UNIVERSITAS TRISAKTI

dr. Yenny <yennyfarmako@trisakti.ac.id>

[InaBJ] M2026166 Article Review Request

3 messages

Secretariat of InaBJ <secretariatinabj@gmail.com> Mon, Jun 15, 2026 at 4:52 PM
To: Yenny Trisakti <yennyfarmako@trisakti.ac.id>, Yenny Y <yenfarmako@gmail.com>

Dear Dr. dr. Yenny Sp. FK,

Good day, doc. How are you? This is from the secretariat of Indonesian Biomedical Journal.

We believe that you would serve as an excellent reviewer of the manuscript, "**Temozolomide Resistance Associated with MICB Expression and Secretion in Glioblastoma Multiforme Cells**," which has been submitted to The Indonesian Biomedical Journal. The submission's abstract is inserted below, and we hope that you will consider undertaking this important task for us.

Please log into the journal web site by 2026-06-17 to indicate whether you will undertake the review or not, as well as to access the submission and to record your review and recommendation. The review itself is due **2026-06-19**.

Once you have finished your review, you can submit the review result in the link provided below, or simply send us an email. Submission URL: https://inabj.org/index.php/ibj/reviewer/submission/2722?key=ACCESS_KEY.

Thank you for considering this request. Please let us know when you have read this email and whether you are able to take this request or not. We wish you a nice day.

"Temozolomide Resistance Associated with MICB Expression and Secretion in Glioblastoma Multiforme Cells"

Abstract

Background: Glioblastoma multiforme (GBM) is an aggressive and malignant cancer, having the highest incidence rate among primary malignant tumors of the central nervous system. Standard GBM treatment, including temozolomide (TMZ) chemotherapy, remains suboptimal due to potential GBM resistance to TMZ. Previous studies indicate the suppression of immunosurveillance of natural killer group 2 member D (NKG2D) receptor towards its ligand, NKG2DL, on cancer cells during cancer progression. However, how cancer chemoresistance regulates the NKG2DL expression and secretion remains unclear. This study aimed to examine the association of TMZ-chemoresistance with the expression and secretion of an NKG2DL subtype, MHC class I chain-related protein B (MICB), in GBM cells.

Methods: The expression and secretion of MICB were analyzed in GBM cells owing intrinsic (T98G) and acquired (U87MG-R) TMZ chemoresistance using quantitative reverse transcription polymerase chain reaction, flow cytometry, and enzyme-linked immunosorbent assay.

Results: Our results showed that MICB protein levels in TMZ-resistant cell surface were lower, while in their secretome were higher compared to those in TMZ-sensitive U87MG cells. Nonethesless, TMZ treatment significantly increased the mRNA expression in U87sMG-R cells, but decreased in T98G and U87MG cells.

Conclusion: Therefore, we conclude that the development of TMZ chemoresistance in GBM cells associates with its protein levels in the cell surface and secretome. Further studies are required to its effect on the expression of NKG2D receptor of NK cells.

Best Regards,

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Secretariat of The Indonesian Biomedical Journal
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2 attachments

M2026166 Manuscript - Round 1.docx
3876K

F09 Manuscript Review Form [ver 2022].doc
254K

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dr. Yenny <yennyfarmako@trisakti.ac.id> Tue, Jun 16, 2026 at 5:12 PM
To: Secretariat of InaBJ <secretariatinabj@gmail.com>

Dear Editor InaBJ

I sent you my review comments on this manuscript.
I hope you can send me the certificate of the reviewer
Best regards
Yenny

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2 attachments

F09 Manuscript Review Form [ver 2022] (2).doc
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3885K

Secretariat of InaBJ <secretariatinabj@gmail.com> Wed, Jun 17, 2026 at 3:59 PM
To: "dr. Yenny" <yennyfarmako@trisakti.ac.id>

Dear Dr. dr. Yenny, Sp.FK,

Thank you for completing the review of the submission, "Temozolomide Resistance Associated with MICB Expression and Secretion in Glioblastoma Multiforme Cells," for The Indonesian Biomedical Journal. We appreciate your contribution to the quality of the work that we publish.

Thank you. We wish you a nice day.

Best regards,

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> [Quoted text hidden]
>
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Certificate for Reviewer M2026166 - Yenny [signed].pdf
247K

The Indonesian Biomedical Journal

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Manuscript Review Form

Reviewer	:	Dr.dr.Yenny,Sp.FK
Manuscript #	:	M2026166
Manuscript Title	:	Temozolomide Resistance Associated with MICB Expression and Secretion in Glioblastoma Multiforme Cells

No.	Manuscript Components	Yes	No
1.	Does this manuscript present new ideas or results that have not been previously published?	**x**	
	Notes: **Yes**, this manuscript presents new results and conceptual insights that address a specific, poorly understood gap in the existing literature. The manuscript offers sufficient novelty by bridging the gap between GBM chemoresistance and NK-cell immune evasion via MICB dysregulation.		
2.	Are the title and abstract of the manuscript appropriate?	x	
	Notes: Yes		
3	Do the title and abstract reflect the study result/content?	x	
	Notes: Yes, the title and abstract accurately and honestly reflect the results and content of the research		
4.	Is the significance of the study well explained at the Background?	x	
	Notes: The significance of this research has been explained quite well and coherently in the Introduction chapter (Background), but there are still crucial gaps that need to be sharpened so that this manuscript has a strong appeal for readers. Suggestion: - Provide a specific rationale for selecting MICB over MICA or other ULBP ligands. - Explain that mapping the MICB profile of resistant cells (intrinsic vs. adaptive) is crucial for designing targeted chemo-immunotherapy combinations, preventing NK cells from being desensitized by sMICB secreted by tumor cells.		

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5.	Are the research study methods technically correct, accurate, and complete enough to be reproduced/cited by other scientists?		x

Notes: This research method is technically correct and accurate, but it is NOT complete enough to be perfectly reproducible by other scientists.

Culture cell & reagen:

- Have the U87MG and T98G cells gone through the authentication process? Please add information about the method used.
- Add a statement regarding the passage number of cells used and confirmation that the cells are Mycoplasma free.
- Add Media Specification information: The author mentions using DMEM media, but does not mention the concentration of Fetal Bovine Serum (FBS) (was it 10%?), Glutamine content, or antibiotics (Penicillin/Streptomycin) used during routine maintenance.

Protokol Flow Cytometry:

- Include the catalog number, antibody clone (e.g., Clone 236511), and the name of the manufacturing company (producer) of the anti-human MICB antibody-conjugated PE used.
- How many cells (events) were acquired per sample (10,000 or 20,000 cells?)
- What software was used for data analysis (FlowJo, BD CellQuest, etc.)?

Protokol RT-qPCR

- The authors provide the primer sequences for MICB but completely omitted the primer sequences for the reference gene, 18S rRNA, or GAPDH if used, or a commercial primary ID number if they purchased it ready-to-use.
- Please provide the exact forward and reverse 5' → 3' nucleotide sequences for all reference genes in a table
- Add information about thermocycling conditions (Temperature and duration for denaturation, annealing (primer attachment), and extension stages)
- What media conditions when taking secretome serum, and what steps are taken to avoid protein interference from FBS?

Write the manufacturer, catalog number, and country of origin for the RNA isolation kit, cDNA kit, Flow Cytometry antibody, and ELISA kit.

6.	Are the results, ideas, and data presented in this manuscript important enough for publication?		x

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	Notes: The idea of distinguishing responses between intrinsic resistance (native T98G cells carrying the MGMT enzyme) and adaptive/acquired resistance (U87MG-R cells forced to become resistant through chronic exposure) is a major strength of this manuscript. This provides clinical insight into the immunological behavior of tumors that relapse after chemotherapy (adaptive) from those that are initially recalcitrant (intrinsic). The authors concluded that this increased secretion of MICB (sMICB) triggered immune evasion, but they did not demonstrate this directly in experiments. Are data available on a short functional NK cell cytotoxicity test using secretome fluid? If not, what recommendations could be added to the discussion?		
7.	Are all figures and tables necessarily presented?		x
	Notes: - Figure 1 (C), contains the sentence: ...counting the number of viable cells over a specified number of days. Internal instructions in Indonesian that the author forgot to delete when translating the manuscript into English (replace it with an objective time span). - In the draft manuscript, between the captions of Figures 2 and 3, there are two identical/twin images of U87MG vs. T98G cells inserted consecutively without clear captions. The author had to remove one of the duplicate images because it disrupted the layout of the manuscript. - In the results text and abstract, the authors repeatedly refer to the adaptive resistant cells as "U87MG-R." However, if you look at the label visualizations in the bar graphs in Figure 1B and Figure 2A, the label is "U87MG-R (+TMZ)." Authors should ensure consistency in this naming throughout the manuscript to avoid reader confusion.		
8.	Is there a logical flow of argument in the Discussion which elucidate all the presented/obtained data?		x
	Notes: The logical flow of the argument constructed by the author is coherent (and has succeeded in explaining almost all of the data obtained from the experiment. In the seventh paragraph of the Discussion chapter, the author states, "...reveals that these cells still receive extracellular signals as an up-regulatory mechanism to re-enhance MICB expression on the cell membrane; thereby, regaining their sensitivity to TMZ." This argument lacks sound evolutionary biology in cancer. Cancer cells that have adapted to resistance for 62 days will not actively seek to regain sensitivity to the drug. Most likely, the increased mRNA transcription is a cellular stress response to TMZ-induced DNA damage, but the protein is immediately excreted through the secretome to avoid detection by NK cells. The sentence in question needs to be reviewed.		

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9.	Are the conclusions and interpretations valid and supported by the data?		
	Notes: Overall, the main conclusions drawn by the author are valid and supported by the data. However, there is one specific interpretation in the seventh paragraph of the Discussion chapter that is less biologically valid and requires minor revision to make the argument of this manuscript fully robust.		
10.	Is the manuscript clear, comprehensible, and written in a good English structure?		x
	Notes: In terms of scientific substance and presentation of ideas, this manuscript is very comprehensible. The logic between paragraphs flows smoothly. However, due to several annoying typos and one Indonesian phrase that leaked into the draft (sebutkan semua hari), this manuscript requires professional copyediting/proofreading.		

Specific Reviewer's Comments and Suggestions:

1. Title and Abstract

The title is clear, descriptive, and accurately mirrors the scope of the study. The structured abstract summarizes the main points well, but it contains several critical typos.

2. Introduction (Background)

Add 1–2 sentences in the final paragraph of the Introduction to justify the specific selection of MICB over MICA or other ULBP ligands in your experimental setting.

3. Methods → Reproducibility needs more information in some section in method.
   Ethical clearence number of this study?
4. Results and Figures

- Figure 1 Caption:The phrase *"sebutkan semua hari"* is an internal drafting note in Bahasa Indonesia that was accidentally left un-translated. Correct this immediately to an English equivalent, such as *"...over a 9-day culture period"* or *"...over 3, 5, 7, and 9 days.*
- Review the image files embedded between Figure 2 and Figure 3. There appears to be a redundant duplication of cell schematics without clear, unique figure captions. Ensure each visual panel corresponds to only one labeled figure.
- Ensure that the naming convention used in the text ("U87MG-R") matches the labels on the graphs perfectly ("U87MG-R (+TMZ)") to prevent reader confusion.

5. Discussion

The discussion provides a commendable conceptual bridge connecting transcriptional changes to post-translational shedding. However, there is a fundamental flaw in biological interpretation on

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paragraph

Reviewer's Recommendation (Please tick only one option)	
Accept Submission (No significant alterations suggested)	
Revisions Required (Suggest changes to the manuscript as specified in this review)	v
Resubmit for Review (Major revisions should be made and suggestions as specified in this review must be addressed. Revised manuscript should be resubmitted to the reviewer for further review)	
Decline Submission (Do not encourage a rewrite, manuscript is totally rejected)	

Further Reviewer's Comments Regarding Disposition of the Manuscript:

This paper presents solid data with a clear clinical perspective, effectively showing that TMZ resistance leads to the molecular shedding of MICB. If the author completes the missing data, revises it, and proofreads this manuscript, it has a chance of being published.

Date and Sign:
June 16, 2026

Yenny

Temozolomide Resistance Associated with MICB Expression and Secretion in Glioblastoma Multiforme Cells

Abstract

Background: Glioblastoma multiforme (GBM) is an aggressive and malignant cancer, having the highest incidence rate among primary malignant tumors of the central nervous system. Standard GBM treatment, including temozolomide (TMZ) chemotherapy, remains suboptimal due to potential GBM resistance to TMZ. Previous studies indicate the suppression of immunosurveillance of natural killer group 2 member D (NKG2D) receptor towards its ligand, NKG2DL, on cancer cells during cancer progression. However, how cancer chemoresistance regulates the NKG2DL expression and secretion remains unclear. This study aimed to examine the association of TMZ-chemoresistance with the expression and secretion of an NKG2DL subtype, MHC class I chain-related protein B (MICB), in GBM cells.

Methods: The expression and secretion of MICB were analyzed in GBM cells owing intrinsic (T98G) and acquired (U87MG-R) TMZ chemoresistance using quantitative reverse transcription polymerase chain reaction, flow cytometry, and enzyme-linked immunosorbent assay.

Results: Our results showed that MICB protein levels in TMZ-resistant cell surface were lower, while in their secretome were higher compared to those in TMZ-sensitive U87MG cells. Nonethesless, TMZ treatment significantly increased the mRNA expression in U87sMG-R cells, but decreased in T98G and U87MG cells.

Conclusion: Therefore, we conclude that the development of TMZ chemoresistance in GBM cells associates with its protein levels in the cell surface and secretome. Further studies are required to its effect on the expression of NKG2D receptor of NK cells.

Commented [Y1]: nonetheless

Commented [Y2]: Typo? U87MG-R or U87sMG-R

Commented [Y3]: investigate/determine

Keywords: Glioblastoma multiforme (GBM), Temozolomide (TMZ), Cancer chemoresistance, MHC class I chain-related protein B (MICB), natural killer group 2D receptor (NKG2D)

Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive primary malignant brain tumor, with poor prognosis (1-3) despite standard treatments including surgery, radiotherapy, and Temozolomide (TMZ) chemotherapy in combination with the immunotherapy (4). The common therapeutic issue in GBM patients is due to tumor recurrence and resistance to TMZ, as they can decrease the responsiveness of GBM cells to treatment and lead to therapeutic failure and eventually to patient's death (5). TMZ resistance in GBM can be intrinsic—due to factors like upregulation of O6-methylguanine-DNA methyltransferase (MGMT) and enhanced base excision repair (BER), and suppression of mismatch repair (MMR) (6, 7)-or acquired, through mechanisms such as glioma stem cell (GSC) induction and increased of manganese superoxide dismutase (MnSOD) as antioxidant agent (8, 9).

Cancer chemoresistance can be affected by the host responses (10) and correlates with immune evasion to facilitate cancer progression (11). The dysregulation of NKG2D ligands (NKG2DL), including MHC class I chain-related proteins A and B (MICA and MICB), is known as one of cancer immune escape mechansms (12). The interaction of NKG2DL with its receptor, the natural killer group 2D receptor (NKG2D), normally activate natural killer (NK) and cytotoxic T cells to eliminate malignantly transformed cells (13). However, cancer cells can escape this immune surveillance by degrading surface NKG2DL using proteases like a disintegrin and metalloproteinase (ADAM) and matrix metalloproteinase (MMP) (14, 15), or by secreting soluble forms of NKG2DL (16, 17), thus promoting tumor survival.

The association between chemoresistance and NKG2DL-mediated immune surveillance, particularly in GBM, remains poorly understood. Therefore, this study aimed to analyze the correlation between TMZ resistance and MICB expression and secretion in GBM lines T98G and U87MG, as a therapy approach to restore the native immune recognition of cancer cells.

Commented [Y4]: Add 1–2 sentences in the final paragraph of the Introduction to justify the specific selection of MICB over MICA or other ULBP ligands in your experimental setting.

Methods

GBM cell cultures and TMZ treatment

Cell line with intrinsic TMZ resistance (T98G/CRL-1690) was provided by Prof. Dr. Alexander Brehm from the Institut für Molekularbiologie und Tumorforschung, Philipps-Universität Marburg, Germany. Meanwhile, TMZ-sensitive cell line (U87MG/HTB-14) was provided by Dr. dr. Christine T.U. Banjarnahor, Sp.Onk.Rad (K). All GBM cell lines was grown in Dulbecco's modified eagle medium (DMEM; Gibco; Thermo Fisher Scientific Inc.), supplemented with 3.7 g/L sodium bicarbonate (NaHCO3; Sigma-Aldrich; Merck KGaA), 10% fetal bovine serum (FBS; Gibco; Thermo Fisher Scientific Inc.), 1% penicillin-streptomycin (P/S; Gibco; Thermo Fisher Scientific Inc.), and 1% amphotericin B (Gibco; Thermo Fisher Scientific Inc.) under standard cell culture condition (37°C, 5% CO2, and 20% O2). For TMZ treatment, about 1x105 cells were treated with cytotoxic-50 (CC50) dose of TMZ (26 µM) in DMEM medium without FBS for two days. Afterwards, cells were harvested and prepared for analysis of MICB expression and secretion using quantitative reverse transcription polymerase chain reaction (qRT-PCR), flow cytometry, and enzyme-linked immunosorbent assay (ELISA).

Cell viability assay

Following cell harvesting, the number of viable cells was determined using trypan blue solution (Gibco; Thermo Fisher Scientific Inc.) and an automated cell counter (LUNA-II™; Logos Biosystems; Aligned Genetics, Inc.). Cell viability was calculated by comparing the number of live cells in the treated samples to the number of live cells in control.

Establishment of TMZ-adaptive resistance of U87MG GBM Cells. To induce TMZ adaptive resistance, about 1x10^5 U87MG cells/well in a 12-well plate were grown in 1 ml DMEM medium with complete supplementation (10% FBS, 1% P/S, and 1% amphotericin B) under

Commented [Y5]: Ethical clearence?

Commented [Y6]: -Have the U87MG and T98G cells gone through the authentication process? Please add information about the method used.
-Add a statement regarding the passage number of cells used and confirmation that the cells are Mycoplasma free.
-Add Media Specification information: The author mentions using DMEM media, but does not mention the concentration of Fetal Bovine Serum (FBS) (was it 10%?), Glutamine content, or antibiotics (Penicillin/Streptomycin) used during routine maintenance.

standard cell culture condition and repeatedly treated with the CC50 dose of temozolomide (TMZ; TEMOTERO; PT Amarox Pharma Global) every two days for 62 days. To assess changes in cell sensitivity to TMZ, percentage of cell viability was calculated by comparing the lived cell number between TMZ-treated and untreated (control). For further use, treated cells with reduced sensitivity to TMZ (U87MG-R) were cultured in DMEM medium with complete supplementation containing CC50 dose of TMZ.

qRT-PCR

Total RNA was extracted from approximately $1x10^5$ to $3x10^5$ cells using Tripure Isolation Reagent (TRIpure reagent; Cat. No. ATB2700; PT INDOGEN INTERTAMA). The isolated RNA was then used for RT-qPCR analysis with the SensiFAST SYBR No-ROX One-Step qPCR KIT (Cat. No. BIO-72005; Meridian Bioscience Inc.) and the 7500 Fast Real-Time PCR System (Thermo Fisher Scientific Inc.). The primer sequences for the MICB target gene were 5'-CTG AGA AGC TGG CGA CGT A-3' (forward) and (5'-CGA AGA CTG TGG GGC TCA-3' (reverse). The reference gene, 18S rRNA, was used with the primer sequences forward (5'-AAA CGG CTA CCA CAT CCA AG-3') and reverse (5'-CCT CCA ATG GAT CCT CGT TA-3'). The relative mRNA expression was analyzed using Livak's formula ($2-\Delta\Delta Cq$), and the Cq values of each sample were normalized to the Cq value of U87MG cells without TMZ, labeled as U87MG (-TMZ).

Flow cytometry

After harvesting, approximately $1x10^6$ cells were resuspended in a staining buffer containing FACSFlow Sheath Fluid (BD Biosciences; BD) and 2% fetal bovine serum (FBS; Gibco; Thermo Fisher Scientific Inc.). The cells were then treated with the MICA/B antibody, anti-human, PE (Cat. No. 130-100-889; Miltenyi Biotec B.V. & Co. KG). The antibody incubation was carried out in the dark at 4°C for about 15 min. Following incubation, the cells were washed with staining buffer to remove any excess antibodies and were resuspended in

Commented [Y7]: -The authors provide the primer sequences for MICB but completely omitted the primer sequences for the reference gene, 18S rRNA, or GAPDH if used or a commercial primary ID number if they purchased it ready-to-use.
-Please provide the exact forward and reverse 5' → 3' nucleotide sequences for all reference genes in a table
-Add information about thermocycling conditions (Temperature and duration for denaturation, annealing (primer attachment), and extension stages)
-media conditions when taking secretome serum, what steps are taken to avoid protein interference from FBS?

Commented [Y8]: -Include the catalog number, antibody clone (e.g., Clone 236511), and the name of the manufacturing company (producer) of the anti-human MICB antibody-conjugated PE used.
-How many cells (events) were acquired per sample (10,000 or 20,000 cells?)
-What software was used for data analysis (FlowJo, BD CellQuest, etc.)

phosphate-buffered saline (PBS; Cat. No. 003002; Invitrogen; Thermo Fisher Scientific Inc.) before being analyzed using the BD FACSCanto™ II Clinical Flow Cytometry System (BD Biosciences; BD). The median fluorescence intensity (MFI) of the antibody-stained cells was then compared to the MFI of the unstained cells to assess differences in MICB surface protein expression between samples.

ELISA

The collected secretome or conditioned medium (CM) from the GBM cell line culture was collected using centrifugation in 1000xg for 20 min, followed by centrifugation using an Amicon® Ultra-4 Centrifugal Filter Unit with a 10 kDa MWCO column (Millipore; Merck KGaA) and Microsep™ Centrifugal Filters with a 10 kDa MWCO (PALL; Pall Corporation) in 5000 rpm for 15 min to concentrate the protein concentration of the samples. The MICB concentration in the CM concentrate was then measured using a MICB ELISA based on the sandwich principle, with the Human MICB ELISA Kit (Cat. No. E-EL-H2458; Elabscience; Elabscience Bionovation Inc.). The intensity of the resulting color was measured by absorbance at a wavelength of 450 nm (A450) using the Varioskan LUX Multimode Microplate Reader (Thermo Fisher Scientific Inc.). The MICB concentration in each sample was determined by plotting the A450 value on a standard curve of known concentrations.

Statistical analyses. Data were shown as the mean ± standard deviation (SD) of the mean. Differences between treatment and control groups were assessed using a one-way ANOVA test followed by Tukey's post hoc test. Statistical analysis was carried out using GraphPad Prism 8.3.0 software (Dotmatics).

Results

U87MG cells acquired resistance after repeated TMZ exposure

Commented [Y9]: Write the manufacturer, catalog number, and country of origin for the RNA isolation kit, cDNA kit, Flow Cytometry antibody, and ELISA kit.

Commented [Y10]: -Figure 1 (C), contains the sentence: ...counting the number of viable cells over a specified number of days. Internal instructions in Indonesian that the author forgot to delete when translating the manuscript into English (replace it with an objective time span).
-In the draft manuscript, between the captions of Figures 2 and 3, there are two identical/twin images of U87MG vs. T98G cells inserted consecutively without clear captions. The author had to remove one of the duplicate images because it disrupted the layout of the manuscript.
-In the results text and abstract, the authors repeatedly refer to the adaptive resistant cells as "U87MG-R." However, if you look at the label visualizations in the bar graphs in Figure 1B and Figure 2A, the label is "U87MG-R (+TMZ)." Authors should ensure consistency in this naming throughout the manuscript to avoid reader confusion.

Administering the CC50 dose of TMZ (26 μM) to U87MG cells every two days resulted in the reduction of cell sensitivity to TMZ, as shown by changes in cell viability over 60 day(s) following the initial treatment (Fig. 1A). Percentage of cell viability was 77.841 ± 5.596% two days after TMZ treatment, reducing to 35.252 ± 5.048% by day 6. However, by day 13, percentage of cell viability increased to 77.470 ± 12.720%, then eventually reaching nearly 100% afterwards (103.387±15.241% on day 32; 102.121±10.997% on day 42; 105.446±4.637% on day 62).

Furthermore, U87MG cells that had developed resistance to TMZ (U87MG-R) were continuously cultureds and treated repeatedly with TMZ every two days to maintain their resistance. Further analysis of parental U87MG cells showed a significant reduction (P=0.0043) in cell viability post 48 h-TMZ treatment compared to U87MG cells without treatment (control) (Fig. 1C). Additionally, Fig. 1C also demonstrated that the TMZ-resistant GBM cells, showed a significant increase in cell viability of both the intrinsic (T98G) and adaptive (U87MG-R) cells compared to their sensitive counterparts, with P=0.0054 and P=0.0063, respectively, after TMZ treatment for 2 day(s).

To compare the growth rates of U87MG, U87MG-R, and T98G cells, the proliferation curves and doubling times of each GBM cell line were analyzed after 3-, 5-, 7-, and 9-day(s) culture (Fig. 1C and 1D). The proliferation data indicated that the growth rates of the three GBM cell lines were similar until day 5. Afterwards, the TMZ-sensitive U87MG cells began to proliferate faster than the TMZ-resistant U87MG-R and T98G cells. Doubling time analysis (Fig. 1E) also revealed that U87MG cells grew significantly faster than U87MG-R (P=0.0193) and T98G cells (P=<0.0001). Interestingly, a significant difference in growth rate was observed between the intrinsically resistant T98G cells and the adaptively resistant U87MG-R cells (P=0.0002).

Expression of MICB mRNA and protein on the surface of TMZ-resistant cells

Analysis of MICB mRNA and surface protein expression was performed in TMZ-resistant GBM cells compared to the sensitive cells, either without or with the CC50 dose of TMZ treatment for 2 day(s). The results of the mRNA relative expression analysis (Fig. 2A) revealed a significant decrease in the MICB expression post TMZ-treatment for 2 day(s), both in the U87MG cells and T98G cells, with P=0.0487 and P=0.0027, respectively. In addition, Fig. 2A also revealed that MICB expression was significantly higher in adaptively TMZ-resistant U87MG-R cells, as well as in intrinsically TMZ-resistant T98G cells, compared to their sensitive counterparts after TMZ-treatment for 2 day(s) (U87MG-R vs U87MG (+TMZ), P<0.0001); T98G (+TMZ) vs. U87MG (+TMZ), P=0.0461).

The analysis of MICB surface protein expression (Fig. 2B) showed a significant reduction of MICB surface protein levels in TMZ-resistant GBM cells compared to their sensitive counterparts (U87MG-R vs. U87MG (+TMZ), P=0.0023; T98G (+TMZ) vs. U87MG (+TMZ), P<0.0001). The effect of TMZ treatment over 2 day(s) showed differing effects on U87MG and T98G cells. In U87MG cells, there was a tendency for MICB surface protein expression to increase following TMZ treatment. Meanwhile, in T98G cells, MICB surface protein expression tended to decrease, although, these changes were not statistically significant.

TMZ-resistant cells tended to elevate MICB secretion

To evaluate MICB protein secretion in GBM cells, MICB concentrations were measured using ELISA in the conditioned medium (CM) with and without 2-day(s) TMZ exposure. The results (Fig. 2C) showed significant increase of MICB secretion both in intrinsically resistant T98G cells and in adaptively resistant U87MG-R cells compared to TMZ-sensitive U87MG cells, respectively with P=0.0021 and P=0.0004. Additionally, TMZ treatment for 2 day(s) did not have a significant impact on MICB secretion levels in either U87MG or T98G cells.

Discussion

To date, chemoresistance remains the primary obstacle to effective cancer therapy, manifesting either intrinsically or adaptively. Previous studies have suggested that the drug response of cancer cells is closely related with the cancer immune evasion due to the factors of tumor microenvironment (TME) (18, 19). Immunosuppresive properties of TME can affect immune surveillance of cancer and facilitate drug resistance. This study proposes that TMZ resistance in GBM cells correlates with the immune surveillance mechanisms of NK cells by regulating the expression and secretion of MICB, a known NKG2D ligand.

MICB, likewise MICA, is a protein expressed on the cell surface that has a molecular structure similar to that of other MHC class I molecules. The molecular structure of MICA/B consists of a cytoplasmic domain, a transmembrane domain, and α1-3 domains located on the extracellular side of the cell (12). MICB is usually absent or present in low levels on normal cells, but its expression increases when cells are stressed, damaged, or transformed (13). MICB acts as ligand for cells that express the NKG2D receptor and signals NK cells and T cells to "kill me". NKG2D is a homodimer receptor that consists of two type II transmembrane glycoproteins with a C-type lectin-like structure on the extracellular side of the cell membrane (20).

In this study, two GBM cell lines with contrasting TMZ sensitivities were utilized: U87MG cells (sensitive to TMZ) and T98G cells (intrinsically resistant to TMZ). U87MG is a cell line with epithelial morphology and derived from human grade IV glioma (21). On the other hand, T98G display a fibroblast-like cell morphology and was isolated from the brain of a glioblastoma multiforme, 61-year-old, Caucasian male (22). U87MG cells are among the most sensitive GBM cells to TMZ treatment, with a decrease in cell viability of about 75%, while T98G cells are inherently resistant to TMZ (23). We repeatedly treated U87MG cells with TMZ at the CC50 concentration until their sensitivity to TMZ declined to approximately 95-100% viability. This condition was maintained for more than two months under continuous

TMZ treatment, indicating that these cells have begun to acquire TMZ resistance and are subsequently referred to as U87MG-R cells. This study highlights the effects of acquired TMZ resistance in U87MG-R cells on the regulation of MICB expression and secretion, in comparison to those observed in T98G cells.

Firstly, the present study verified the differences in the response to TMZ treatment between TMZ sensitive and resistant GBM cells. The results of this study demonstrate differences in the response to TMZ treatment between TMZ sensitive and resistant GBM cells. After 2 days of TMZ treatment at the concentration of 26 μM, there was no significant difference in viability between U87MG-R and T98G cells, both of which maintained approximately 100% viability; in contrast, U87MG cells exhibited a significant decline in viability, dropping to approximately 50%. This finding indicates that the U87MG-R cells are insensitive to TMZ treatment, similar to T98G cells. Furthermore, U87MG cells significantly exhibited the fastest growth rate and thus displayed the lowest doubling time among the three cells. A study by Ramão et al. reported metabolic differences between U87MG and T98G cells that may influence their proliferation rates (24). In U87MG cells, an increase in enzymes associated with glycolysis, such as triosephosphate isomerase (TPIS) and lactate dehydrogenase B (LDHB), was observed, whereas T98G cells showed increased expression of Glucose-6-Phosphate 1-Dehydrogenase, an enzyme that plays a role in redirecting metabolism toward the Pentose Phosphate Pathway. These metabolic differences may be a key factor determining the proliferation rates of GBM cells.

In addition to assessing cell viability, this study also observed differences between TMZ sensitive and resistant cells in MICB expression, specifically in both surface and soluble proteins. In cells undergoing stress, such as malignant transformation or DNA damage caused by chemotherapy, the immune surveillance system mediated by NK cells can be activated to recognize NKG2DL such as MICB on tumor cell membranes (25). This recognition leads to

the activation of various intracellular signaling pathways, including phosphatidylinositol 3-kinase, growth factor receptor-bound protein 2, and c-Jun N-terminal kinase, which may induce NK cell cytotoxicity (26). Additionally, the interaction between MICB and NKG2D activates Janus kinase 2/signal transducer and activator of transcription 4 (JAK2/STAT5) signaling, which triggers NK cells to release cytokines, thereby enhancing the elimination of tumor cells (13). The expression of NKG2DL can be inhibited by factors such as proteolytic enzymes and exosomal secretion. Cancer cells can shed NKG2DL into sNKG2DL, which may induce endocytosis and lysosomal degradation of NKG2D receptor; thereby disrupting NKG2D immune surveillance function. Additionally, proteolysis of NKG2DL can interfere with recognition, migration, cytotoxicity capabilities, and homeostasis of NK cells, allowing cancer cells to escape detection by NK cells and T cells (13, 27). Higher levels of sMICB are often found in serum of patients with cancer (28). The expression of sNKG2DL is correlated with therapy outcome of metastatic melanoma patients (29).

Our results reveal that, prior to TMZ treatment, the TMZ-resistant T98G cells expressed significantly higher level of MICB mRNA, lower level of MICB surface protein, and higher level of MICB soluble protein compared to the TMZ-sensitive U87MG cells, suggesting a dysregulation of MICB protein expression and secretion. The discrepancy between MICB mRNA and surface protein levels may stem from post-translational regulatory mechanisms, such as proteolysis, ubiquitination and sumoylation, which contribute to intracellular degradation of MICB protein and decrease its expression on the cell membrane (30, 31). Other mechanisms contributed to the dysregulation of NKG2DL expression in cancer immune escape have been reviewed by Duan et al. at the transcriptional, translational, and post-translational levels through transcription factors such as p53, miRNAs such as miR-20a, miR-93, miR-106, and miR-10b, and proteolytic enzymes or exosomes, respectively (12).

Following TMZ treatment, we found that the TMZ-sensitive U87MG cells maintained both surface and soluble MICB protein levels similar to the untreated cells. However, these cells exhibited a capacity to decrease the MICB mRNA synthesis as a compensatory response to TMZ treatment, indicating a negative feedback mechanism for cell survival. Subsequently, repeated TMZ treatment induced the development of adaptive resistance in U87MG-R cells, as evidenced by lower surface protein levels and higher soluble protein levels of MICB compared to the untreated counterparts. These protein expression profiles were similar to those observed in T98G cells, suggesting an association with TMZ resistance properties that may facilitate immune evasion by TMZ-resistant GBM cells. Moreover, TMZ-resistant GBM cells significantly showed higher MICB secretion than the TMZ-sensitive cells, potentially affecting the immune system's ability to recognize GBM cells. Several studies have demonstrated that cancer progression often results in increased NKG2DL secretion which associates with decreased survival rates in patients (32, 33). Interestingly, we observed opposing MICB mRNA expression levels between U87MG-R and T98G cells following TMZ treatment. In U87MG-R cells, increased MICB mRNA accompanied with decreased level of MICB surface protein, reveals that these cells still receive extracellular signals as an up-regulatory mechanism to re-enhance MICB expression on the cell membrane; thereby, regaining their sensitivity to TMZ. Conversely, T98G cells downregulated MICB mRNA synthesis after TMZ treatment to permanently maintain low surface protein level according to their nature as intrinsic TMZ-resistant cells. This property is influenced by intrinsic factors, either genetic or epigenetic factors, as well as signaling pathways associated with intrinsic TMZ resistance.

Commented [Y11]: This argument lacks sound evolutionary biology in cancer. From a cancer evolutionary biology standpoint, a cell line that has successfully adapted to survive a toxic chemotherapeutic environment over 62 days does not actively attempt to "regain sensitivity" to be killed

Conclusion

In conclusion, the findings of the present study highlight that GBM resistance to TMZ is associated with the suppression of MICB on cell surface, as summarized in Fig. 3. While on

the other hand, it correlates with the intracellular accumulation and the upregulation of MICB release in the extracellular fluid, thus, it may impact the immune surveillance of GBM. Therefore, further studies are required to explore and to deepen understanding of the mechanisms underlying GBM chemoresistance in order to enhance patient immune system and develop more effective GBM treatment management.

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Authors' Contributions

SIW and FCI contributed to the concept and design of this study, as well as data validation and analysis. SIW was responsible for managing the funding and critical revision of the manuscript. KJK performed the experiments and wrote the manuscript. All authors read and approved the final manuscript.

Artificial Intelligence (AI) Disclosure

The authors used the ChatGPT-4 as AI-assisted editing tool, to improve spelling, grammar, clarity, and readability during manuscript preparation. However, the authors carefully reviewed and corrected the text afterwards and take full responsibility for the final content of this manuscript.

References

1. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231-51.
2. Miller KD, Ostrom QT, Kruchko C, Patil N, Tihan T, Cioffi G, et al. Brain and other central nervous system tumor statistics, 2021. CA Cancer J Clin. 2021;71(5):381-406.
3. Oronsky B, Reid TR, Oronsky A, Sandhu N, Knox SJ. A Review of Newly Diagnosed Glioblastoma. Front Oncol. 2020;10:574012.
4. Sánchez LM. Glioblastoma: Multidisciplinary treatment approaches. Applied Radiation Oncology. 2016:17-25.
5. Lee SY. Temozolomide resistance in glioblastoma multiforme. Genes Dis. 2016;3(3):198-210.
6. Singh N, Miner A, Hennis L, Mittal S. Mechanisms of temozolomide resistance in glioblastoma - a comprehensive review. Cancer Drug Resist. 2021;4(1):17-43.
7. Indraccolo S, Lombardi G, Fassan M, Pasqualini L, Giunco S, Marcato R, et al. Genetic, Epigenetic, and Immunologic Profiling of MMR-Deficient Relapsed Glioblastoma. Clin Cancer Res. 2019;25(6):1828-37.
8. Chen J, Li Y, Yu TS, McKay RM, Burns DK, Kernie SG, Parada LF. A restricted cell population propagates glioblastoma growth after chemotherapy. Nature. 2012;488(7412):522-6.
9. Hardiany NS, Sadikin M, Siregar N, Wanandi SI. The suppression of manganese superoxide dismutase decreased the survival of human glioblastoma multiforme T98G cells. Medical Journal of Indonesia. 2017;26(1):19-25.
10. Deo A, Sleeman JP, Shaked Y. The role of host response to chemotherapy: resistance, metastasis and clinical implications. Clin Exp Metastasis. 2024;41(4):495-507.

11. Lim YY, Zaidi AMA, Haque M, Miskon A. Relationship between tumorigenesis, metastasis, immune evasion, and chemoresistance in osteosarcoma therapy. Journal of Applied Pharmaceutical Science. 2023.
12. Duan S, Guo W, Xu Z, He Y, Liang C, Mo Y, et al. Natural killer group 2D receptor and its ligands in cancer immune escape. Mol Cancer. 2019;18(1):29.
13. Siemaszko J, Marzec-Przyszlak A, Bogunia-Kubik K. NKG2D Natural Killer Cell Receptor-A Short Description and Potential Clinical Applications. Cells. 2021;10(6).
14. Hilpert J, Grosse-Hovest L, Grunebach F, Buechele C, Nuebling T, Raum T, et al. Comprehensive analysis of NKG2D ligand expression and release in leukemia: implications for NKG2D-mediated NK cell responses. J Immunol. 2012;189(3):1360-71.
15. Zingoni A, Cecere F, Vulpis E, Fionda C, Molfetta R, Soriani A, et al. Genotoxic Stress Induces Senescence-Associated ADAM10-Dependent Release of NKG2D MIC Ligands in Multiple Myeloma Cells. J Immunol. 2015;195(2):736-48.
16. Lundholm M, Schroder M, Nagaeva O, Baranov V, Widmark A, Mincheva-Nilsson L, Wikstrom P. Prostate tumor-derived exosomes down-regulate NKG2D expression on natural killer cells and CD8+ T cells: mechanism of immune evasion. PLoS One. 2014;9(9):e108925.
17. Clayton A, Mitchell JP, Court J, Linnane S, Mason MD, Tabi Z. Human tumor-derived exosomes down-modulate NKG2D expression. J Immunol. 2008;180(11):7249-58.
18. Liu Y, Liang J, Zhang Y, Guo Q. Drug resistance and tumor immune microenvironment: An overview of current understandings (Review). Int J Oncol. 2024;65(4).
19. Kim SK, Cho SW. The Evasion Mechanisms of Cancer Immunity and Drug Intervention in the Tumor Microenvironment. Front Pharmacol. 2022;13:868695.

20. Diefenbach A, Tomasello E, Lucas M, Jamieson AM, Hsia JK, Vivier E, Raulet DH. Selective associations with signaling proteins determine stimulatory versus costimulatory activity of NKG2D. Nat Immunol. 2002;3(12):1142-9.
21. Allen M, Bjerke M, Edlund H, Nelander S, Westermark B. Origin of the U87MG glioma cell line: Good news and bad news. Sci Transl Med. 2016;8(354):354re3.
22. Stein GH. T98G: An anchorage-independent human tumor cell line that exhibits stationary phase G1 arrest in vitro. Journal of cellular physiology. 1979;99(1):43-54.
23. Panzarini E, Tacconi S, Carata E, Mariano S, Tata AM, Dini L. Molecular Characterization of Temozolomide-Treated and Non Temozolomide-Treated Glioblastoma Cells Released Extracellular Vesicles and Their Role in the Macrophage Response. Int J Mol Sci. 2020;21(21).
24. Ramao A, Gimenez M, Laure HJ, Izumi C, Vida RC, Oba-Shinjo S, et al. Changes in the expression of proteins associated with aerobic glycolysis and cell migration are involved in tumorigenic ability of two glioma cell lines. Proteome Sci. 2012;10(1):53.
25. Weiss T, Schneider H, Silginer M, Steinle A, Pruschy M, Polic B, et al. NKG2D-Dependent Antitumor Effects of Chemotherapy and Radiotherapy against Glioblastoma. Clin Cancer Res. 2018;24(4):882-95.
26. Burgess SJ, Maasho K, Masilamani M, Narayanan S, Borrego F, Coligan JE. The NKG2D receptor: immunobiology and clinical implications. Immunol Res. 2008;40(1):18-34.
27. Chitadze G, Bhat J, Lettau M, Janssen O, Kabelitz D. Generation of soluble NKG2D ligands: proteolytic cleavage, exosome secretion and functional implications. Scand J Immunol. 2013;78(2):120-9.
28. Holdenrieder S, Stieber P, Peterfi A, Nagel D, Steinle A, Salih HR. Soluble MICB in malignant diseases: analysis of diagnostic significance and correlation with soluble MICA. Cancer Immunol Immunother. 2006;55(12):1584-9.

29. Maccalli C, Giannarelli D, Chiarucci C, Cutaia O, Giacobini G, Hendrickx W, et al. Soluble NKG2D ligands are biomarkers associated with the clinical outcome to immune checkpoint blockade therapy of metastatic melanoma patients. Oncoimmunology. 2017;6(7):e1323618.
30. Molfetta R, Zitti B, Santoni A, Paolini R. Ubiquitin and ubiquitin-like modifiers modulate NK cell-mediated recognition and killing of damaged cells. AIMS Allergy and Immunology. 2017;1(4):164-80.
31. Fox BM, Janssen A, Estevez-Ordonez D, Gessler F, Vicario N, Chagoya G, et al. SUMOylation in Glioblastoma: A Novel Therapeutic Target. Int J Mol Sci. 2019;20(8).
32. Zingoni A, Vulpis E, Cecere F, Amendola MG, Fuerst D, Saribekyan T, et al. MICA-129 Dimorphism and Soluble MICA Are Associated With the Progression of Multiple Myeloma. Front Immunol. 2018;9:926.
33. Tamaki S, Kawakami M, Ishitani A, Kawashima W, Kasuda S, Yamanaka Y, et al. Soluble MICB serum levels correlate with disease stage and survival rate in patients with oral squamous cell carcinoma. Anticancer Res. 2010;30(10):4097-101.Sandra F, Esposti MD, Ndebele K, Gona P, Knight D, Rosenquist M, *et al*. Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Alters Mitochondrial Membrane Lipids. Cancer Res. 2005; 65: 8286-97.

Figures/Tables

Figure 1. Establishment of TMZ-resistant cells. (A) Percentage of U87MG cell viability in day 2, 6, 13, 32, 42, and 62 after repeated TMZ treatment every two days. (B) Percentage of U87MG, U87MG-R, and T98G cell viability post 2-day(s)-treatment with 26 µM TMZ. **P<0.01. (C) Proliferation and (D) doubling time of GBM cell lines were assessed by counting the number of viable cells over a sebutkan semua hari. *P<0.05, ***P<0.001, ****P<0.0001. Data were shown as mean ± standard deviation (SD). Statistical significance was evaluated using one-way ANOVA and Tukey's post hoc test. (-TMZ) indicates untreated samples, while (+TMZ) denotes samples treated with TMZ.

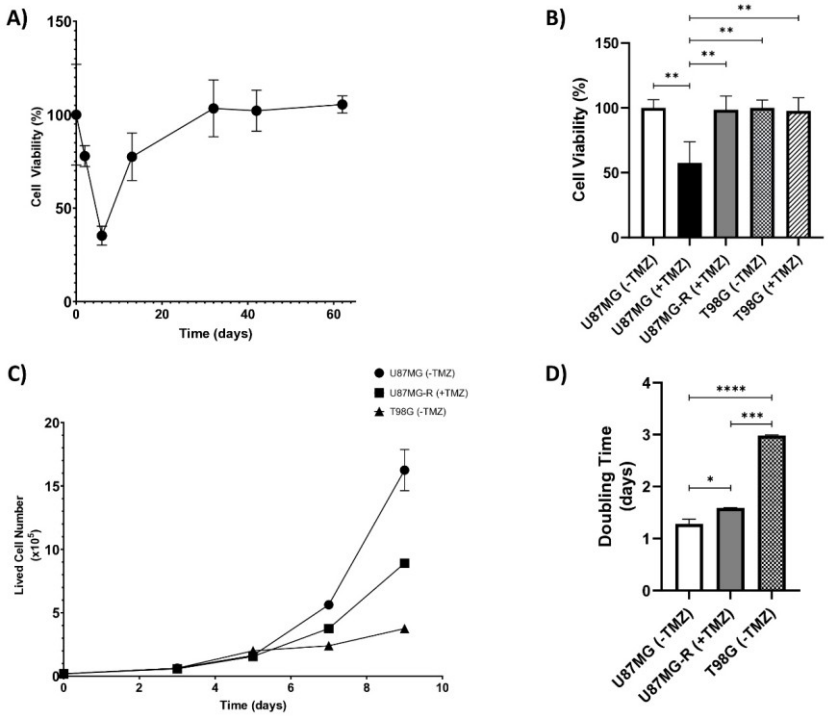


Figure 2. MICB expression and secretion in TMZ-resistant GBM cells compared to their sensitive counterparts. In addition, the GBM cells were exposed to 26 µM TMZ for 2 day(s) to observe the effect of TMZ treatment on MICB expression. (A) MICB relative mRNA analysis was performed using RT-qPCR. (B) MICB surface protein expression was analyzed by flow cytometry. (C) Secretion levels of MICB in GBM cells analyzed by sandwich ELISA. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. All experiments were conducted in triplicate (n=3). Data were shown as mean ± standard deviation (SD). Statistical significance was evaluated using one-way ANOVA and Tukey's post hoc test. (-TMZ) indicates untreated samples, while (+TMZ) denotes samples treated with TMZ.

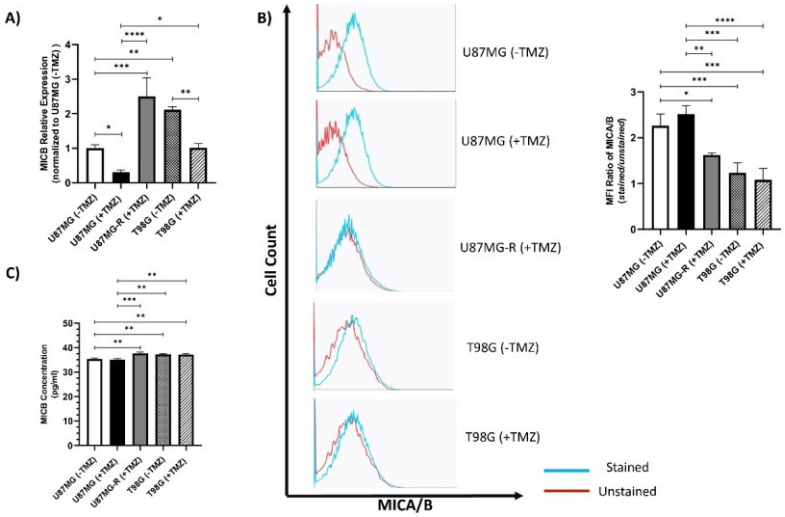
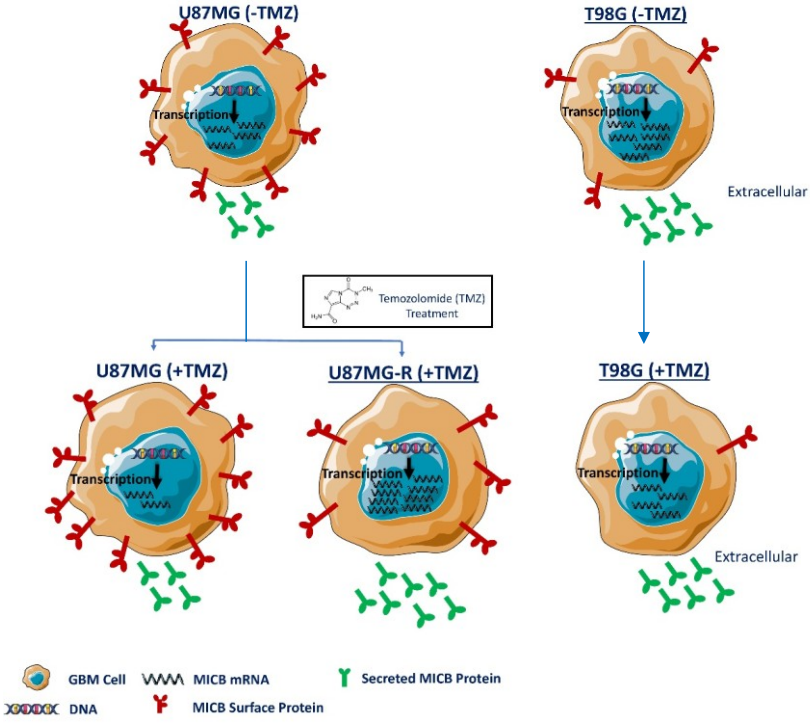


Figure 3. Regulation of MICB mRNA and protein in GBM cells pre- and post-TMZ-treatment. TMZ treatment to U87MG cells did not lead to significant changes of surface and soluble MICB protein levels in comparison to the untreated cells. However, these cells tend to decrease the MICB mRNA expression as a survival mechanism under TMZ treatment. Unlike U87MG cells, adaptively TMZ-resistant U87MG-R cells showed elevated MICB mRNA expression alongside reduced MICB surface protein levels compared to the untreated counterparts, following TMZ-treatment with the dose of 26 μM for 2 day(s). On the other hand, intrinsically TMZ-resistant T98G cells exhibited a concurrent decrease in both MICB mRNA and protein expression due to intrinsic factors supporting their resistance to TMZ. Furthermore, TMZ treatment led to higher MICB protein secretion in TMZ-resistant GBM cells (U87MG-R and T98G) compared to TMZ-sensitive GBM cells (U87MG).



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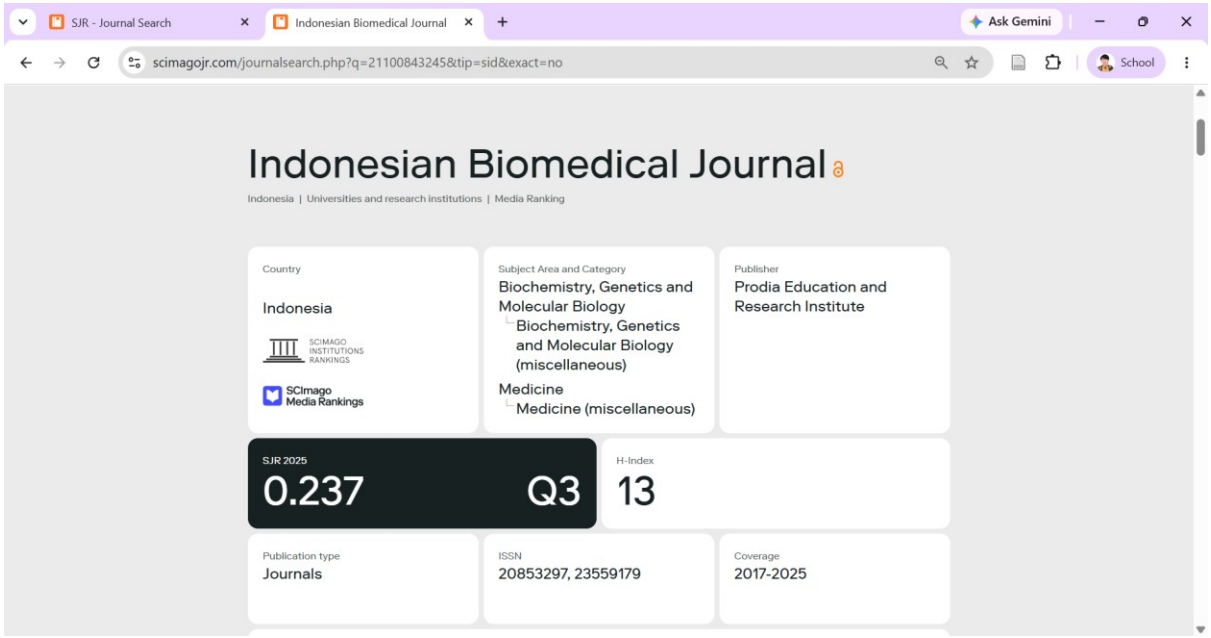
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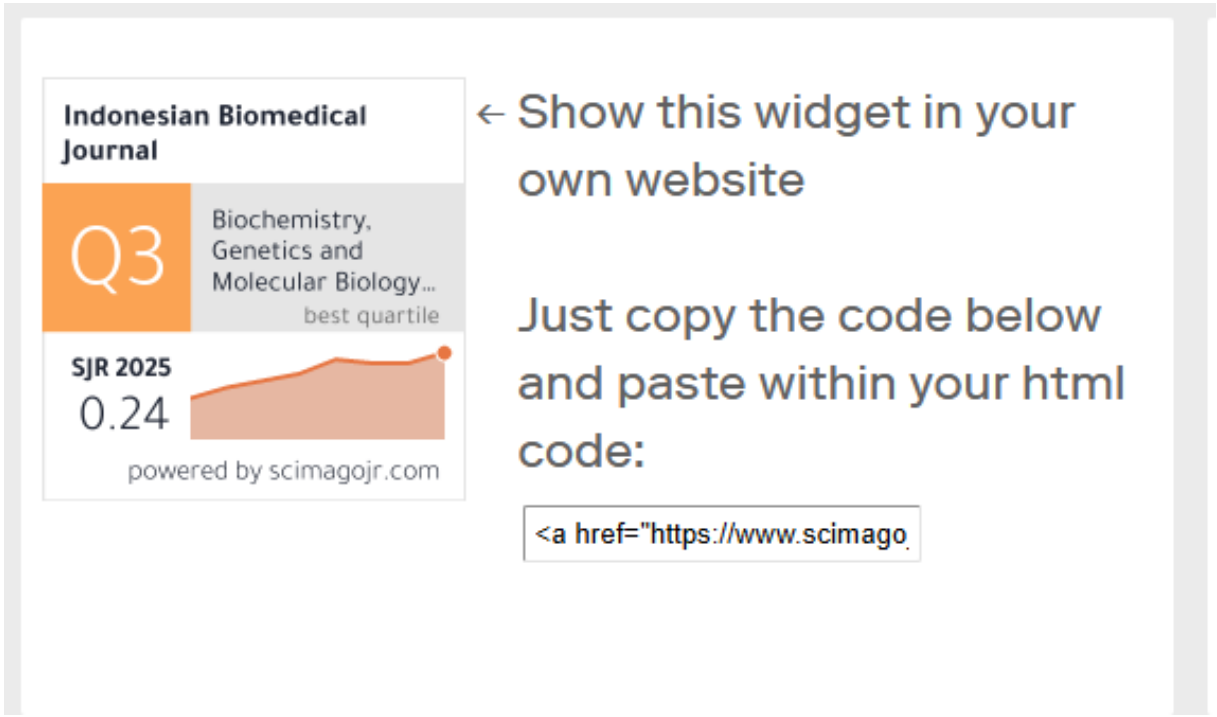
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