Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

The UV filter 4-methylbenzylidene camphor perturbs genome maintenance across fish and human cells

Chen Li
The Second Hospital of Shandong University
Shan Jin
Shandong University
Ruomei Li
Qilu Hospital of Shandong University
Jingwen Wang
Qilu Hospital of Shandong University
Lin Sun
Qilu Hospital of Shandong University
Helgi B. Schiöth
helgi.schioth@uu.se
Uppsala Universitet https://orcid.org/0000-0001-7112-0921
Chengxi Sun
Qilu Hospital of Shandong University
Chuanxin Wang
The Second Hospital of Shandong University

Research Article

Keywords:

Posted Date: November 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11486958/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

The UV filter 4-methylbenzylidene camphor perturbs genome maintenance across fish and human cells

Chen Li[1, 2#], Shan Jin[3#], Ruomei Li[4], Jingwen Wang[5], Lin Sun[4], Helgi B. Schiöth[6, 7*], Chengxi Sun[4, 6*], Chuanxin Wang[1, 4*]

[1] Department of Clinical Laboratory, The Second Qilu Hospital of Shandong University, No. 247 Beiyuan Street, Jinan 250033, Shandong, China

[2] Suzhou Research Institute of Shandong University, No. 388 Ruoshui Road, Suzhou Industrial Park, Suzhou 215123, Jiangsu, China

[3] Department of Clinical Laboratory, Shandong Mental Health Center, Shandong University, No. 49 Wenhua East Road, Jinan 250014, Shandong, China

[4] Department of Clinical Laboratory, Qilu Hospital of Shandong University, No. 107 Wenhua West Road, Jinan 250012, Shandong, China

[5] Department of Hepatology, Qilu Hospital of Shandong University, No. 107 Wenhua West Road, Jinan 250012, Shandong, China

[6] Department of Surgical Sciences, Functional Pharmacology and Neuroscience, Uppsala University, Husargatan 3, Uppsala 751 24, Sweden

[7] Laboratory of Pharmaceutical Pharmacology, The National Institute of Research and Innovation (NIRI), Riga LV-1006, Latvia

[#] These authors contributed equally to this work

[*] Corresponding authors

Author information

Chen Li

Email: li.chen@sdu.edu.cn

ORCID: https://orcid.org/0000-0002-7199-4298

Shan Jin

Email: i_jinshan@mail.sdu.edu.cn

ORCID: https://orcid.org/0009-0001-8888-5530

Ruomei Li

Email: li.ruomei@mail.sdu.edu.cn

ORCID: https://orcid.org/0009-0004-7103-2760

Jingwen Wang

Email: wang.jingwen@email.sdu.edu.cn

ORCID: https://orcid.org/0000-0003-2359-7738

Lin Sun

Email: sunlin9977@mail.sdu.edu.cn

ORCID: https://orcid.org/0009-0002-7429-2694

Helgi B. Schiöth

Email: Helgi.schioth@uu.se

ORCID: https://orcid.org/0000-0001-7112-0921

Chengxi Sun

Email: sunchengxi_qljy@sdu.edu.cn

ORCID: https://orcid.org/0000-0002-1050-5956

Chuanxin Wang

Email: cxwang@sdu.edu.cn

ORCID: https://orcid.org/0000-0002-3796-6293

Abstract

Ultraviolet filters protect against UV-induced DNA damage, yet their direct effects on cellular genome maintenance remain poorly understood. We investigated 4-methylbenzylidene camphor (4-MBC), an endocrine-disrupting UV filter, using African turquoise killifish and primary human dermal fibroblasts as complementary organismal and cellular models. After three days of exposure to 10 μM 4-MBC, killifish exhibited 1,887 differentially expressed genes despite no obvious histopathological alterations. Transcriptomic analyses revealed suppression of genome maintenance programs, including homologous recombination, mismatch repair, base excision repair and nucleotide excision repair, alongside negative enrichment of DNA replication and cell-cycle pathways (NES = -2.87 and -3.00, respectively). RT-qPCR validation further confirmed the reduced expression of *rad51*, *rad51ap1* and other DNA repair-associated genes, supporting the observed suppression of genome-maintenance pathways. In human fibroblasts, overlapping DNA damage response genes showed non-monotonic concentration-dependent changes, with reduced expression at lower exposures and increased expression of several genes at higher exposures. Increased p53, p21, and RAD51 protein abundance accompanied DNA strand breaks at higher concentrations. The RAD51-associated repair machinery emerged as an important shared molecular target of 4-MBC. These findings extend the biological effects of 4-MBC beyond endocrine disruption and highlight genome-maintenance endpoints as an important consideration in future UV-filter safety assessments alongside established photoprotective benefits.

Keywords: Ultraviolet filter, 4-Methylbenzylidene camphor, African turquoise killifish, Transcriptomic analysis, DNA damage response, Genome maintenance, Human dermal fibroblasts, Complementary cross-species models, Environmental toxicology, Safety assessment

Introduction

4-Methylbenzylidene camphor (4-MBC) is a synthetic UVB filter widely used in sunscreens and personal-care products that has been detected in aquatic environments, wildlife, and human biological samples [1–7]. Growing concerns about its ecological and human-health effects have prompted regulatory restrictions. Previous studies have primarily emphasized its endocrine-disrupting properties, including estrogen receptor activation, altered thyroid hormone signaling, and reproductive and developmental toxicity across aquatic and mammalian models [8–17]. However, although UV filters are intended to protect against UV-induced DNA damage, whether 4-MBC itself affects the cellular machinery responsible for maintaining genomic integrity remains poorly understood.

The DNA damage response coordinates DNA repair, replication, and cell-cycle regulation to preserve genomic integrity [18–20]. Perturbation of these interconnected processes may reflect adaptive cellular responses or potentially adverse effects, depending on exposure conditions. Whether 4-MBC affects these pathways, and whether related responses occur across biological systems, remains unclear. The African turquoise killifish (*Nothobranchius furzeri*) has emerged as a powerful vertebrate model organism, combining the scalability advantages of invertebrate models with the physiological complexity of vertebrates [21,22]. Here, we combined whole-organism transcriptomic profiling in killifish with molecular and cellular analyses in primary human dermal fibroblasts. This complementary approach enabled us to investigate genome-maintenance pathways in an aquatic vertebrate and examine overlapping DNA repair-associated machinery, concentration-dependent responses, and DNA damage in a human skin-relevant model.

Experimental

4-MBC exposure in African turquoise killifish and primary human dermal fibroblasts

Juvenile killifish larvae at 5 days post-hatching (dph) were exposed to 10 μM 4-MBC or the corresponding DMSO vehicle control for 3 days. At the end of exposure, the juvenile killifish were collected for transcriptomic analysis, reverse transcription quantitative PCR (RT-qPCR), and hematoxylin and eosin-based histological analysis. Primary human dermal fibroblasts were cultured under standard conditions and exposed to 10 nM, 100 nM, 1 μM, 10 μM, or 100 μM 4-MBC for 72 h. Detailed information on killifish husbandry, human cell culture, sample collection, and histological processing is provided in Text S1.

Bioinformatic analysis

To characterize the overall transcriptional changes induced by 4-MBC exposure, principal component analysis (PCA), sample correlation analysis, hierarchical clustering, and differential expression analysis were performed. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, as well as gene set enrichment analysis (GSEA), were subsequently conducted. Further details are provided in Text S2.

Molecular and functional analyses

RT-qPCR was performed to determine the expression of representative genes related to the DNA damage response in killifish and primary human dermal fibroblasts. Western blotting and alkaline comet assays were performed in human fibroblasts. Detailed experimental procedures are provided in Text S3-5.

Results and discussion

We found that 4-MBC exposure induced widespread transcriptional changes in African turquoise killifish, characterized by coordinated downregulation of genes involved in multiple aspects of the DNA damage response, spanning damage sensing, repair initiation and execution, as well as DNA replication and cell-cycle regulation. Particularly notable was the downregulation of homologous recombination-associated genes, including *rad51* and several interacting repair factors, suggesting perturbation of an interconnected network essential for genome maintenance. Interestingly, the complementary experiments in primary human dermal fibroblasts identified overlapping DNA repair-associated changes, particularly involving RAD51-associated machinery, while revealing non-monotonic concentration-dependent transcriptional responses. These cellular experiments further extended the organism-level findings by revealing increased p53, p21, and RAD51 protein abundance, together with increased DNA strand breaks following 4-MBC exposure. The convergence of molecular findings across the two models, combined with their distinct contributions at organismal and cellular levels, identifies genome maintenance as an underrecognized biological target of 4-MBC and extends its toxicological profile beyond endocrine disruption.

4-MBC induces transcriptomic perturbations in African turquoise killifish

Juvenile killifish were exposed to 10 μM 4-MBC for 3 days, followed by histological and transcriptomic analyses (Fig. S1). Although no obvious histopathological alterations were observed (Fig. 1a), transcriptomic profiling revealed clear separation between exposed and control groups (PC1, 44.20%; PC2, 18.59%; Fig. 1b). We identified 1,887 differentially expressed genes ($|\log_2 FC| \geq 1$ and false discovery rate (FDR) < 0.05), including 816 upregulated and 1,071 downregulated genes (Fig. 1c, d). Notably, substantial transcriptional alterations occurred in the absence of overt histopathological changes, indicating that molecular responses to 4-MBC may precede tissue-level effects detectable by conventional histological examination.

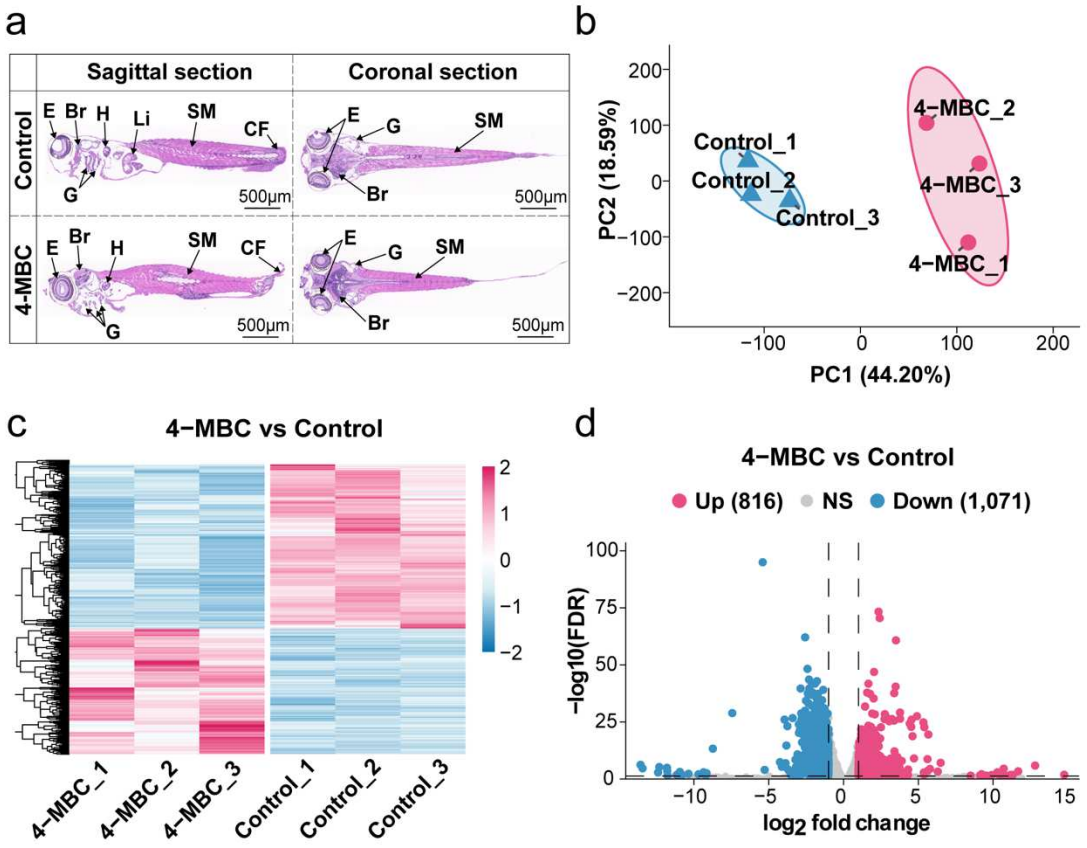

Fig. 1 Transcriptomic responses of African turquoise killifish (*Nothobranchius furzeri*) to 4-methylbenzylidene camphor (4-MBC) exposure (a) Representative histological sections of juvenile African turquoise killifish following 10 μM 4-MBC exposure for 3 days. Sagittal and coronal hematoxylin and eosin-stained sections from the control and 4-MBC-exposed groups are shown. Major anatomical structures are indicated: E, eye; Br, brain; H, heart; Li, liver; G, gill; SM, skeletal muscle and CF, caudal fin. Scale bars = 500 μm. (b) Principal component analysis (PCA) of RNA sequencing data from killifish after 3 days of 10 μM 4-MBC exposure (n = 3 per group). PC1 and PC2 represent the first and second principal components, respectively. (c) Heatmap showing hierarchical clustering of differentially expressed genes ($|\log_2 FC| \geq 1$ and false discovery rate (FDR) < 0.05) between control and 4-MBC-treated groups. (d) Volcano plot of differentially expressed genes. Red and blue dots denote significantly upregulated and downregulated genes, respectively, whereas grey dots indicate genes not significantly differentially expressed. The x- and y-axes represent the $\log_2$ fold change and $-\log_{10}$ (FDR), respectively. NS, not significant.

4-MBC coordinately disrupts genome-maintenance pathways

To determine the biological processes affected by 4-MBC exposure, we first performed Voronoi analysis of the differentially expressed genes. DNA repair, DNA replication, and cell-cycle processes emerged as major functional modules (Fig. 2a). Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses further identified

multiple DNA repair-related pathways, including homologous recombination, mismatch repair, and base excision repair, together with DNA replication and cell-cycle regulation (Fig. S2a, b). Gene set enrichment analysis (GSEA) confirmed coordinated downregulation of these pathways, with DNA repair, replication, and cell-cycle programs preferentially enriched in controls (Fig. 2b-d; Fig. S3a-c). These findings reveal a coherent transcriptional signature involving interconnected genome-maintenance processes rather than isolated DNA repair pathways.

Transcription factor analysis revealed alterations in several families, including Forkhead, bZIP, ETS and NGFIB-like factors (Fig. S4a). Notably, reduced *foxm1* expression coincided with the downregulation of DNA repair, DNA replication, and cell-cycle programs, whereas induction of AP-1 components (*jun*, *fosb*, *fosl1* and *atf3*) [23,24] pointed to a concurrent stress-responsive transcriptional shift (Fig. S4b). These opposing transcriptional patterns suggest coordinated perturbation of cell-cycle-associated and stress-responsive regulatory networks following 4-MBC exposure.

Previous studies have primarily linked 4-MBC to endocrine, developmental, reproductive, and oxidative effects [25–28]. Consistent with its established endocrine activity, estrogen signaling was also enriched following 4-MBC exposure (Fig. S5a, b). Importantly, DNA replication, cell-cycle regulation, and DNA damage response pathways are functionally interconnected [18–20]. The coordinated changes observed here therefore identify genome maintenance as an additional molecular process affected by 4-MBC, extending its recognized biological activity beyond endocrine disruption.

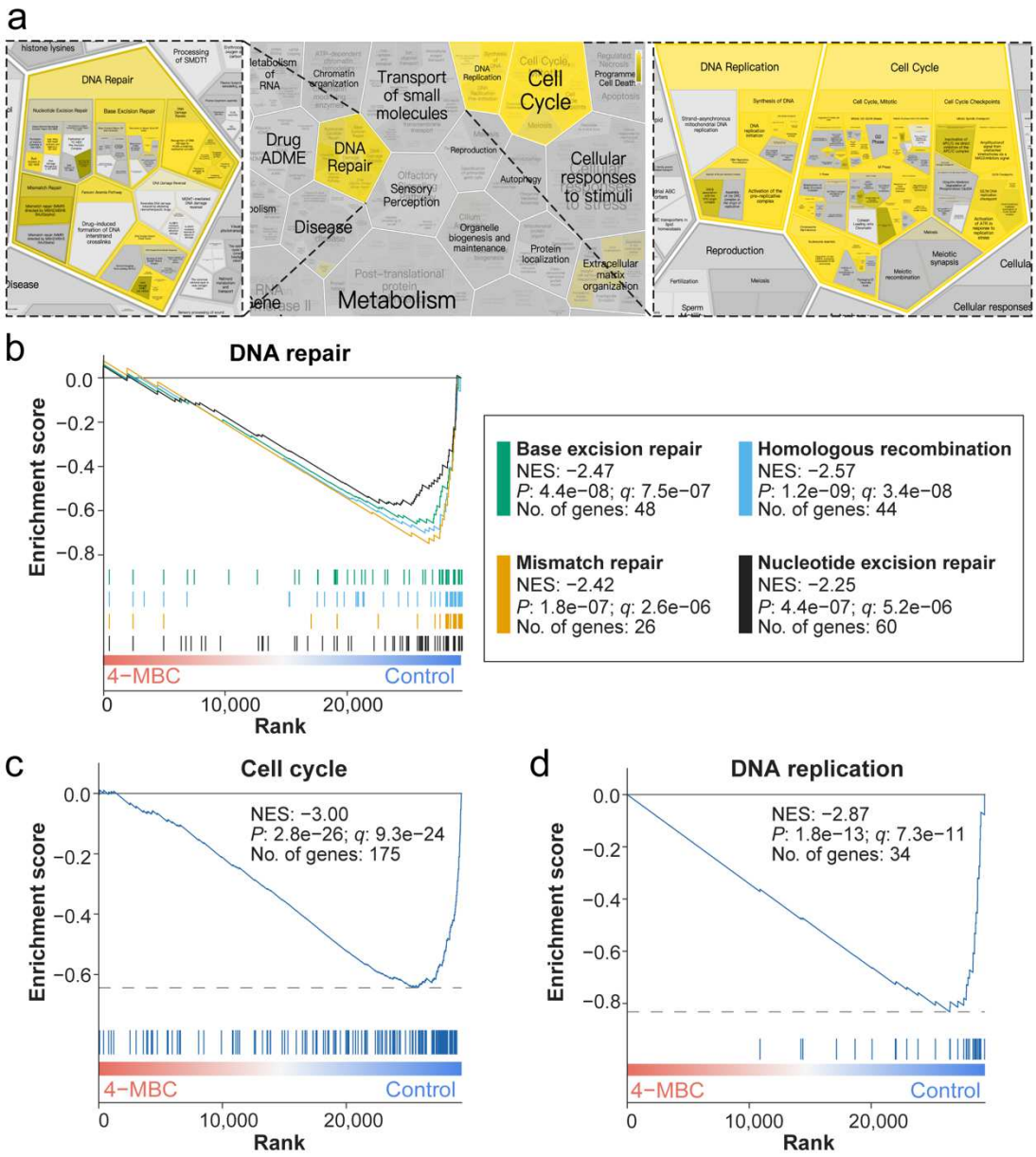

Fig. 2 Coordinated disruption of genome-maintenance pathways by 4-MBC in killifish (a) Voronoi analysis of Reactome pathway enrichment among genes downregulated following 4-MBC exposure. The central panel shows the major Reactome pathway categories, with the left inset highlighting DNA repair pathways and the right inset highlighting DNA replication and cell-cycle pathways. Yellow tiles indicate significantly enriched pathways, whereas grey tiles indicate pathways that were not significantly enriched. (b-d) Gene set enrichment analysis (GSEA) plots for base excision repair, homologous recombination, mismatch repair, and nucleotide excision repair (b), the cell cycle (c), and DNA replication (d). *P* values, *q* values, NES values, and set sizes are indicated in each panel.

4-MBC alters DNA damage response-associated genes

To characterize the molecular basis of the genome-maintenance signature, we examined 11 genes involved in DNA damage sensing, repair initiation, and repair execution (Fig. 3a). These

included *h2ax* and *tp53* (damage sensing and signaling), *rbbp8*, *rpa1*, and *brip1* (repair initiation), and *rad51*, *rad51ap1*, *swi5*, *rad54b*, *mms22l*, and *rmi2* (repair execution) [29,30]. All 11 genes showed reduced expression following 4-MBC exposure, with RT-qPCR confirming the transcriptional changes (Fig. 3b). STRING analysis further revealed extensive functional interactions among these proteins, consistent with their coordinated involvement in DNA repair processes (Fig. 3c).

Importantly, the simultaneous downregulation of genes spanning multiple stages of the DNA damage response suggests that 4-MBC exposure affects an interconnected repair-associated network rather than individual molecular targets. Particularly notable is the suppression of RAD51 and its associated factors, which are central components of homologous recombination, a major pathway for maintaining genomic integrity [29]. This coordinated transcriptional response identifies specific molecular components underlying the broader genome-maintenance signature and raises the possibility that 4-MBC exposure may influence cellular DNA repair capacity.

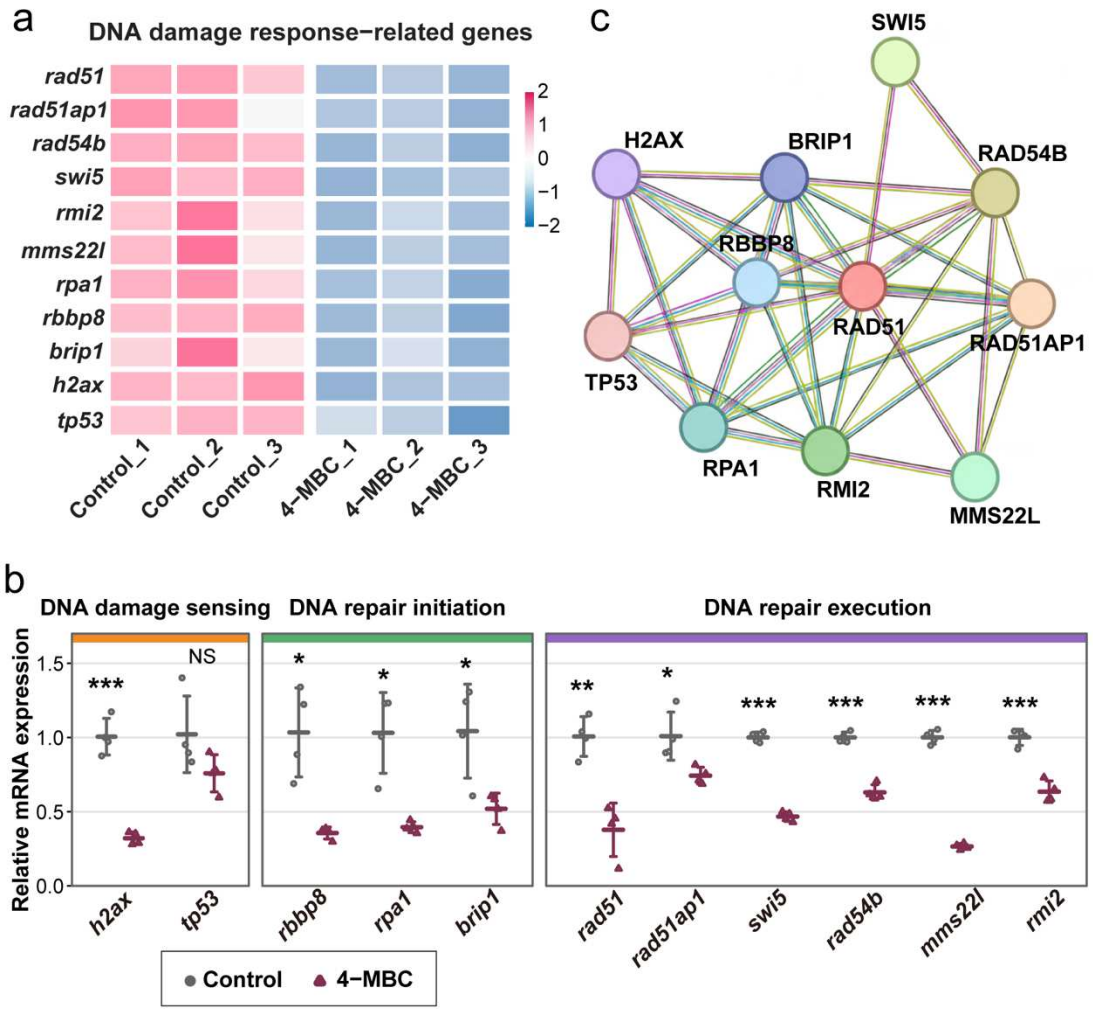

Fig. 3 4-MBC-induced alterations in DNA damage response-associated genes in killifish (a) Heatmap showing RNA sequencing-based expression patterns of 11 DNA damage response-associated genes in

control and 4-MBC-treated groups (n = 3 per group). Expression values were standardized by gene as row Z-scores; pink and blue indicate relatively high and low expression, respectively, and white indicates expression near the row mean. (b) RT-qPCR validation of genes involved in DNA damage sensing (*h2ax* and *tp53*), repair initiation (*rbbp8*, *rpa1*, and *brip1*), and repair execution (*rad51*, *rad51ap1*, *swi5*, *rad54b*, *mms22l*, and *rmi2*). Data are presented as mean ± SD of four independent biological replicates. Statistical significance was determined by unpaired two-tailed Student's *t*-test; $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$, NS, not significant. (c) Protein-protein interaction network of the 11 DNA damage response-associated proteins constructed using the STRING database. Nodes represent proteins, and edges represent known or predicted functional associations.

Convergent genome-maintenance responses in fish and human cells

To determine whether the repair-associated machinery identified in killifish also responds to 4-MBC in human cells, we examined primary human dermal fibroblasts, a skin-relevant model of potential topical exposure. Several genes implicated in the killifish response, including *H2AX*, *TP53*, *RBBP8*, *RPA1*, *BRIP1*, *RAD51*, *RAD51AP1*, *SWI5*, *RAD54B*, *MMS22L*, and *RMI2*, showed concentration-dependent expression changes (Fig. 4a; Figs. S6-S8). Many of these genes showed reduced expression at lower concentrations but increased expression at 10 - 100 μM, revealing non-monotonic patterns that differed among genes.

At the protein level, 4-MBC increased p53, p21, and RAD51 abundance (Fig. 4b). The comet assay showed no significant increase in DNA strand breaks at lower concentrations, whereas higher concentrations were associated with increased strand breaks (Fig. 4c). These observations link transcriptional changes to cellular stress-associated proteins and, at higher exposures, an adverse DNA-damage endpoint.

Importantly, the two models converge on overlapping DNA damage response pathways, particularly RAD51-associated homologous-recombination machinery, even though their experimental designs and response patterns differ. Killifish reveal coordinated downregulation of genome-maintenance transcriptional programs *in vivo*, whereas human fibroblasts reveal concentration-dependent regulation of overlapping genes, accompanied by protein changes and DNA strand breaks at higher exposures. Increased repair-associated expression may reflect a response to damage rather than improved repair capacity; conversely, reduced expression alone does not demonstrate defective repair. Thus, these complementary results identify genome maintenance as a target of 4-MBC while showing why the biological significance of DNA damage response depends on exposure and cellular context. They also raise the broader question of how the direct cellular actions of UV filters should be evaluated alongside their photoprotective function.

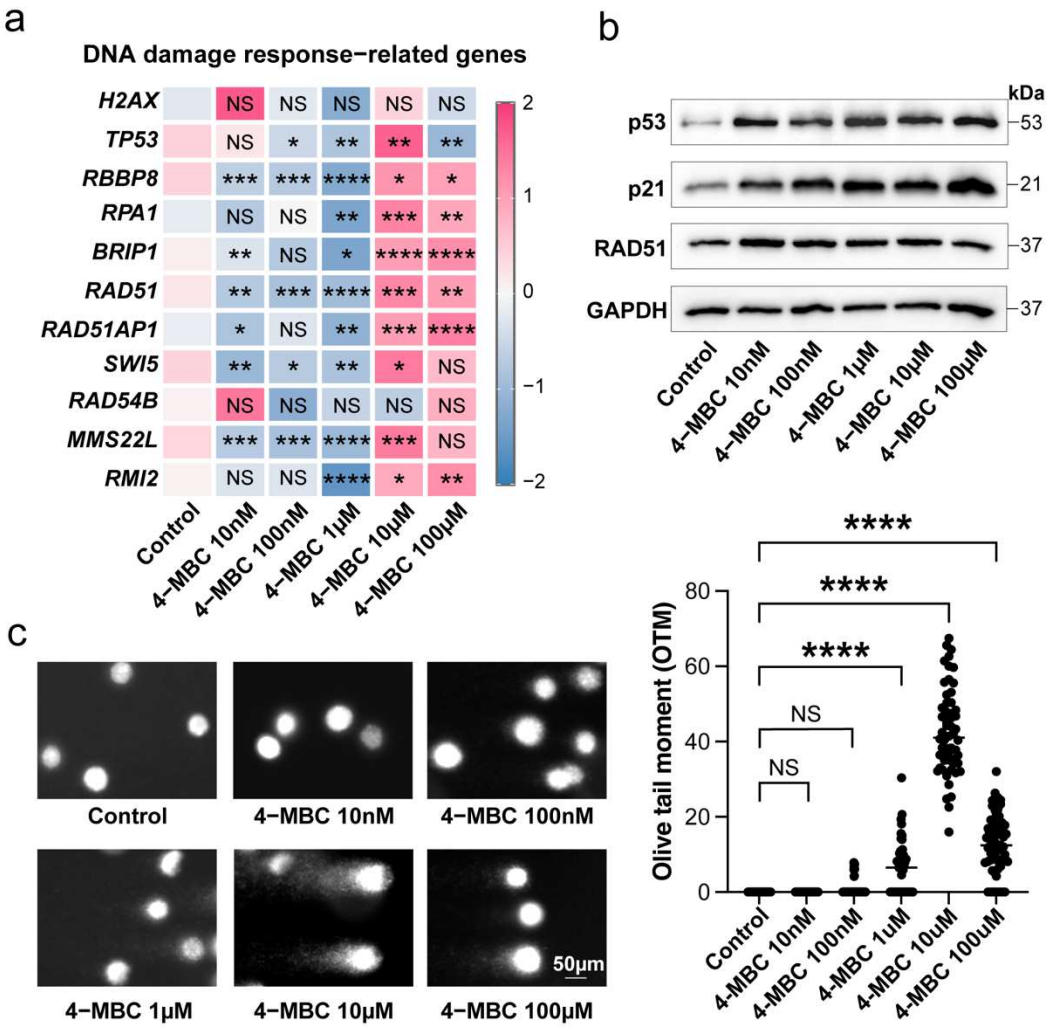

Fig. 4 Convergent genome-maintenance responses induced by 4-MBC in fish and human cells (a) Heatmap showing mRNA expression levels of selected DNA damage response-associated genes in primary human dermal fibroblasts exposed to increasing concentrations of 4-MBC, as determined by RT-qPCR (n = 3 independent experiments). Expression values were standardized by gene as row Z-scores; pink and blue indicate relatively high and low expression, respectively, and white indicates expression near the row mean. Statistical significance was assessed by one-way ANOVA followed by Dunnett's multiple-comparison test; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$, NS, not significant. (b) Western blot analysis of P53, P21, and RAD51 protein levels in cells exposed to vehicle or 4-MBC at 10 nM, 100 nM, 1 μM, 10 μM, or 100 μM. GAPDH served as the loading control. Protein molecular masses (kDa) are indicated on the right. (c) Alkaline comet assay assessing DNA damage in cells exposed to the indicated concentrations of 4-MBC. Left, representative fluorescence images of comets; right, quantification of tail moment. At least 50 cells were randomly selected and analyzed per group. Data are presented as mean ± SD. Statistical significance was determined by one-way ANOVA followed by Dunnett's multiple-comparison test; ****$P < 0.0001$, NS, not significant. Scale bars = 50 μm.

Conclusion

By integrating whole-organism transcriptomics in African turquoise killifish with molecular and cellular analyses in human dermal fibroblasts, we identify genome maintenance as an underrecognized target of 4-MBC exposure. The convergence of DNA repair-associated responses across models, together with concentration-dependent transcriptional changes and DNA damage at higher exposures, highlights the significance of exposure context in determining cellular outcomes. These results support thus the inclusion of DNA damage response-associated molecular endpoints in future investigations of UV-filter safety, particularly when conventional assessments do not reveal overt morphological alterations.

Acknowledgements

We thank Dr. Wei Wang from the National Institute of Biological Sciences, Beijing (NIBS), for kindly providing the African turquoise killifish (*Nothobranchius furzeri*) model used in this study. We thank the Research Center for Basic Medical Sciences at Qilu Hospital of Shandong University for technical consultation and access to research facilities and instrumentation.

Authors' Contributions

Chuanxin Wang, Chengxi Sun and Helgi B. Schiöth contributed to conceptualization and study design. Chen Li and Shan Jin performed the experiments and bioinformatic analyses. Chen Li, Shan Jin, Ruomei Li, Jingwen Wang, Lin Sun and Chengxi Sun contributed to validation, formal analysis and data curation. Chen Li and Shan Jin wrote the original draft. Chengxi Sun and Helgi B. Schiöth contributed to writing, review and editing. Chuanxin Wang supervised the study. All authors read and approved the final manuscript.

Declarations

Artificial intelligence

Non-applicable

Funding

This work was supported by the Shandong Provincial Natural Science Foundation (ZR2024QH577, ZR2020QH287), the Basic Research Program of Jiangsu (BK20250416), the China Postdoctoral Science Foundation (2025M772080), Postdoctoral Fellowship Program of CPSF (GZC20240925) and the Swedish Cancer Society (grants 20090 Pj, and 23 3033 PJ).

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

Ethical approval

All animal experiments were approved by the Ethics Committee of Qilu Hospital of Shandong University (approval No. DWLL-202400090-2).

Consent to participate

Non-applicable

Consent for publication

All co-authors consent to publication.

Availability of data

The RNA sequencing data that support the findings of this study have been deposited in the Gene Expression Omnibus under the accession number GSE351197. All other data are available from the corresponding author upon request.

Code availability

The custom code supporting the findings of this study is available from the corresponding author upon request.

References

[1] M.G. Pintado-Herrera, C. Wang, J. Lu, Y.-P. Chang, W. Chen, X. Li, P.A. Lara-Martín, Distribution, mass inventories, and ecological risk assessment of legacy and emerging contaminants in sediments from the Pearl River Estuary in China, J Hazard Mater 323 (2017) 128–138. https://doi.org/10.1016/j.jhazmat.2016.02.046.

[2] P. Emnet, A.S. Mahaliyana, G. Northcott, S. Gaw, Organic Micropollutants in Wastewater Effluents and the Receiving Coastal Waters, Sediments, and Biota of Lyttelton Harbour (Te Whakaraupō), New Zealand, Arch Environ Contam Toxicol 79 (2020) 461–477. https://doi.org/10.1007/s00244-020-00760-9.

[3] A. Chowdhury, J. Mizikovsky, 4-MBC in Australian sunscreens as an unmonitored discharge pathway into Great Barrier Reef coastal waters, Discov Water 6 (2026) 124. https://doi.org/10.1007/s43832-026-00463-7.

[4] S. Ren, X. Jin, T.G. Bekele, M. Lv, J. Ding, F. Tan, L. Chen, Development and application of diffusive gradients in thin films for in situ sampling of the organic UV filter 4-methylbenzylidene camphor (4-MBC) in waters, Environ Sci Pollut Res 30 (2023) 92651–92661. https://doi.org/10.1007/s11356-023-28844-8.

[5] N.R. Colás-Ruiz, M.G. Pintado-Herrera, M. Santonocito, B. Salerno, F. Tonini, P.A. Lara-Martín, M. Hampel, Bioconcentration, biotransformation, and transcriptomic impact of the UV-filter 4-MBC in the manila clam Ruditapes philippinarum, Sci Total Environ 912 (2024) 169178. https://doi.org/10.1016/j.scitotenv.2023.169178.

[6] H. Frederiksen, M. Krause, N. Jørgensen, A. Rehfeld, N.E. Skakkebæk, A.-M. Andersson, UV filters in matched seminal fluid-, urine-, and serum samples from young men, J Expo Sci Environ Epidemiol 31 (2021) 345–355. https://doi.org/10.1038/s41370-020-0209-3.

[7] D. Molins-Delgado, M.D.M. Olmo-Campos, G. Valeta-Juan, V. Pleguezuelos-Hernández, D. Barceló, M.S. Díaz-Cruz, Determination of UV filters in human breast milk using turbulent flow chromatography and babies' daily intake estimation, Environ Res 161 (2018) 532–539. https://doi.org/10.1016/j.envres.2017.11.033.

[8] C. Lax, E. Wicksell, A. Grip, J.V.L. Niemi, W. Liu, A. Rafeletou, B. Kudłak, H.B. Schiöth, The effect of sunscreen 4-methylbenzylidene camphor in different and reproductive models, its bioaccumulation and molecular effects on ligand-receptor interaction, and protein expression, Basic Clin Pharmacol Toxicol 133 (2023) 130–141. https://doi.org/10.1111/bcpt.13901.

[9] M. Krause, A. Klit, M. Blomberg Jensen, T. Søeborg, H. Frederiksen, M. Schlumpf, W. Lichtensteiger, N.E. Skakkebaek, K.T. Drzewiecki, Sunscreens: are they beneficial for health? An overview of endocrine disrupting properties of UV-filters, Int J Androl 35 (2012) 424–436.

https://doi.org/10.1111/j.1365-2605.2012.01280.x.
[10] S.O. Mueller, M. Kling, P. Arifin Firzani, A. Mecky, E. Duranti, J. Shields-Botella, R. Delansorne, T. Broschard, P.-J. Kramer, Activation of estrogen receptor alpha and ERbeta by 4-methylbenzylidene-camphor in human and rat cells: comparison with phyto- and xenoestrogens, Toxicol Lett 142 (2003) 89–101. https://doi.org/10.1016/s0378-4274(03)00016-x.
[11] S. Durrer, K. Maerkel, M. Schlumpf, W. Lichtensteiger, Estrogen target gene regulation and coactivator expression in rat uterus after developmental exposure to the ultraviolet filter 4-methylbenzylidene camphor, Endocrinology 146 (2005) 2130–2139. https://doi.org/10.1210/en.2004-1272.
[12] R. Søgaard, H. Holbech, U. Nørum, P. Bjerregaard, Investigation of the in vivo estrogenicity of the UV-filters 4-methylbenzylidene camphor and octyl methoxy cinnamate in rainbow trout (Oncorhynchus mykiss), Ecotoxicol Environ Saf 224 (2021) 112657. https://doi.org/10.1016/j.ecoenv.2021.112657.
[13] H. Xian, Z. Li, R. Ye, M. Dai, Y. Feng, R. Bai, J. Guo, X. Yan, X. Yang, D. Chen, Z. Huang, 4-Methylbenzylidene camphor triggers estrogenic effects via the brain-liver-gonad axis in zebrafish larvae, Environ Pollut 335 (2023) 122260. https://doi.org/10.1016/j.envpol.2023.122260.
[14] Y. Zhang, L. Tu, J. Chen, L. Zhou, Interference Mechanisms of Endocrine System and Other Systems of Endocrine-Disrupting Chemicals in Cosmetics-In Vitro Studies, Int J Endocrinol 2024 (2024) 2564389. https://doi.org/10.1155/ije/2564389.
[15] C. Schmutzler, I. Hamann, P.J. Hofmann, G. Kovacs, L. Stemmler, B. Mentrup, L. Schomburg, P. Ambrugger, A. Grüters, D. Seidlova-Wuttke, H. Jarry, W. Wuttke, J. Köhrle, Endocrine active compounds affect thyrotropin and thyroid hormone levels in serum as well as endpoints of thyroid hormone action in liver, heart and kidney, Toxicology 205 (2004) 95–102. https://doi.org/10.1016/j.tox.2004.06.041.
[16] N.R. Janjua, B. Mogensen, A.-M. Andersson, J.H. Petersen, M. Henriksen, N.E. Skakkebaek, H.C. Wulf, Systemic absorption of the sunscreens benzophenone-3, octyl-methoxycinnamate, and 3-(4-methyl-benzylidene) camphor after whole-body topical application and reproductive hormone levels in humans, J Invest Dermatol 123 (2004) 57–61. https://doi.org/10.1111/j.0022-202X.2004.22725.x.
[17] C. Quintaneiro, B. Teixeira, J.L. Benedé, A. Chisvert, A.M.V.M. Soares, M.S. Monteiro, Toxicity effects of the organic UV-filter 4-Methylbenzylidene camphor in zebrafish embryos, Chemosphere 218 (2019) 273–281. https://doi.org/10.1016/j.chemosphere.2018.11.096.
[18] A. Sancar, L.A. Lindsey-Boltz, K. Unsal-Kaçmaz, S. Linn, Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints, Annu Rev Biochem 73 (2004) 39–85. https://doi.org/10.1146/annurev.biochem.73.011303.073723.
[19] L.A. Yates, X. Zhang, P.M. Burgers, DNA Damage and Replication Stress Checkpoints, Annu Rev Biochem 94 (2025) 195–221. https://doi.org/10.1146/annurev-biochem-072324-031915.
[20] M. Stanic, K. Mekhail, Integration of DNA damage responses with dynamic spatial genome organization, Trends in Genetics 38 (2022) 290–304. https://doi.org/10.1016/j.tig.2021.08.016.
[21] C. Li, S. Winberg, C. Sun, H.B. Schiöth, The turquoise killifish (Nothobranchius furzeri) as emerging ageing model: Systematic review and comparison with zebrafish, medaka and fugu, Ageing Research Reviews 117 (2026) 103064. https://doi.org/10.1016/j.arr.2026.103064.
[22] F. Boos, J. Chen, A. Brunet, The African Turquoise Killifish: A Scalable Vertebrate Model for Aging and Other Complex Phenotypes, Cold Spring Harb Protoc 2024 (2024) 107737.

https://doi.org/10.1101/pdb.over107737.
[23] M.Y. Kim, A.R. Jung, D. Shin, H. Kwon, H.J. Cho, U.-S. Ha, S.-H. Hong, J.Y. Lee, S.W. Kim, Y.H. Park, Niclosamide exerts anticancer effects through inhibition of the FOXM1-mediated DNA damage response in prostate cancer, Am J Cancer Res 11 (2021) 2944–2959.
[24] F.J. Ferreira, M. Galhardo, J.M. Nogueira, J. Teixeira, E. Logarinho, J. Bessa, FOXM1 expression reverts aging chromatin profiles through repression of the senescence-associated pioneer factor AP-1, Nat Commun 16 (2025) 2931. https://doi.org/10.1038/s41467-025-57503-4.
[25] M. Schlumpf, H. Jarry, W. Wuttke, R. Ma, W. Lichtensteiger, Estrogenic activity and estrogen receptor beta binding of the UV filter 3-benzylidene camphor. Comparison with 4-methylbenzylidene camphor, Toxicology 199 (2004) 109–120. https://doi.org/10.1016/j.tox.2004.02.015.
[26] D. Seidlová-Wuttke, H. Jarry, J. Christoffel, G. Rimoldi, W. Wuttke, Comparison of effects of estradiol (E2) with those of octylmethoxycinnamate (OMC) and 4-methylbenzylidene camphor (4MBC)--2 filters of UV light - on several uterine, vaginal and bone parameters, Toxicol Appl Pharmacol 210 (2006) 246–254. https://doi.org/10.1016/j.taap.2005.05.006.
[27] M. Santonocito, B. Salerno, C. Trombini, F. Tonini, M.G. Pintado-Herrera, G. Martínez-Rodríguez, J. Blasco, P.A. Lara-Martín, M. Hampel, Stress under the sun: Effects of exposure to low concentrations of UV-filter 4- methylbenzylidene camphor (4-MBC) in a marine bivalve filter feeder, the Manila clam Ruditapes philippinarum, Aquat Toxicol 221 (2020) 105418. https://doi.org/10.1016/j.aquatox.2020.105418.
[28] A. Cuccaro, L. De Marchi, M. Oliva, F. Battaglia, V. Meucci, G. Fumagalli, R. Freitas, C. Pretti, Ecotoxicological effects of the UV-filter 4-MBC on sperms and adults of the mussel Mytilus galloprovincialis, Environ Res 213 (2022) 113739. https://doi.org/10.1016/j.envres.2022.113739.
[29] P. Sung, H. Klein, Mechanism of homologous recombination: mediators and helicases take on regulatory functions, Nat Rev Mol Cell Biol 7 (2006) 739–750. https://doi.org/10.1038/nrm2008.
[30] A. Ciccia, S.J. Elledge, The DNA damage response: making it safe to play with knives, Mol Cell 40 (2010) 179–204. https://doi.org/10.1016/j.molcel.2010.09.019.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx
- Supplementarytable.xlsx