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The IAP inhibitor GDC-0152 suppresses cell proliferation and induces apoptosis in colon cancer cell lines

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Inhibitors of apoptosis (IAPs), a protein family, which regulates various cellular processes, such as proliferation, migration, and cell death. IAPs are commonly overexpressed in various cancers, including colon cancer, making them appealing therapeutic targets. **Aim.** The present study was aimed to explore the impact of inhibitor of apoptosis protein (IAP) small molecule inhibitor GDC-0152 on colon cancer cells (HCT-116 and HT-29). **Methods.** The effects of GDC-0152 on colon cancer cells, cell viability, and proliferation were assessed using WST-1 assay and Real Time Cell Analysis System (xCELLigence), while apoptosis was detected using AO/EBr staining and Annexin V/Flow cytometry assays. The expression of XIAP were analyzed using western blotting analysis. **Results.** It was shown that GDC-0152 can inhibit the proliferation and clonogenic potential of colon cancer cells. We used a viability assay to demonstrate that GDC-0152 inhibited cell growth with IC_{50} values 28,90 μM in HCT-116, and 24,32 μM in HT-29. A wound healing assay showed that GDC-0152 inhibited migration of colon cancer cells. Further validation found that GDC-0152 induced apoptosis in colon cancer cells. **Conclusions.** Taken together, our results suggest that GDC-0152 suppressed the CC cell proliferation, migration, and induces apoptosis in a concentration-dependent manner. GDC-0152, a IAP inhibitor, can be considered as a valid approach to target cell death in colon cancer.

Keywords: GDC-0152, inhibitors of apoptosis (IAPs), colorectal cancer, apoptosis.

Introduction

Colon cancer is one of the most common and deadly cancers worldwide, with an estimated 1.9 million new cases and 881,000 deaths in 2020 [1]. Despite advances in diagnosis and treatment, many patients, particularly those with colorectal cancer, still face a poor prognosis and limited treatment options [2]. Apoptosis is regulated by a complex network

of proteins, including inhibitors of apoptosis proteins (IAPs), a family of intracellular proteins that can bind to and inhibit the activity of caspases, the enzymes that drive apoptosis [3]. IAP proteins are characterized by baculoviral IAP repeat domains, also known as BIR domains. IAPs inhibit cell death by binding to caspases, specifically Caspase-3 and Caspase-7, and inhibiting their activities [4]. In addition to the BIR domain, IAP proteins have an N-terminal caspase recruitment domain (CARD) and a RING domain, which is responsible for ubiquitin ligase activity [5, 6]. There are eight different IAP proteins identified in humans, including neuronal apoptosis inhibitory protein, cellular apoptosis protein inhibitor-1 (c-IAP1), cellular apoptosis protein inhibitor-2 (c-IAP2), X-linked inhibitor of apoptosis protein (XIAP), baculovirus IAP repeat domain-6 (Apollon), Livin, ILP-2, and BIR domain-5 (Survivin) [7, 8]. Some IAP proteins (c-IAP1, c-IAP2, XIAP) have RING domains involved in the ubiquitination process, which modifies proteins for degradation and biological activation. By blocking caspases, IAPs prevent activation of the apoptotic pathway and protect cancer cells from death [9, 10]. Several studies have shown that IAPs are overexpressed in several types of cancer, including colorectal cancer, and are associated with treatment resistance and poorer survival [4]. IAPs may mediate chemoresistance in CRC through a number of mechanisms, including inhibition of caspase activation, activation of NF-κB [11] and enhancement of DNA repair [12]. Therefore, IAPs have been proposed as attractive therapeutic targets in CRC and several IAP antagonists have been developed and tested in preclinical and clinical trials. IAP antagonists are small molecules that bind to and cleave IAPs, thereby restoring the apoptotic pathway and sensitising cancer cells to death [13]. The earliest report on GDC-0152, a pan-IAP antagonist, being developed as an anti-cancer drug goes back to 2012 [14]. The anti-cancer effectiveness of GDC-0152 has been studied in the patients with glioblastoma, breast cancer, leukemia, and osteosarcoma [14–17]. GDC-0152 is a small drug that inhibits the apoptosis (IAP) proteins XIAP, cIAP1, cIAP2, and ML-IAP. The medicine attaches to particular proteins' BIR3 domains, preventing them from suppressing caspases, which are important enzymes in apoptosis. As a result, GDC-0152 activates caspases, inhibits phosphoinositide 3-kinase (PI3K), and promotes death in cancer cells. The unexplored antineoplastic potential of IAP/GDC-0152 small molecule inhibitor on colorectal cancer cell lines raises interest. The study will provide insights into the therapeutic efficacy of IAP/GDC-0152. In the present study, we investigated the effects of GDC-0152 *in vitro* on the colon cancer cell viability, proliferation colony survival, cell migration, and cell death by apoptosis.

Materials and Methods

Model cell lines. Human colon cancer cells HCT-116 and HT-29, and the normal cell line COS-7, were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA). The cells were maintained in complete growth medium composed of Dulbecco's modified Eagle medium (DMEM, GIBCO, Thermo Fisher Scientific, Inc. Waltham, MA, USA) supplemented with 10% fetal bovine

serum (GIBCO; Thermo Fisher Scientific, Inc.), penicillin 100 U/mL, and streptomycin 100 U/mL, at 37 °C in a 5% humidified CO_2 atmosphere.

WST-1 Cell Viability Assay. The WST-1 cell viability kit was used to analyze cell viability. Briefly, HCT-116, HT-29 and COS7 cells were grown in 75 cm^2 cell culture flasks and harvested. Cells were seeded in 96-well flasks with 5×10^3 cells/well. Cells were cultured overnight, and then incubated with various concentrations of GDC-0152 dissolved in DMSO. After 24 hours, 100 µl of GDC-0152 (1,7.5,15,30,60 µM) various concentrations was added to the wells. After 48 hours, 5 µl of WST-1 reagent were added to each well and after 4 hours of incubation, the absorbance was measured at 450–480 nm by the Microplate (Molecular devices LLC, USA). The IC50 value was calculated by the Graphpad Prism software.

Colony Formation Experiment. Colon cancer cells were seeded in 6-well flasks at a density of 500 cells/well and treated with various concentrations of GDC-0152 for 48 h. After 2 weeks of culture, colonies were fixed with 4% paraformaldehyde and stained with Giemsa. Flask was photographed using an imaging system (Fluorchem E, Proteinsimple, USA) and colonies were counted. A cell total of >50 cells was considered a positive colony.

Real Time Cell Analysis System (xCELLigence). We measured the cell proliferation of GDC-0152 with xCELLigence Real Time Cell Analysis System according to manufacturer's instructions. HCT-116 and HT-29 cells 1×10^3 were seeded into an 8-well plate (E-plate). After that, the plates were placed in the CO_2 incubator. Then after the incubation period of 24 hours the medium was discarded and GDC-0152 (0, 1, 5, 10, 20, 30 µM) were added. Again, the CO_2 was put into the device in the incubator and measurement was taken in the device during the treatment period. The treatment period was over, the experiment was terminated and the graphic result was obtained.

Acridine Orange / Ethidium Bromide Staining. In 6-well plates, HCT-116 and HT-29 (per well 1×10^5) cells were maintained in DMEM medium at 37 °C in a 5% CO_2 incubator. Cells were treated with concentrations of GDC-0152 (5 and 25 µM) for 48 h and then, removed by trypsin-EDTA, followed by centrifugation. Final step 1 µl of AO/EB solution and 25 µl of cell suspension (0.5×10 to 2.0×10^6 cells/ml) was incubated. 10 µl of cell suspension were placed on a microscopic slide, covered with a glass coverslip, and cells were examined in a fluorescence microscope using a fluorescent filter and 20× objective.

Wound healing assay. HCT-116 and HT-29 cells were seeded in well-tissue culture plates with media containing FBS for 24 hours to achieve monolayer formation. Since strips of uniform diameter were desired, a scratch was made with the help of a 100 µl pipette tip and then the plates were washed with PBS. The wound areas of cells treated with serum-free DMEM/media containing different concentrations of the tested compound were photographed at certain time intervals, and then the distance of the gaps formed was recorded with an inverted microscope [18].

Western blot. Western blot analysis was carried out according to a method described previously [19]. The scraped cells were washed with cold phosphate buffered saline (PBS) and lysed with Protease inhibitor (Merck, Darmstadt,

Germany) and cold cell lysis buffer [20mM Tris [pH 8.0], 150mM NaCl, 10% Glycerol, 1% NP-40, 5mM EDTA [pH 8.0], 0.5mM EGTA [pH 8.0], 50mM NaF, 20mM β-glycerophosphate and 1mM Na3VO4]. The concentrations of the samples were determined at 595 nm by the Bradford method. Proteins were separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) were then transferred to the PVDF membrane. Then the membranes were blocked by skim milk 5 %. In this procedure, it was incubated with primary antibody in 5 ml of 5% BSA for 24 h, then washed with Tris Buffered Saline Tween-20 (TBS-T) and then incubated with secondary antibody for 1 h. The membrane was then washed again and imaging was performed with ECL (based on chemiluminescence method). Human XIAP monoclonal antibody (sc-55550) and GAPDH (sc-365062) antibody were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA).

The determination of apoptosis by flow cytometry. The induction of apoptosis in HCT116 and HT-29 cells were determined by flow cytometry using an Annexin-V/PI method. Briefly, HCT116 and HT-29 cells were seeded on 6-well plates with density of 3×10^5 cells/well for O/N and then were treated with concentrations of GDC-0152 (5 and 25 μM). The cells were prepared according to the manufacturer's protocol FITCAnnexin-V Apoptosis Detection Kit (BioLegend, Cat: 640914, USA). The cells were treated with 10 μL of Annexin V-FITC and 10 μL of PI, and incubated for 20 min in the dark at room temperature. Binding buffer (500 μl) was then added. Fluorescence intensity of the cells was detected by flow cytometry (Beckman Coulter, Cytoflex, USA).

Statistical analysis. All results were assessed using the Graph Pad Prism 8.0 program. Statistical analysis was performed through one-way ANOVA followed by post-hoc Tukey test and was repeated three times for reproducibility. $P < 0.05$ was considered statistically significant.

Results and Discussion

The aim of this study was to examine the effects of IAP/GDC-0152 on cell viability, proliferation, colony survival, cell migration, and cell death in colon cancer cell lines HCT-116 and HT-29. To investigate whether GDC-0152 may impaire viability of colon cancer cell lines HCT116 and HT-29, and normal cell COS-7 were treated with 1, 7.5, 15, 30, and 60 μM GDC-0152 for 48 h (Fig. 1). Cell viability was significantly inhibited in a dose-dependent manner (Fig. 1A and B). Our results also show that IC50 values of GDC-0152 are 28,90 μM in HCT-116 and 24,32 μM in HT-29 cell lines (Figure 1D). The results of the earlier study, investigating the effect of GDC-0152 on signaling mechanisms in human leukemia cells, were rather similar to the results of our study. It was established that the treatment of leukemia cells with GDC-0152 caused a loss of cell viability depending on dose and time of IAP exposition [15]. In line with these results, it is among the findings that GDC-0152 inhibitor significantly reduces the cell viability in hematopoietic tumors as well as solid tumors [20]. After treatment of cells with GDC-0152, dose-dependent disappearance of the typical morphological features of these cells was determined by phase contrast microscopy. In particular, HCT-116 cells began to

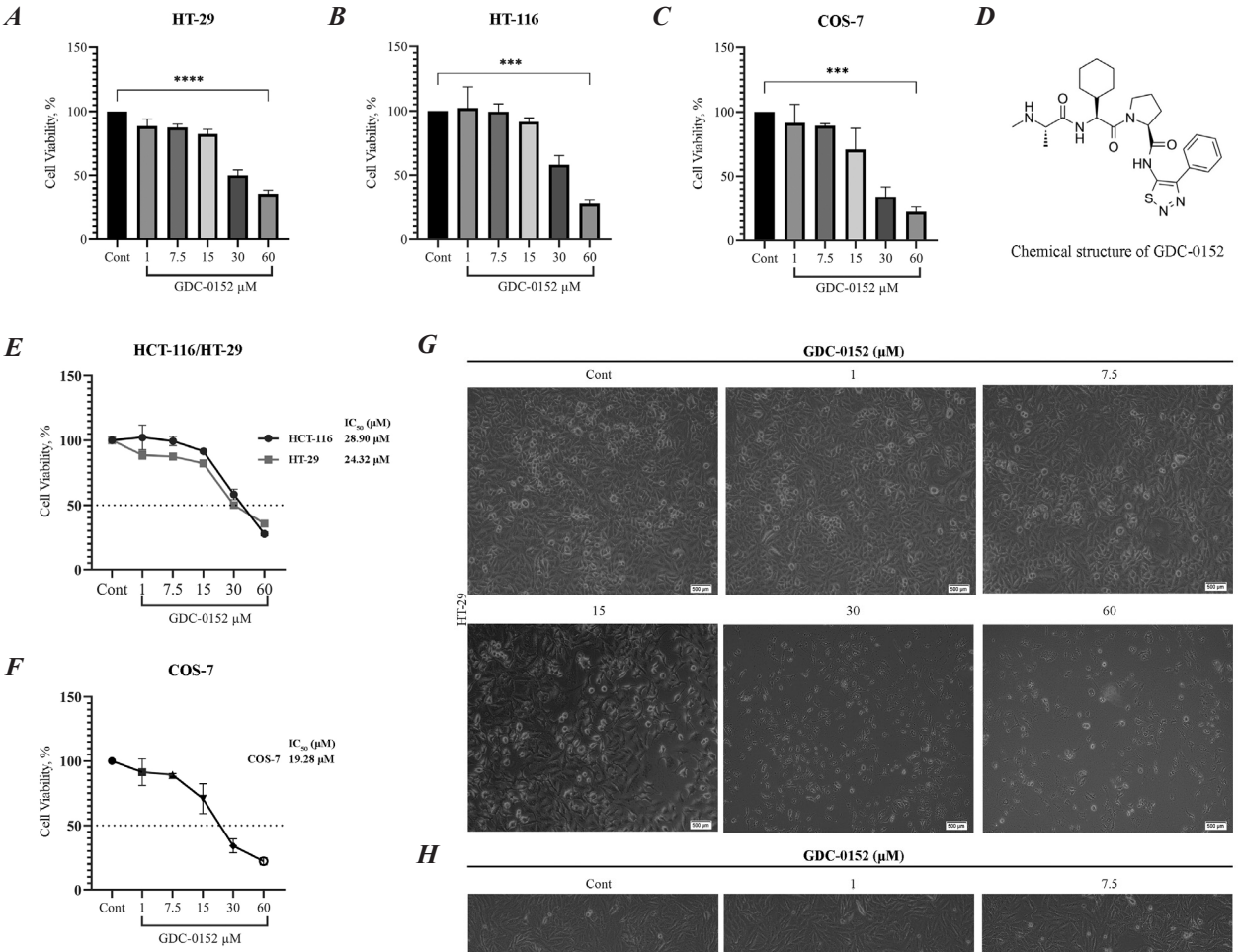

Fig. 1. The effects of GDC-0152 on colon cancer viability. The cell lines HT-29 (*A*) and HCT116 (*B*), and normal cell COS-7 (*C*) were exposed to various concentrations of GDC-0152 (1, 7.5, 15, 30, and 60 µM) for 48 h. HCT116, HT-29, cell viability was suppressed in a concentration dependent manner by GDC-0152 treatment, as assessed by WST-1 assay. The IC50 value (*E* and *F*) was calculated by the Graphpad Prism software. GDC-0152-induced morphologic alteration 48 h as visualized by Olympus CKX41 inverted phase contrast fluorescence microscope (*G* and *H*)

lose their normal characteristic shape, acquiring rounder shape, and eventually detach from the culture (Fig. 1G).

To determine whether GDC-0152 impairs proliferation, colony formation, and migration of HCT116 and HT-29 cells, we performed Real Time Cell Analysis, colony formation and wound healing assay for 48 h. We analyzed XIAP protein expression level in GDC-0152-treated cells (1, 5, and 20 μM) using Western blot analysis. As expected, GDC-0152 exposure decreased XIAP protein levels in HCT116 and HT-29 cells (Fig. 2A). HCT116 and HT-29 cells were treated with increasing concentrations of GDC-0152 (1, 5, 10, 20 and 30 μM), and cell proliferation was monitored in real time for every 15 min for 48 h. The cell index results showed that the lower concentrations (1 and 5 μM) did not affect the cell proliferation in both cell line. On the other hand, 10, 20, and 30 μM doses of GDC-0152 had an anti-proliferative effect (Fig. 2C and D).

In the present study, the colony-forming ability of the colon cancer cell lines HCT-116 and HT-29 were examined. It was observed that the colony-forming ability gradually decreased in the cell lines treated with GDC-0152 in a dose-dependent manner (Fig. 2B). It was determined that the cells had colony-forming abilities, especially in the control group, but there was a significant decrease in the number of colonies in the 2, 4 and 8 μM dose groups. These findings indicate that GDC-0152 altered lines HCT-116 and HT-29 morphology and reduced the number of colonies formed by colon cancer cells. A recent study showed that cIAP1 increased colony numbers and that deletion of BIR1 eliminated the capacity of cIAP1 to stimulate cell growth [21]. The real-time cell proliferation tracking experiment revealed that cell proliferation decreased significantly in both cell lines, in the dose-dependent manner. A recent study showed that WX20120108, a novel IAP antagonist, exhibits strong inhibitory activity in all cancer cell lines tested. It was also determined that, in contrast to the differential antiproliferative effect of GDC-0152 on these cancer cells, it showed an almost comparable effect except on Hela-bcl-2 cells treated with Wx20120108 [22].

In addition, wound healing assay was performed to determine the migration ability of the cells. It was observed that GDC-0152 reduced the migration ability of colorectal cancer cells in a dose–dependent manner (Fig. 2E and F). Yang *et al.* [23] reported that GDC-0152 indirectly reduced the malignant progression of osteosarcoma promoted by angiopoietin-like protein 2, known as ANGRT22. The same authors showed that ANGPT22 significantly increased SaOS2 cell migration, while the treatment with GDC–0152 did not inhibit SaOS2 cell migration, which was increased by ANGPT22. It has also been shown that LCL161, DIABLO/SMAC mimetic promotes the migration of the human lung A549 cancer cells [24], whereas GDC–0152 did not promote neither the migration nor the invasion of NTUB1 and NTU0.017 cancer cells *in vitro* [20].

The flow cytometry Annexin V-FITC/PI dual labeling results showed that GDC-0152 increased the early and late apoptotic and dead cells in HCT-116 and HT-29 cell lines (Fig. 3A). In addition, consistent with Annexin V-FITC/PI dual labeling, AO/EB staining confirmed that GDC-0152 induced the cell death after treatment with GDC-0152. The results of

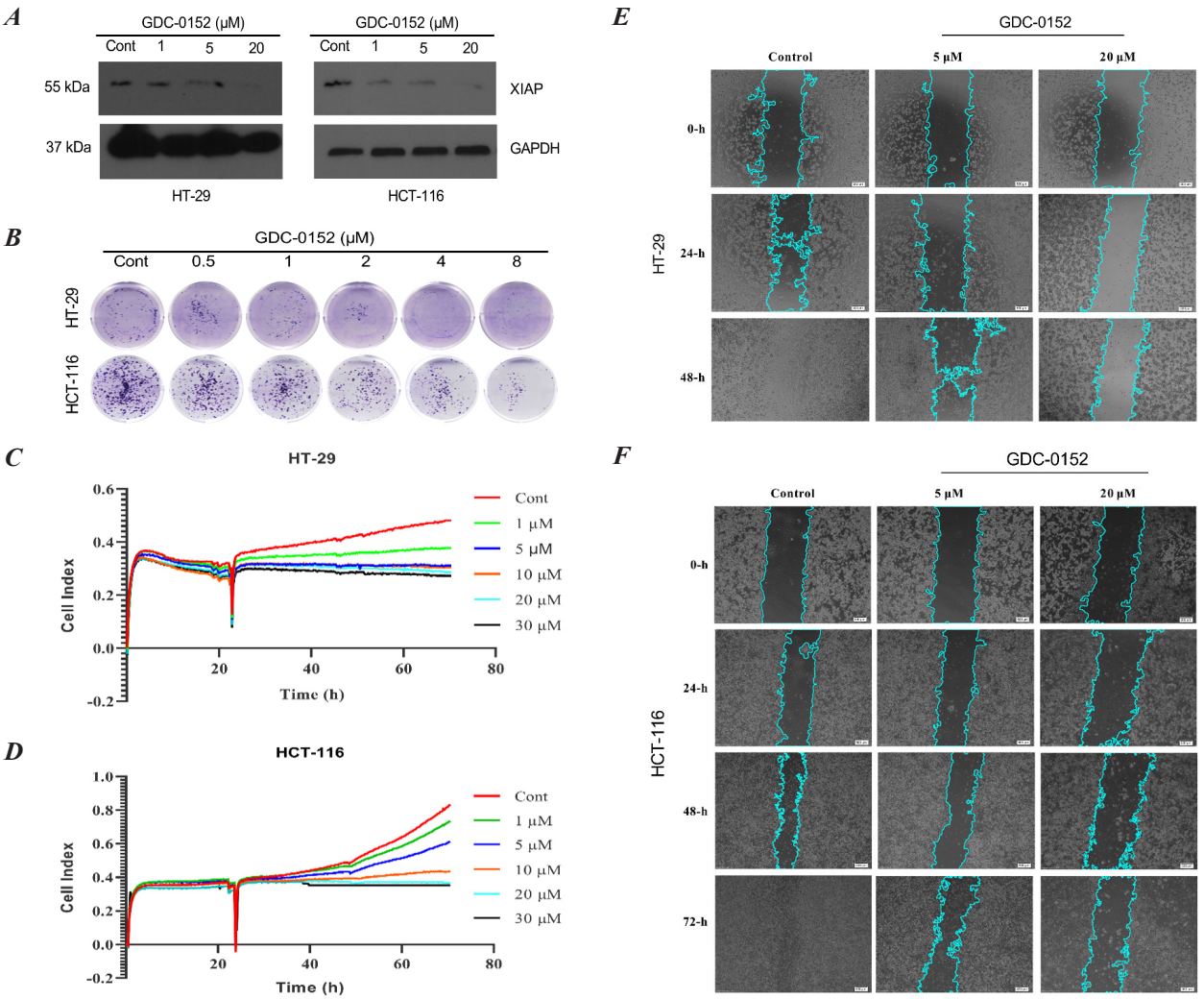

Fig. 2. GDC-0152 inhibited proliferation, colony formation and migration. The cells were treated with or without GDC-0152 for 48 h. *A* — Western blot showing expression of XIAP (Treatment-GDC-0152: 1, 5, and 20 μM). *B* — Colony formations are shown and number of colony decreased in colon cancer cells at 48 h. (GDC-0152: 0.5 1, 2, 4, and 8 μM). Cells were plated in 6-well plates, and 12–14 days later after treatment, the cells were stained. *C* and *D* — The real time cell analysis system was used to detect cell proliferation (GDC-0152: 1, 5, 10, 20 and 30 μM). *E* and *F* — The cells incubated in 12 well plate at 37 °C until cells reach 100% confluence to form a monolayer. The cells were scratched with a p100 pipet tip to create a scratch of the cell monolayer. The well plates were observed under a microscope and recorded the migration of the cells

fluorescence observation showed that untreated cells (control) and treated cells with lower concentrations of the compounds had normal nuclei, presented as bright green. Treatment with GDC-0152 (20 μM) showed late apoptotic cells that were stained as yellowish-

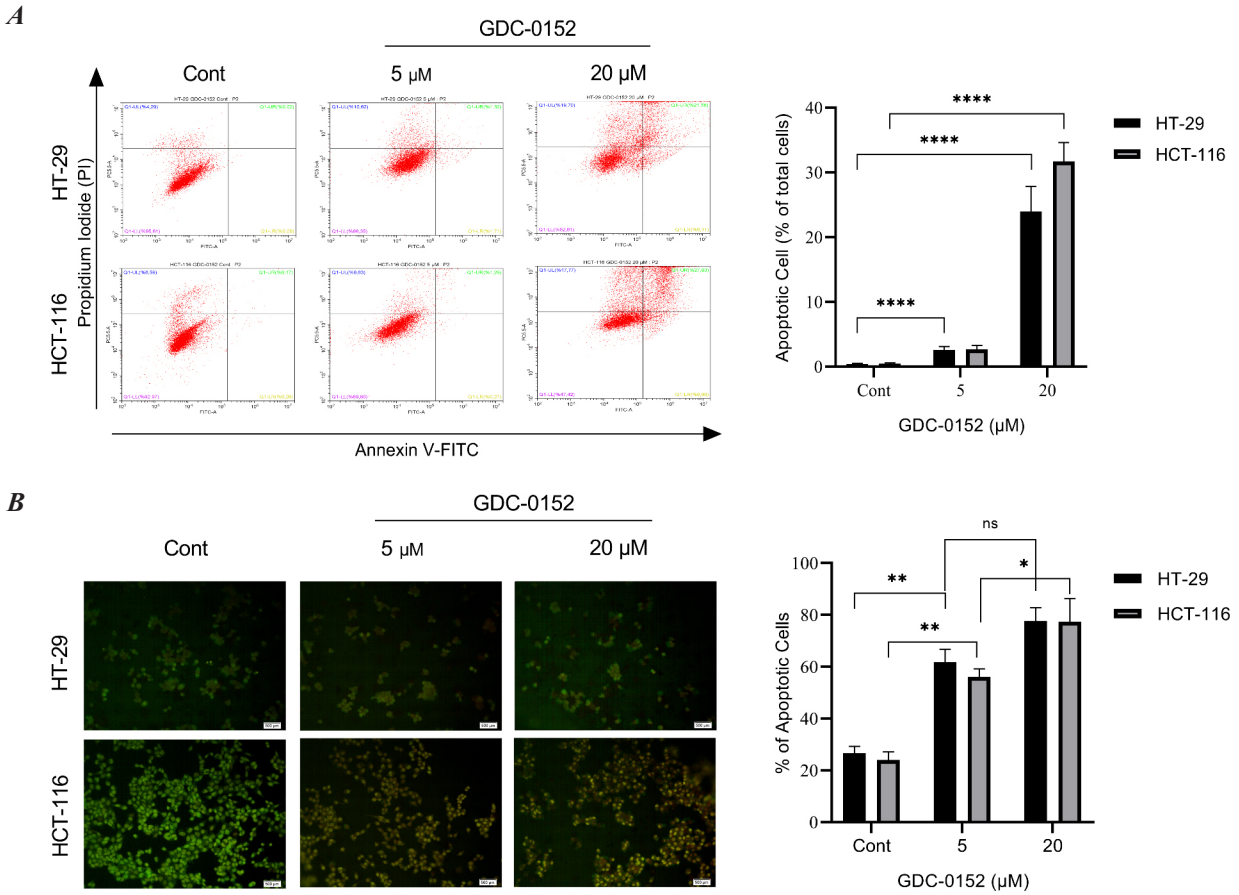

Fig. 3. Treatment of HCT-16 and HT-29 cells with GDC-0152 induces their apoptosis. HCT-16 and HT-29 cells were analyzed by flow cytometry (*A*) and were stained with AO/EB staining (*B*)

orange. The results indicated that early and late apoptotic cells increased gradually with the increase of dose (Fig. 3B). Similar to our findings, previous study has reported that GDC-0152 induces apoptosis via a caspase-mediated pathway in K562 and HL60 cells [15]. Similar results were reported by Zhang *et al.* [24] who reported the effects of LCL161, a SMAC mimetic, which induced apoptosis in the lung cancer cell line WX20120108. An analogue of GDC-0152 (a known IAP antagonist) was observed to promote caspase-mediated apoptosis and activated TNFα-dependent extrinsic apoptosis in HeLa and MDA-MB-231 cells [22]. It was reported that besides inducing apoptosis, WX20120108 also promoted autophagy.

Conclusion

In summary, we have demonstrated that GDC-0152 inhibits migration of HCT-116 and HT-29 cells and exhibits anti-proliferative effects by inducing apoptotic cell death. Our findings

could contribute to the potential therapeutic strategies for colon cancer treatment.

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Інгібітор IAP GDC-0152 пригнічує клітинну проліферацію та індукує апоптоз у лініях клітин раку товстої кишки

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Інгібітори апоптозу (IAP) належать до сімейства протеїнів, що регулюють різні клітинні процеси, у тому числі клітинну загибель, проліферацію та міграцію. Надекспресія протеїнів IAP часто має місце в клітинах різних злоякісних новоутворень, включаючи рак товстої кишки, що робить їх потенційними терапевтичними мішенями. **Мета.** Представлене дослідження було спрямоване на вивчення впливу низькомолекулярного IAP-інгібітора GDC-0152 на клітини раку товстої кишки ліній HCT-116 і HT-29. **Методи.** Вплив GDC-0152 на життєздатність і проліферативну активність клітин раку товстої кишки оцінювали за допомогою аналізу WST-1 і системи аналізу клітин у реальному часі (×CELLigence), детекцію апоптозу проводили за допомогою фарбування клітин AO/EBr з подальшим визначенням рівня анексину V протоковою цитофлуориметрією. Рівень XIAP визначали за допомогою Вестерн блоту. **Результати.** Було показано, що GDC-0152 може пригнічувати як проліферацію, так і клоногенний потенціал клітин раку товстої кишки. У тесті на життєздатність було продемонстровано, що GDC-0152 інгібує проліферацію клітин та характеризується значеннями IC_{50} 28,90 мкМ для лінії HCT-116 та 24,32 мкМ для лінії HT-29. Результати міграційного тесту показали, що GDC-0152 пригнічує міграцію та індукує апоптоз клітин колоректального раку. **Висновки.** Результати проведених досліджень свідчать про те, що GDC-0152 пригнічує проліферацію та міграцію, а також індукує апоптоз у клітинах раку прямої кишки в залежний від концентрації спосіб. Отже, інгібітор IAP GDC-0152 може розглядатися як ефективний протипухлинний засіб, що індукує загибель клітин раку товстої кишки.

Ключові слова: GDC-0152, інгібітори апоптозу (IAP), колоректальний рак, апоптоз.

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