses with 3 mL buffer, and buffer (5 mL) addition to the separation tube to quickly wash out CD133 positive cells (CD133° TPC-1) and negative cells (CD133· TPC-1) adsorbed in the magnetic bead separation tube. Cell purity was verified by flow cytometry (FCM, FACSymphony A1 Flow Cytometer, BD USA) within 30 min and cells were collected for later use and cells after digestion were treated with 5 min of centrifugation at 1000 r/min, two PBS rinses, and addition of 20μL of fluorescent marker CD133 antibody, with mouse FITC-IgG2b antibody (ab136125, Abcam, USA) as a control. After incubating at 4°C for 30 min and washing with buffer twice, the percentage of CD133° cells was detected by FCM. The differences in the expression of TC stem cell markers OCT-4 and ABCG2 were compared and identified. Identification method: after the addition of protein lysate to verify the purity, the cells were electrochemically transferred to a PVDF membrane, where they were cultured at 4°C with OCT4 (1:1000, ab265606, Abcam, USA), ABCG2 (1:1000, ab207732, Abcam, USA), and β-actin (1:1000, ab8226, Abcam, USA) primary antibodies for 24 h. The second antibody was added to the membrane the next day, and the gray value was analyzed after ECL (WJ103L, Shanghai Epizyme Biomedical Technology Co., Ltd) development.

2.3. Cytotoxicity Test. MTT and cell cloning assays were performed to confirm the optimal treatment dose of DHMEQ, with the method described below.

2.4. MTT Assay. Blank, control, and drug groups were set up, with 5 replicate wells in each of them. Log-phase TPC-1 cells (4×10⁴/100μL) were inoculated into the wells of a 96-well cell culture plate. After cell adherence, different concentrations of DHMEQ-containing medium were added. MTT reagent (11465007001, Merck, USA) and DMSO (D2650, Merck, USA) were added, respectively, 24 h after intervention. The absorbance at 490 nm was measured by ELISA and the IC50 was calculated.

2.5. Cell Cloning Assay. Log-phase TPC-1 cells were divided into the following groups for corresponding intervention [20]: (1) Blank control group; (2) DHMEQ group: only treated with 15μg/mL DHMEQ; (3) Radiation group: 1Gy irradiation; (4) Joint group: cells were treated with 15μg/mL DHMEQ for 4 h and then irradiated with 1Gy. After treatment, cell culture was continued for 24 h, and fresh medium was used for routine culture for 7–10 d. The surviving colonies after crystal violet (Y0000418, Merck, USA) staining were observed and microscopically counted. The clone formation rate was calculated for each colony > 50 cells. Clone formation rate (PE%) = number of clones in control group/number of cells in experimental group × 100%.
2.6. FCM for Apoptosis. Apoptosis rate: according to the above groupings, cells were treated accordingly. Cells were collected 24 h and 48 h after culture, centrifuged, and washed, and apoptosis was detected by FCM with Annexin V-FITC/PI (APOAF, Merck, USA) double staining. Cell cycle: cells collected after continued culture for 24 h and 48 h were cleaned with PBS and fixed with 70% ethanol. After centrifugation, they were washed twice with PBS at an ambient temperature. They were then treated with 50 μL ribonuclease A, after which propidium iodide was added. Following 15 min of light tight incubation, FCM was used for detection.

2.7. Statistical Analysis. SPSS25.0 software processed the data. All assays were repeated 3 times, and the results were expressed as (x ± s). The t-test was used for between-group comparisons, and analysis of variance and the Tukey-HSD post-hoc test were performed to identify differences among multiple eligible means, with P < 0.05 indicating the presence of significance.

3. Results

3.1. Summary of Results. The results of this experiment found that DHMEQ inhibited CD133+ and CD133- TPC-1 proliferation and their clonogenesis after irradiation. DHMEQ + radiation contributed to a growth inhibition rate and an apoptosis rate higher than either or them alone (P < 0.05).

3.2. Cell Isolation Results. OCT4 and ABCG2 levels were found to be higher in CD133+ TPC-1 than in CD133- TPC-1 (P < 0.05). FCM analysis showed and identified the deletion of CD133 positivity, indicating successful isolation of stem cells (Figure 1).

3.3. Cytotoxicity Test Results. After treating CD133+ TPC-1 with different doses of DHMEQ, MTT assay was performed to examine cell growth. It showed that the cell growth capacity of CD133+ TPC-1 decreased gradually with the increase of DHMEQ concentration, and the activity reached the lowest when 100 μg/mL DHMEQ was used, with an IC50 of 38.57 μg/mL (P < 0.05). Cell cloning assay showed too potent an influence of the irradiation dose of 3Gy on cell viability; instead, 1-Gy irradiation slightly inhibited cell growth ability, which was more suitable for subsequent experiments. Then, DHMEQ with drug concentrations of 0, 15, and 30 μg/mL was used in combination with irradiation doses of 0Gy and 1Gy, respectively. 15 μg/mL DHMEQ plus 1-Gy irradiation was found to have a sensitization effect on cells, and flow cytometry showed that CD133+ TPC-1 cells
were positive for CD133, so the optimal dose for subsequent formal experiments was confirmed (Figure 2).

3.4. Influence of DHMEQ on Cell Activity. Among the four groups of cells, the control group had the strongest colony-forming ability ($P < 0.05$), slightly higher than the DHMEQ group and radiation group ($P < 0.05$). The ability of CD133$^+$ TPC-1 and CD133$^-$ TPC-1 cells in the joint group to form colonies was the lowest among the four groups ($P < 0.01$). Compared with CD133$^-$ TPC-1, the same treatment conditions inhibited the clonogenesis ability of CD133$^+$ TPC-1 less ($P < 0.05$) (Figure 3).

3.5. Influence of DHMEQ on Apoptosis. FCM analysis results identified that the apoptosis rate of DHMEQ group and control group was the lowest among the four groups at 24 h, while that of the joint group was higher compared with the radiation group ($P < 0.05$). At 48 h, the apoptosis rate was the lowest in the control group among the four groups and the highest in the joint group, while that of the DHMEQ group was higher versus the radiation group ($P < 0.05$). Similarly, under the same conditions, there were fewer apoptotic cells of CD133$^+$ TPC-1 (Figure 4).

3.6. Impacts of DHMEQ on Cell Cycle. Finally, it can be seen that a large number of cells in the joint group were arrested in the G2 phase. At 24 h and 48 h, the G2-phase cell distribution of CD133$^+$ TPC-1 and CD133$^-$ TPC-1 in the joint group was higher than that in the other three groups ($P < 0.05$). Thus, DHMEQ + radiation can redistribute the cell cycle in the G2 phase, which is more sensitive to radiation (Figure 5).

4. Discussion

Although most TC is difficult to cure, there are still a small number of patients with RR-DTC suffering from adverse

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**Figure 2:** Cytotoxicity test results ($n=3$). (a) MTT assay of cell viability after treatment with different doses of DHMEQ. (b) Cell cloning experiments to detect cell viability after different irradiation doses. (c) Cell cloning rate. (d) Cell cloning assay to detect cell viability after DHMEQ combined with radiation treatment. (e) Cell cloning rate. (f) CD133 expression detected by flow cytometry. $^* P < 0.05$, $^{**} P < 0.01$. 
Figure 3: Influence of DHMEQ on cell activity (n=3). (a) Results of cell cloning experiment. (b) Cell cloning rate. *P < 0.05, **P < 0.01.

Figure 4: Influence of DHMEQ on apoptosis (n=3). (a) Flow cytometry results at 24 h. (b) Flow cytometry results at 48 h. (c) Apoptosis rate at 24 h. (d) Apoptosis rate at 48 h. *P < 0.05, **P < 0.01.

The chemosensitization effect of NF-κB inhibitors on undifferentiated TC cells has been repeatedly demonstrated, which can explain the increasing clinical attention of the involvement of NF-κB pathway in malignant tumor stem cells (including TC stem cells) [22–24]. At present, there is no report about the radiosensitization effect of NF-κB inhibitor DHMEQ on thyroid stem cell-like cells at home and abroad, which may be due to the lack of TC-specific stem cell markers. In the current research, the TPC-1 cell
Figure 5: Continued.
A study involving experiments with DHMEQ and TC cells revealed how DHMEQ, alone or in combination with other treatments, affects cell activity and inhibitory effect. Specifically, the use of DHMEQ led to a decreased CD133 marker expression, an increase in IC50 values for DHMEQ, and an increased sensitivity to 131I radiotherapy. This suggests that DHMEQ may be an effective treatment in TC, potentially as a combination therapy with radiotherapy.

The study further evaluated the differences in cell cycle distribution and cell cycle changes under various DHMEQ concentrations. It was observed that the number of CD133+ TPC-1 cells decreased significantly compared to CD133- TPC-1. Additionally, the CD34+ side population cells were also analyzed, and it was found that the IC50 of DHMEQ to TPC-1 cells was 38.57 μg/mL, increased with the concentration of DHMEQ, and it was consistent with the characteristics of CD133+ TPC-1. OCT4 and ABCG2 protein expression levels increased in CD133+ TPC-1 cells, indicating successful isolation of the stem cells. Furthermore, the data showed that the number of S-phase CD133- TPC-1 of DHMEQ group was significantly higher than that in normal cells, and its main function is to regulate the release of inflammatory factors. Glycolysis in tumor cells produces more Adenosine triphosphate than oxidative phosphorylation, and glucose is an essential component of their energy metabolism.

In conclusion, the study supports the use of DHMEQ for TC treatment, particularly in combination with radiotherapy, indicating its potential as a promising therapeutic strategy.

**Figure 5:** Impact of DHMEQ on cell cycle (n=3). (a) Cell cycle distribution at 0 h. (b) Cell cycle changes at 0 h. (c) Cell cycle distribution at 24 h. (d) Cell cycle changes at 24 h. (e) Cell cycle distribution at 48 h. (f) Cell cycle changes at 48 h.
nutrient for tumor and normal cell proliferation [28]. Thus, in tumor cells, NF-κB orchestrates many signals of cell activation and proliferation in immune, inflammatory, and carcinogenesis processes [29]. Second, many tumors have activated NF-κB, which keeps cells proliferating and protects them from apoptosis [30]. In addition, the tumor microenvironment often has constitutive NF-κB signaling, which can promote the accumulation of inflammatory factors and tumor-promoting cytokines, further maintaining a favorable environment for tumor growth [31]. In the process of radiotherapy or chemotherapy, NF-κB in tumor cells will be further activated due to the damage of drug toxicity and side effects; high-activity NF-κB can promote the massive production of anti-apoptotic factors, such as Bcl-xL, Bcl-2, IAPs, XIAP, and survivin, and inhibit cancer cell apoptosis, resulting in drug resistance [32]. The increase of NF-κB in TC cells is also related to the occurrence, progression, and chemoradiotherapy tolerance of TC [33]. In the treatment of related tumor diseases, inhibition of NF-κB has become a new generation of therapeutic targets [34]. At present, strategies to inhibit NF-κB signaling mainly include inhibition of protein kinases and phosphatases related to the NF-κB pathway, ubiquitination, acetylation, methylation, and DNA binding steps of NF-κB activity [35]. DHMEQ inhibits its DNA binding by covalently binding to specific cysteine residues of NF-κB components and simultaneously inhibits the activation of macrophages and the maturation of dendritic cells [36]. In this study, DHMEQ induces cancer cell apoptosis through the suppression of NF-κB and can increase the sensitivity of tumor to chemotherapy, which may also be the direct mechanism by which DHMEQ enhances 131I radiosensitivity. Of course, more experiments are needed to confirm this. In this study, we can also see that under the same treatment conditions, the effect of DHMEQ on CD133 TPC-1 was not as significant as that on CD133-TPC-1. This may be related to the stem-like properties of CD133+ cells, indicating that CD133+ cells have a stronger carcinogenic ability, which is consistent with previous studies [37, 38].

However, due to the limited experimental conditions, we were unable to analyze the mechanism of the effect of DHMEQ on TC cells. Therefore, we need to further analyze the mechanism of DHMEQ’s effect on TC cells in subsequent studies. In addition, we should also add other TC cell lines for validation experiments to further confirm the effect of DHMEQ on TC cancer stem cells, and verify the effect of DHMEQ on living tumor through nude mouse tumorigenesis experiment, so as to lay a reliable foundation for the future clinical application of DHMEQ, so as to realize the clinical use of DHMEQ and improve the treatment effect and prognosis of TC patients.

5. Conclusion

DHMEQ can increase the radiosensitivity of TC cells to 131I, inhibit tumor cell growth, and promote apoptosis. However, its effect is less significant on CD133+ TPC-1 compared with CD133-TPC-1, which may be related to the stem cell-like properties of CD133+ cells.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors’ Contributions

Jie Liu and Hu Cai contributed equally to this work.

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References

[1] S. M. Ferrari, P. Fallahi, G. Elia et al., "Thyroid autoimmune disorders and cancer," Seminars in Cancer Biology, vol. 64, pp. 135–146, 2020.
[2] A. Prete, P. Borges de Souza, S. Censi, M. Muzza, N. Nucci, and M. Spontizillo, "Update on fundamental mechanisms of thyroid cancer," Frontiers in Endocrinology, vol. 11, p. 102, 2020.
[3] K. A. Araque, S. Gubbi, and J. Klubo-Gwiezdzinska, "Updates on the management of thyroid cancer," Hormone and Metabolic Research, vol. 52, no. 8, pp. 562–577, 2020.
[4] P. Fallahi, S. M. Ferrari, M. R. Galdiero et al., "Molecular targets of tyrosine kinase inhibitors in thyroid cancer," Seminars in Cancer Biology, vol. 79, pp. 180–196, 2022.
[5] N. Pozdeyev, M. M. Rose, D. W. Bowles, and R. E. Schweppe, "Molecular therapeutics for anaplastic thyroid cancer," Seminars in Cancer Biology, vol. 61, pp. 23–29, 2020.
[6] J. A. DiDonato, F. Mercurio, and M. Karin, "NF-κB and the link between inflammation and cancer," Immunological Reviews, vol. 246, no. 1, pp. 379–400, 2012.
[7] Z. J. Zhang, Q. Xiao, and X. Y. Li, "NF-κB-activated miR-574 promotes multiple malignant and metastatic phenotypes by targeting BNIP3 in thyroid carcinoma," Molecular Cancer Research, vol. 18, no. 7, pp. 955–967, 2020.
[8] J. P. Bruce, K. F. To, V. W. Y. Lui et al., "Whole-genome profiling of nasopharyngeal carcinoma reveals viral-host cooperation in inflammatory NF-κB activation and immune escape," Nature Communications, vol. 12, no. 1, p. 4193, 2021.
[9] S. Morita, K. Shioda, T. Yoshida et al., "Dehydroxymethyldehyquinnominic, a novel nuclear factor-κB inhibitor, prevents
the development of cyclosporine A nephrotoxicity in a rat model,” *BMC Pharmacology and Toxicology*, vol. 21, no. 1, p. 60, 2020.

[10] H. Fujisaki, Y. Nakano, S. Matsuda et al., “Intravenous administration of dehydroxymethylpoxyquinoiminic with polymer enhances the inhibition of pancreatic carcinoma growth in mice,” *Anticancer Research*, vol. 41, no. 12, pp. 6003–6012, 2021.

[11] H. Tatetsu, Y. Okuno, M. Nakamura et al., “Dehydroxymethylpoxyquinnomycin, a novel nuclear factor-κB inhibitor, induces apoptosis in multiple myeloma cells in an IκBα-independent manner,” *Molecular Cancer Therapeutics*, vol. 4, no. 7, pp. 1114–1120, 2005.

[12] M. I. Vega, M. Martinez-Paniagua, A. R. Jazirehi et al., “The NF-κB inhibitor (bortezomib and DHMEQ) sensitizes rituximab-resistant AIDS-B-non-Hodgkin lymphoma to apoptosis by various chemotherapeutic drugs,” *Leukemia & Lymphoma*, vol. 49, no. 10, pp. 1982–1994, 2008.

[13] X. Jiang, H. He, Z. Xie et al., “Dehydroxymethylpoxyquinomycin suppresses atopic dermatitis-like lesions in a stratum corneum-removed murine model through NF-κB inhibition,” *Immunopharmacology and Immunotoxicology*, vol. 41, no. 1, pp. 32–39, 2019.

[14] H. Zhang, W. T. Yang, Z. Wang et al., “Dehydroxymethylpoxyquinomycin selectively ablates T-CAEBV cells,” *Frontiers in Bioscience-Landmark*, vol. 20, no. 3, pp. 502–514, 2015.

[15] L. Walcher, A. K. Kistenmacher, H. Suo et al., “Cancer stem cells-origins and biomarkers: perspectives for targeted personalized therapies,” *Frontiers in Immunology*, vol. 11, p. 1280, 2020.

[16] V. Veschi, F. Verona, M. Lo Iacono et al., “Cancer stem cells in thyroid tumors: from the origin to metastasis,” *Frontiers in Endocrinology*, vol. 11, p. 566, 2020.

[17] S. Mirshahidi, A. Simental, S. C. Lee et al., “Subpopulations of cancer stem cells found in papillary thyroid carcinoma,” *Experimental Cell Research*, vol. 362, no. 2, pp. 515–524, 2018.

[18] Z. Meng, N. Mitsutake, M. Nakashima et al., “Dehydroxymethylpoxyquinomycin, a novel nuclear factor-kappaB inhibitor, enhances antitumor activity of taxanes in anaplastic thyroid cancer cells,” *Endocrinology*, vol. 149, no. 11, pp. 5357–5365, 2008.

[19] H. Namba, V. Saenko, and S. Yamashita, “Nuclear factor-kb in thyroid carcinogenesis and progression: a novel therapeutic target for advanced thyroid cancer,” *Arquivos Brasileiros de Endocrinologia e Metabologia*, vol. 51, no. 5, pp. 843–851, 2007.

[20] S. Jiang, M. Yu, H. Wang et al., “131I-radioisotope modified in PEGylation metal organic frameworks for sensitization in refractory differentiated thyroid cancer treatment,” *Journal of Biomaterials Applications*, vol. 36, no. 5, pp. 851–858, 2021.

[21] H. Zhang, H. L. Duan, S. Wang, Y. Liu, G. N. Ding, and R. X. Lin, “Epigenetic signature associated with thyroid cancer progression and metastasis,” *Seminars in Cancer Biology*, vol. 83, pp. 261–268, 2022.

[22] S. Ahmad, M. Abbas, M. F. Ullah et al., “Long non-coding RNAs regulated NF-κB signaling in cancer metastasis: Micromanaging by not so small non-coding RNAs,” in *Seminars in Cancer Biology*, Academic Press, 2021.

[23] M. A. Ansari, M. Thiruvengadam, B. Venkidasamy et al., “Exosome-based nanomedicine for cancer treatment by targeting inflammatory pathways: current status and future perspectives,” in *Seminars in Cancer Biology*, Academic Press, 2022.

[24] R. R. Rasmi, K. M. Sakhivel, and C. Guruvayoorappan, “NF-κB inhibitors in treatment and prevention of lung cancer,” *Biomedicine & Pharmacotherapy*, vol. 130, p. 110569, 2020.

[25] Y. Ando, Y. Sato, A. Kudo et al., “Anti-inflammatory effects of the NF-κB inhibitor dehydroxymethylpoxyquinomycin on ARPE-19 cells,” *Molecular Medicine Reports*, vol. 224, no. 1, pp. 582–590, 2020.

[26] Q. Xu, R. P. Mackay, A. Y. Xiao, J. A. Copland, and P. M. Weinberger, “Ym155 induces oxidative stress-mediated DNA damage and cell cycle arrest, and causes programmed cell death in anaplastic thyroid cancer cells,” *International Journal of Molecular Sciences*, vol. 22, no. 4, p. 1961, 2021.

[27] L. Barnabei, E. Laplantine, W. Mbongo, F. Rieux-Laucat, and R. Weil, “NF-κB: at the borders of autoimmunity and inflammation,” *Frontiers in Immunology*, vol. 12, p. 716469, 2020.

[28] Z. Abbaszadeh, S. Çaşmeli, and A. C. Biray, “Crucial players in glycolysis: cancer progress,” *Gene*, vol. 726, p. 144158, 2020.

[29] C. Peng, Y. Ouyang, N. Lu, and N. Li, “The NF-κB signaling pathway, the microbiota, and gastrointestinal tumorigenesis: recent advances,” *Frontiers in Immunology*, vol. 11, p. 1387, 2020.

[30] G. Lalle, J. Twardowski, and Y. Grinberg-Bleyer, “NF-κB in cancer immunity: friend or foe,” *Cell*, vol. 10, no. 2, p. 355, 2021.

[31] H. Fukatsu, N. Koide, S. Tada-Oikawa et al., “NF-κB inhibitor DHMEQ inhibits titanium dioxide nanoparticle-induced interleukin-1β production: inhibition of the PM2.5-induced inflammation model,” *Molecular Medicine Reports*, vol. 18, no. 6, pp. 5279–5285, 2018.

[32] N. Pozdeyev, A. Berlinberg, Q. Zhou et al., “Targeting the NF-κB pathway as a combination therapy for advanced thyroid cancer,” *PLoS One*, vol. 10, no. 8, article e0134901, 2015.

[33] B. Liu, L. Sun, Q. Liu et al., “A cytoplasmic NF-κB interacting long noncoding RNA blocks IκB phosphorylation and suppresses breast cancer metastasis,” *Cancer Cell*, vol. 27, no. 3, pp. 370–381, 2015.

[34] K. Song and S. Li, “The role of ubiquitination in NF-κB signaling during virus infection,” *Viruses*, vol. 13, no. 2, p. 145, 2021.

[35] C. Kalschmidt, J. F. W. Greiner, and B. Kalschmidt, “The transcription factor NF-κB in stem cells and development,” *Cell*, vol. 10, no. 8, p. 2042, 2021.

[36] K. Horie, J. Ma, and K. Umewaza, “Inhibition of canonical NF-κB nuclear localization by (-)DHMEQ via impairment of DNA binding,” *OncoResearch*, vol. 22, no. 2, pp. 105–115, 2015.

[37] M. Aghajani, B. Mansoori, A. Mohammadi, Z. Asadzadeh, and B. Baradaran, “New emerging roles of CD133 in cancer stem cell: signaling pathway and miRNA regulation,” *Journal of Cellular Physiology*, vol. 234, no. 12, pp. 21642–21661, 2019.

[38] B. Bussolati, F. Collino, and G. Camussi, “CD133+ cells as a therapeutic target for kidney diseases,” *Expert Opinion on Therapeutic Targets*, vol. 16, no. 2, pp. 157–165, 2012.