Preferential Enhancement of Tumor Radioresponse by a Cyclooxygenase-2 Inhibitor

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ABSTRACT

Cyclooxygenase-2 (COX-2), an inducible isofrom of cyclooxygenase, is overexpressed in many types of malignant tumors, where it mediates production of prostaglandins (PGs), which in turn may stimulate tumor growth and protect against damage by cytotoxic agents. This study investigated whether SC-9236, a selective inhibitor of COX-2, potentiates anti-tumor efficacy of radiation without increasing radiation injury to normal tissue. Mice bearing the sarcoma FSA in the hind legs were treated daily for 10 days with SC-9236 (6 mg/kg given in the drinking water) when tumors were 6 mm in diameter. When tumors reached 8 mm in diameter, the mice were given 11- to 50-Gy single-dose local tumor irradiation with or without SC-9236. SC-9236 inhibited tumor growth on its own, and it greatly enhanced the effect of tumor irradiation. The growth delay was increased from 14.8 days after 25-Gy single dose to 28.4 days after the combined treatment (P = .01). SC-9236 reduced TCD50 (radiation dose yielding 50% local tumor cure) from 39.2 Gy to 20.9 Gy (enhancement factor = 1.87). SC-9236 did not appreciably alter radiation damage to jejunal crypt cells and tissue involved in the development of radiation-induced leg contractures. The SC-9236-induced enhancement of tumor radioresponse was associated with a decrease in PGE2 levels in FSA tumors. The drug had no effect on radiation-induced apoptosis. Neoaangiogenesis was inhibited by SC-9236, which could account for some of the increase in tumor radioresponse. Overall, our findings demonstrated that treatment with a selective inhibitor of COX-2 greatly enhanced tumor radioresponse without markedly affecting normal tissue radioresponse. Thus, COX-2 inhibitors have a high potential for increasing the therapeutic ratio of radiotherapy.

INTRODUCTION

Recently, it was established that there exist two isofroms of the enzymes that synthesize PGs: COX-1 and COX-2. COX-1 is a ubiquitous constitutive enzyme that has a housekeeping physiological function, whereas COX-2 is an inducible form that is induced by diverse inflammatory stimuli, oncoproteins, and growth factors (1–5).

Increasing evidence shows that COX-2 promotes carcinogenesis as well as the growth of established tumors (3, 6). COX-2 is up-regulated in a high percentage of common cancers in humans and is associated with invasive and metastatic tumor behavior (7–12). Thus, the specific expression of COX-2 in tumors but not in normal tissue may serve as a potential target for anticancer therapy. Newly developed selective inhibitors of COX-2 have been shown to prevent carcinogenesis and to slow the growth of tumors in experimental animals (12–15). There is evidence that the mechanism involves PGs, which can modulate cellular injury induced by a wide array of agents, including ionizing radiation (16–18). A number of natural PGs and their synthetic analogues have shown the ability to protect cells and tissue from radiation injury (16, 18). With respect to cancer, production of PG by tumors was found to be associated with tumor radioresistance (16, 17, 19). Tumors were more responsive to radiation when their production of PGs was suppressed by NSAIDs such as indomethacin (17, 20, 21). In addition, NSAIDs increased in vitro radiosensitivity of cancer cells (22).

Because indomethacin and other commonly used NSAIDs inhibit both COX-1 and COX-2, treatment with these agents may be limited by normal tissue toxicity, particularly of that of the gastrointestinal tract (3, 13, 14). Because selective COX-2 inhibitors exert potent anti-inflammatory activity but cause fewer unwanted side effects (1, 15), they may be more suitable as anticancer agents, both in prevention of carcinogenesis and in cancer therapy, than standard NSAIDs. In a short communication, we recently reported that SC-9236, a selective COX-2 inhibitor, dramatically enhanced radiation response of a murine sarcoma, designated NFSa (23). Because the therapeutic potential of SC-9236 might ultimately depend on the response of both tumor and normal tissue, in the present study we investigated the effect in mice of SC-9236 on radioresponse of another sarcoma, designated FSA, and on radioresponse of normal tissues, notably jejunal mucosa and tissue responsible for radiation-induced leg contracture. The present study also explored the mechanism by which SC-9236 enhances tumor radioresponse.

MATERIALS AND METHODS

Mice and Tumors

Inbred C3Hf/Kam mice, bred and maintained in our own specific pathogen-free mouse colony, were used. The mice were 3–4 months of age and weighed 27–34 g at the beginning of the experiments. The mice were housed five per cage and fed sterilized pelleted food (Prolabs Animal Diet; Agway, Syracuse, NY). The tumor was an immunogenic sarcoma, designated FSA, induced by methylcholanthrene in this strain of mice. The FSA tumor produces high levels of PGE2 (24) and was used in our earlier studies that assessed the therapeutic potential of indomethacin when combined with radiation (20, 21). When used for these experiments, the tumor was in its sixth isotransplant generation. Solid tumors were generated in the muscles of the right thighs of mice by the inoculation of 3 × 10^5 viable tumor cells (25). Tumor cell suspensions were prepared by enzymatic preparation of nonneocrotic tumor cell; cell viability was >95% as determined by trypsin blue exclusion and phase microscopy.

COX-2 Inhibitor

Mice were given SC-9236 at a dose of 6 mg/kg body weight (Searle, Skokie, IL) or vehicle (0.05% Tween 20 and 0.95% polyethylene glycol; Sigma Chemical Co., St. Louis, MO) in the drinking water. To achieve this dose, SC-9236 was dissolved in a stock solution of 5% Tween 20 and 95% polyethylene glycol and diluted in distilled water to achieve a final SC-9236 concentration of 0.045 mg/ml. The mice drank ~4 ml/day of this diluted solution. Depending on the individual experiment, the treatment with SC-9236 lasted 6.5 or 10 days. Water bottles were changed every 3 days. The treatment with SC-9236 for 10 days caused no drug-related mortality: only 1 of 67 mice treated with SC-9236 in tumor growth delay and TCD50 experiments died from unknown causes.

Tumor Response to Radiation

The effect of SC-9236 on tumor radioresponse was determined using tumor growth delay and a TCD50 assay. When leg tumors grew to 6 to 6.3 mm in diameter, solitary tumors were generated in the muscles of the right thighs of mice by the inoculation of 3 × 10^5 viable tumor cells (25). Tumor cell suspensions were prepared by enzymatic preparation of nonneocrotic tumor cell; cell viability was >95% as determined by trypsin blue exclusion and phase microscopy.
diameter, mice were treated with SC-236 (6 mg/kg) or vehicle daily for 10 consecutive days. When these tumors grew to 8 mm in diameter, which occurred between 2 and 3 days in vehicle-treated mice and between 2 and 5 days in treated mice, mice were exposed to a 25-Gy single dose (tumor growth delay experiment) or an 11- to 50-Gy single dose of γ-radiation (TCD50 assay). Irradiation to the tumor was delivered from a dual-source 137Cs irradiator at a dose rate of 6.31 Gy/min. During irradiation, unanesthetized mice were immobilized in a jig, and the tumor was centered in a circular radiation field 3 cm in diameter.

To obtain tumor growth curves, three mutually orthogonal diameters of tumors were measured at 1-, 2-, or 3-day intervals with a vernier caliper, and the mean values were calculated. Regression and regrowth of tumors were followed until tumor diameter reached ~14 mm. Tumor growth delay was expressed as the time in days for tumors treated with radiation to grow from 8 to 12 mm in diameter minus the time in days for untreated tumors to reach the same size. This was termed the absolute tumor growth delay. The effect of the combined SC-236 plus irradiation treatment was expressed as the normalized tumor growth delay, defined as the time for tumors treated with both SC-236 and radiation to grow from 8 to 12 mm in diameter minus the time in days for tumors treated with SC-236 alone to reach the same size. Groups consisted of seven or eight mice each.

In the TCD50 assay, the mice were checked for the presence of tumor at the irradiated site at 2- to 7-day intervals after irradiation for up to 120 days. Each TCD50 assay contained 52 mice.

**Normal Tissue Response to Radiation**

**Jejunum.** The microcolony assay introduced by Withers and Elkind (26) was used to determine the survival of crypt epithelial cells in the jejunum of mice exposed to radiation. Non-tumor-bearing mice were exposed to WBI with single doses of X-rays ranging from 9.5 to 13.5 Gy given at a dose rate of 1.62 mGy/min. The mice were given SC-236 (6 mg/kg) in drinking water for 6.5 consecutive days, starting 3 days before WBI, and were killed by CO2 inhalation 3.5 days after WBI. The jejunum was prepared for histological examination, and the regenerating crypts in the jejunal cross-section were counted. To construct radiation survival curves, we converted the number of regenerating crypts to the number of surviving cells by applying a Poisson correction for the number of crypts regenerating from more than one stem cell. Lines were fitted to data points by least squares regression analysis.

**Leg Contracture.** Radiation-induced leg contraction (reduction in the leg extension) was determined on mice in the TCD50 assays for FSA (present study) and NFSA (23) that had no recurrent tumors present. The measurement was performed 120 days after irradiation, when leg contracture was at a plateau. Extensibility of both the treated right- and the control left-hind leg in each mouse was measured using the jig device described previously (27). The tail was placed between two vertical posts and held taut while each leg was extended against a millimeter ruler embedded in the base. Both the control and the irradiated leg could be extended easily to a certain point beyond which there was considerably greater resistance to further extension. Readings were made at this point, measuring to the tip of the central digit, and were reproducible to within ±1 mm when repeated by the same person or a different individual. Irradiation doses ranged from 16 to 65 Gy in the treatment group versus 30–80 Gy in control.

**COX-2 Analysis**

Western blot analysis was used to determine whether FSA tumors expressed the COX-2 isofrom. Fresh nonneoplastic tumor tissue was derived from 8- to 9-mm tumors growing in the right hind leg of mice. The tissue was homogenized using a glass-on-glass tissue homogenizer and thawed in ice-cold lysis buffer [50 mM HEPES, 0.4 M NaCl, 1 mM EDTA (pH 7.9)] containing 2 μg/ml aprotinin, 2 μg/ml leupeptin, 2 μg/ml benzamidine, 5 μg/ml phenylmethylsulfonyl fluoride, 1 mM DTT, and 10 μl/100 μl NP40 (10%). Lysates were sonicated for 30 s on ice and centrifuged at 14,000 rpm for 10 min at 4°C to remove the particulate material. The protein concentration of the supernatant in the sample was measured by the Bio-Rad DC Kit (Bio-Rad Laboratories) according to the manufacturer’s instructions, using BSA as a standard. Eighty micrograms of protein were electrophoresed on a 12% SDS-polyacrylamide gel and then electrophoretically transferred to a polyvinylidene difluoride membrane. Filters were incubated for 5 h at room temperature in blocking solution (Tris-buffered saline containing 5% nonfat dried milk and 0.05% Tween 20). Primary antibody to COX-2 (Cayman Chemical, Ann Arbor, MI) was used at a final dilution of 1:2000 overnight in blocking solution. Filters were washed three times and incubated with horseradish peroxidase-conjugated rabbit antihuman IgG as a secondary antibody (1:2000) for 40 min. After three additional washes, the signal was revealed using the enhanced chemiluminescence detection system ECL-Plus (Amersham, Arlington Heights, IL). The membrane image was digitized and stored in a computer and quantified by imaging software. Ovine recombinant COX-2 (Oxford BioMed, Oxford, MI) was used as a positive control. The same procedure was used to determine COX-2 expression in FSA cells grown in vitro and thus deprived of normal cells. Tumor cells were analyzed for the in vitro response to 12-O-tetradecanoylphorbol-13-acetate, known to induce COX-2 expression (28).

**PGE2 Analysis**

To determine the effect of SC-236 on the catalytic activity of COX-2, the production of PGE2 was measured in FSA tumors treated with SC-236 or vehicle for 3 days. The methods for measurement of PGE2 have been described previously (29). In brief, FSA tumor tissue was homogenized, washed in DMEM, and incubated in 30 μM arachidonic acid for 10 min at 37°C. Supernatants were collected and kept at −20°C until tested. PGE2 formed by the reaction was determined by a commercial ELISA.

**Histological Determination of Apoptosis**

For histological examinations, the tumors were removed and fixed in neutral-buffered 10% formalin. The tissue was embedded in paraffin blocks; 4-μm sections were cut from these blocks and stained with H&E. The mor-
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Fig. 2. Radiation dose-response curves for local tumor control of FSA tumors. Closed symbols, irradiation only; open symbols, irradiation plus SC-236 treatment. Horizontal bars at TCD50 are 95% confidence limits. Treatments with SC-236 and local tumor irradiation are described in the legend for Fig. 1B.

RESULTS

Tumor Angiogenesis

An intradermal assay (21, 32) was used to assess the effect of SC-236 on tumor angiogenesis. A triangular skin flap was created on the right abdominal region of mice anesthetized with Nembutal (0.06 mg/body weight) by making a skin incision along the midline of the abdomen and extending it to the right groin. The skin flap was separated from the s.c. tissue by a gentle pull laterally and then was searched for an area with the fewest tiny blood vessels as determined using a dissecting microscope with a magnification of ×20. After the number of blood vessels at the tumor cell injection site was recorded, 105 FSA cells were injected intradermally in a volume of 0.03 ml of PBS, using a 30-gauge needle. The skin flap was then brought back to the midline and closed with surgical clips. One day after the injection of tumor cells, the mice began receiving treatments with SC-236 (6 mg/kg) in the drinking water, which continued daily for 9 consecutive days. The number of blood vessels as well as tumor size was determined at 2, 4, 6, 8, and 10 days after tumor cell injection. This was performed under a dissecting microscope (×20) in anesthetized animals in which the skin flap was reopened by removing the surgical clips and pulling the flap laterally. The tumor volume was calculated using the formula for an elliptical mass (1/6πab).

Statistical Methods

Statistical analysis was performed using Statistica 5.1 (StatSoft, Tulsa, OK). Comparison of means was carried out by t test; the TCD50 was calculated using maximum likelihood analysis. Differences with P values <0.05 were considered statistically significant.

Tumor Response to Radiation. To determine whether SC-236 affects the growth of FSA, mice bearing 6.3-mm mean diameter tumors were given SC-236 (6 mg/ml) or vehicle in the drinking water for 10 consecutive days. As shown in Fig. 1A, SC-236 slowed the growth of FSA; the effect was evident within 2 days from the start of the treatment. Tumors in the control group doubled in size (from 6.3 to 12.6 mm) in 5.4 ± 0.5 days; those in the SC-236-treated group doubled in 7.7 ± 0.5 days (P = 0.02).

The next experiment tested the effect of SC-236 on the radiore- sponse of FSA. Tumor-bearing mice were treated with SC-236 alone, radiation alone, or a combination of both, and tumor growth delay was measured. The 10-day treatment with SC-236 commenced when tumors were ~6 mm in diameter, and tumors were locally irradiated with a 25-Gy single dose when 8 mm in diameter, which occurred 2–5 days later. Fig. 1B shows that SC-236 greatly increased radiation-induced tumor growth delay. Growth delay after the combined treatment was more than the sum of growth delays caused by either alone. Tumors grew from 8 to 12 mm tumors in 4.1 ± 0.5 days when treated with vehicle, 5.5 ± 0.3 days when treated with SC-236, 14.8 ± 1.0 days when treated with 25 Gy of local tumor irradiation, and 28.4 ± 3.5 days when treated with both agents (P = 0.03, compared with radiation only group). The EF was 2.14. It was obtained by dividing the normalized tumor growth delay of the combined groups (22.9 days) by the absolute tumor growth delay of the radiation-only group (10.2 days).

A TCD50 study was performed to determine whether SC-236 augments tumor radiocurability. As in the tumor growth delay experiment, a 10-day treatment with SC-236 was started when tumors were ~6 mm in diameter, and local irradiation was given when tumors were 8 mm in diameter. Single doses of irradiation ranged from 25 to 50 Gy in mice treated with vehicle and from 11 to 46 Gy in mice treated with SC-236. The radiation dose-response curves for tumor control at 120 days after irradiation are shown in Fig. 2. SC-236 greatly reduced the TCD50 value, from 39.2 Gy (95% confidence limits, 35.0, 43.9 Gy) to 20.9 Gy (95% confidence limits, 16.8, 24.8 Gy). The EF was 1.87, and obtained by dividing the TCD50 of the combined treatment group with that of the radiation-alone group. Thus SC-236 greatly enhanced the radioreresponse of the FSA tumor.

Normal Tissue Response to Radiation. To be therapeutically beneficial, any radiopotentiating agent must increase tumor radiore- sponse more than the radioresponse of dose-limiting normal tissues. Here, we assessed whether SC-236 affects the radioresponse of jejunal mucosa, an example for acute normal tissue damage, and

Fig. 3. Radiation single-dose survival curves for jejunum crypt cells in mice treated with SC-236 (○) or with vehicle (●). Intercepts of survival curves were significantly different at P < 0.0007. Bars, SE.
whether it modifies radiation-induced leg contracture, an example of late radiation damage. In the experiment that assessed jejunal damage, SC'-236 (6 mg/kg) was given in the drinking water for 6.5 consecutive days starting 3 days before the mice were exposed to a single dose of WBI (range, 9.5–13.5 Gy). Fig. 3 shows the survival of crypt epithelial cells as a function of radiation dose. Radiation caused a dose-dependent reduction in crypt cell survival. Treatment with SC'-236 caused a small but significant ($P < 0.007$) shift in the radiation survival curve to lower doses, indicating an EF of 1.03. This small shift would probably not be clinically detectable.

The effect of SC'-236 on radiation-induced leg contracture was determined in the same mice that were used in the TCD$_{50}$ experiment with FSA (see Fig. 2) and in the experiment with NFSA tumor reported previously (23). Mice with no recurrence in the irradiated leg were examined for leg contracture 120 days after irradiation. The degree of leg contracture increased with the increase in radiation dose, and SC'-236 treatment had no effect on its severity (Fig. 4).

**COX-2 Expression and PGE$_2$ Production in FSA.** We previously reported that the FSA tumor produces a number of PGs, in particular PGE$_2$ (24), and that the antitumor and radioenhancing effects of indomethacin were associated with a reduction in PGE$_2$ production (20). The following experiments determined whether FSA expresses COX-2 and whether the expression of COX-2 and PGE$_2$ production by this tumor are influenced by SC'-236. The levels of COX-2 and PGE$_2$ were determined in tumors derived from mice after treatment with vehicle or SC'-236 (6 mg/kg) for 3 consecutive days. Western blot analysis (Fig. 5A) showed that FSA expressed COX-2 protein and that its expression was not influenced by SC'-236 (Fig. 5B). In contrast, SC'-236 reduced the level of PGE$_2$ in FSA tumors from the control value of 1411 $\pm$ 437 ng/g to 400 $\pm$ 112 ng/g ($P = 0.03$).

**Apoptotic Induction.** The possibility that SC'-236 enhanced tumor radioresponse by increasing sensitivity of tumor cells to radiation-induced apoptosis was considered. Tumors in mice treated with SC'-236 or vehicle for 3 days were locally irradiated with 25 Gy and then analyzed for apoptosis 4, 8, or 24 h after irradiation. The controls were tumors treated with SC'-236 or vehicle only. The percentage of apoptotic cells in the control (vehicle) as well as in the treatment groups was <1% (results not shown), which shows that induction of
apoptosis was not a mechanism by which SC-’236 enhanced FSA radioresponse.  

**Tumor Angiogenesis.** Because PGs stimulate angiogenesis, the possibility that SC-’236 slowed tumor growth by inhibiting tumor angiogenesis was investigated. The mice received intradermal injections of tumor cells, and the number of vessels at the injection site was determined 2, 4, 6, 8, and 10 days later. In Fig. 6 is shown that neovascularization preceded measurable tumor growth and that SC-’236 significantly reduced the number of newly formed vessels. Whereas the vessel count in the control group was 38.4 ± 2.1 after 10 days, it reached only 25.7 ± 1.7 in the treatment group. This significant reduction (P < 0.005) in neovascularization was associated with significant tumor growth retardation, from 267.7 ± 9 mm³ in controls to 117.8 ± 9 mm³ after COX-2 inhibitor treatment (P < 0.005).

**DISCUSSION**

PGs are metabolites of polyunsaturated fatty acids synthesized by COXs. They are produced by virtually all mammalian tissues in response to physiological signals or cell injury, and they exert a wide range of pharmacological, physiological, and pathological effects. PGs play a regulatory role in many physiological processes, including vasomotility, platelet aggregation, immunomodulation, and cell growth and differentiation (33–39). They are implicated in the pathogenesis of pathophysiological processes such as inflammation, autoimmune diseases, and tumor development and growth (3, 13, 24, 34, 37, 40).

In this study, we showed that SC-’236, a selective inhibitor of COX-2, was highly effective in the treatment of the murine sarcoma FSA when combined with radiotherapy. SC-’236 greatly enhanced tumor radioresponse as evidenced by the increase in tumor growth delay, by a factor of 2.14, and the augmentation of tumor curability, by a factor of 1.87. These findings support our recent observations using the NFSA sarcoma tumor, where SC-’236 enhanced tumor growth delay by a factor of 3.64 and tumor radiocurability by a factor of 1.77 (23). This radiation-enhancing effect was greater than the effect we reported previously for indomethacin, a NSAID that inhibits both COX-1 and COX-2 (20). In that study, indomethacin enhanced tumor radiocurability of FSA and NFSA tumors by a factor of 1.39 and 1.26, respectively (20).

SC-’236 was also investigated for its ability to influence normal tissue radioresponse. The drug slightly sensitized the acutely responding tissue (jejunum) by a factor of only 1.03 but did not affect late-responding tissues (leg contracture). These observations imply that specific inhibitors of COX-2 have great potential for increasing the therapeutic ratio of radiotherapy.

The present study also addressed a number of possible mechanisms that could have been involved in SC-’236-induced potentiation of tumor radioresponse. FSA expresses COX-2 (Fig. 5A) and produces a number of different PGs, notably PGE₂ (24). Treatment of mice with SC-’236 did not affect COX-2 production but significantly inhibited PGE₂ production. Thus, the antitumor effect of SC-’236 on its own and SC-’236-induced enhancement of tumor radioresponse were associated with a reduction in the production of PGs. In general, PGs are regarded as radioprotective agents, both at the cellular and tissue microenvironment levels (17), whose mechanisms are poorly understood. For example, COX-1-derived PGs protect intestinal crypt cells from radiation damage (17, 18). Therefore, it is logical to assume that a decrease in PG levels in tumors may have caused the loss of radioprotection.

COX-2-derived PGs can stimulate tumor cell proliferation and inhibit apoptosis, which can be reversed by treatment with selective COX-2 inhibitors (41). A possibility that SC-’236 enhanced FSA radioresponse by rendering tumor cells susceptible to radiation-induced apoptosis was tested. We reported previously that cells of this tumor are resistant to induction of apoptosis by radiation and chemotherapy (42, 43). The present study showed that SC-’236 was also not effective in inducing apoptosis of FSA cells, nor did it increase susceptibility of FSA to radiation-induced apoptosis.

PGs stimulate angiogenesis and are vasoactive agents; both activities may influence tumor growth and response to cytotoxic agents. Treatment with SC-’236 was effective in inhibiting FSA vascularization (Fig. 6), which was associated with tumor growth retardation. A similar finding was reported in studies using NFSA (23). In addition, Masferrer et al. (44) reported that celecoxib, another selective inhibitor of COX-2, potently inhibited fibroblast growth factor-induced corneal angiogenesis in rats. Overall, these data show that specific COX-2 inhibitors are potent antiangiogenic agents. It is not clear, however, whether the inhibition of angiogenesis played a role in SC-’236-induced enhancement of tumor radioresponse. However, the involvement of antiangiogenesis is highly possible, based on the increasing recent evidence that the combination of radiation with antiangiogenic compounds, such as angiostatin (45), produces greater than an additive therapeutic effect.

Other mechanisms not explored in the present study could also have been involved in SC-’236-induced enhancement of tumor radiore- sponse. For example, PGs are immunosuppressive substances, and their inhibition might result in the augmentation of antitumor immunological responses that could potentiate tumor response to radiation. Although the mechanisms for the observed enhancement of tumor radiosensitization still remain to be explored in more detail, our findings and those reported previously (23) show that specific inhibitors of COX-2 can enhance the tumor response to radiation. The enhancement was achieved without an appreciable increase in the radiation damage of normal tissues, both acutely and in late-responding tissues. Therefore, SC-’236 was able to increase the therapeutic gain when combined with radiotherapy in a preclinical tumor model, which suggests that selective inhibition of COX-2 has a high potential to increase the effectiveness of radiotherapy for cancer.

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**REFERENCES**


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