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Reassessing Chelerythrine as a Candidate Therapy for Nasopharyngeal Carcinoma

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Abstract

Chelerythrine has recently been proposed as a therapeutic candidate for Nasopharyngeal Carcinoma (NPC) based on its reported effects on proliferation, apoptosis, migration, epithelial-mesenchymal transition and miR-21/PTEN/PI3K/AKT signaling. However, the central experimental models used to support this conclusion, namely the 5-8F and 6-10B cell lines, have been reported to be HeLa-derived, HeLa-contaminated or otherwise misidentified rather than authentic NPC cell lines. This raises major concerns regarding the disease-specific interpretation of the reported findings. Although the data may indicate pharmacological activity of chelerythrine in the tested cellular background, they do not establish anti-NPC efficacy. Similarly, xenograft experiments using 5-8F cells cannot be interpreted as valid NPC models if the implanted cells are misidentified. The proposed miR-21/PTEN/PI3K/AKT mechanism may be internally consistent but remains unvalidated in authentic NPC systems. To support translational claims, key experiments should be repeated in authenticated NPC models, ideally including Epstein-Barr virus-positive and Epstein-Barr virus-negative systems, patient-derived organoids or xenografts and models that recapitulate orthotopic tumor growth or metastatic disease. This short communication highlights the need for rigorous cell line authentication before proposing disease-specific therapeutic conclusions.

Keywords: Nasopharyngeal carcinoma; Chelerythrine; miR-21; PTEN; PI3K/AKT; HeLa contamination; Cell line authentication; Misidentified cell lines; 5-8F; 6-10B

Introduction

NPC is a distinct epithelial malignancy with specific biological, epidemiological, viral and molecular characteristics. Experimental studies aiming to identify novel therapeutic candidates for NPC therefore critically depend on the use of authenticated and disease-relevant model systems.

Zhang et al. recently reported that chelerythrine is a novel candidate for targeting the miR-21/PTEN/PI3K/AKT axis in NPC and concluded that chelerythrine may represent a safe and effective therapeutic candidate for this disease [1]. The study presents extensive *in vitro* and *in vivo* data, including assays for proliferation, apoptosis, migration, invasion, epithelial-mesenchymal transition, xenograft growth and pathway modulation. However, the interpretation of these findings is critically affected by the identity of the cell lines used as the principal disease models. The central experimental premise of the study is that 5-8F and 6-10B are valid NPC cell models. The authors describe these cells as human NPC cell lines selected to study metastatic potential and epithelial-mesenchymal transition, with 5-8F considered highly metastatic and 6-10B having low metastatic potential. This premise is problematic because both cell lines have been reported to be HeLa-contaminated, HeLa-derived or otherwise misidentified rather than authentic NPC cell lines.

Misidentification of 5-8F and 6-10B

The 5-8F cell line was originally considered to be of NPC origin but was later shown by Short Tandem Repeat (STR) profiling to be a HeLa derivative [2]. Similarly, 6-10B has been classified as a hybrid of HeLa and a cell line of unknown origin [2]. Consequently, the International Cell Line Authentication Committee (ICLAC) lists these cell lines in its

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Register of misidentified cell lines with registration IDs ICLAC-00596 for 5-8F and ICLAC-00597 for 6-10B [3]. This issue is not a minor technical limitation. Cell line misidentification directly affects the biological and translational validity of conclusions drawn from such models. If 5-8F and 6-10B are not authentic NPC cells, then experiments performed in these cells cannot be used to establish NPC-specific drug efficacy, mechanism of action, metastatic behavior or epithelial-mesenchymal transition biology.

Implications for the Interpretation of Chelerythrine Activity

Zhang et al. report that chelerythrine inhibits proliferation of 5-8F and 6-10B cells in CCK-8 and real-time cell analysis assays and induces apoptosis, as assessed by annexin V-FITC/PI staining [1]. These results may indicate that chelerythrine has antiproliferative and pro-apoptotic activity in the tested cellular system. However, if the cells are HeLa-derived or HeLa-contaminated, these findings do not establish anti-NPC efficacy. The same concern applies to the reported downregulation of XIAP, PCNA and Bcl-2 after chelerythrine treatment. These molecular changes may reflect pharmacodynamic effects in the HeLa-related background tested, but they cannot support disease-specific therapeutic claims for NPC without validation in authenticated NPC models. Similarly, Zhang et al. report that chelerythrine suppresses migration and invasion in wound-healing and Transwell assays and reverses epithelial-mesenchymal transition-associated marker expression by decreasing snail, N-cadherin and vimentin while increasing E-cadherin [1]. These findings may indicate anti-migratory or anti-invasive effects in the cells used. However, they do not provide valid evidence that chelerythrine suppresses NPC metastasis or NPC-specific epithelial-mesenchymal transition processes.

Limitations of the Xenograft Evidence

The *in vivo* data are affected by the same problem of model-identification. Zhang et al. generated xenografts by injecting 5-8F cells into BALB/c nude mice [1]. The reported reduction in tumor volume and tumor weight after chelerythrine treatment may demonstrate activity against xenografts formed by the implanted cells. However, if these cells are HeLa-derived or otherwise misidentified, the resulting tumors should not be interpreted as NPC xenografts. The histological evidence of tumor necrosis and apoptosis after chelerythrine treatment is pharmacologically interesting, but its disease-specific relevance to NPC is not established. Likewise, the reported safety observations, including the absence of significant body weight loss, major changes in liver or kidney indices and overt liver or kidney histopathology, may support preliminary tolerability in this nude-mouse experiment. However, these findings do not establish clinical safety or NPC-specific therapeutic suitability.

Mechanistic Interpretation of the miR-21/PTEN/PI3K/AKT Axis

The proposed mechanism is also compromised by the cell line issue. Zhang et al. suggest that chelerythrine transcriptionally downregulates miR-21, restores PTEN expression and suppresses PI3K/AKT signaling in NPC [1]. The reported pattern-reduced pri-miR-21, pre-miR-21 and mature miR-21, as well as increased PTEN and decreased phosphorylated PI3K and AKT may be internally consistent in the tested cells.

Nevertheless, if 5-8F and 6-10B are HeLa-derived or HeLa-contaminated, the data support at most a mechanism of chelerythrine action in a HeLa-related cellular background, not in NPC. This distinction is important because the miR-21/PTEN/PI3K/AKT axis is a broad oncogenic signaling pathway present in many tumor types and is not specific to NPC. The rescue experiments using a PI3K activator and lentiviral miR-21 modulation are similarly limited.

Although PI3K activation reportedly counteracted the effects of chelerythrine and miR-21 overexpression attenuated, while miR-21 knockdown enhanced, chelerythrine-mediated phenotypes [1], these experiments cannot validate the pathway as an NPC-specific mechanism unless the experiments are repeated in authenticated NPC models.

Findings that Remain Potentially Relevant

Some observations in the study remain potentially informative. The analysis of the GEO GSE32960 microarray dataset, which showed elevated miR-21 expression in NPC tissues compared with normal tissue samples, is relevant to NPC biology, although it is independent of the chelerythrine experiments. The network pharmacology analysis identifying PI3K/AKT signaling as a candidate pathway is hypothesis-generating.

However, such in silico evidence cannot replace experimental validation in authenticated disease models. The NP69 experiments also provide limited information on chelerythrine cytotoxicity toward a normal nasopharyngeal epithelial cell line, but they do not rectify the invalidated

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status of 5-8F and 6-10B as disease models. Accordingly, the title, abstract, conclusion and translational claims of the study appear overstated. In particular, the statement that chelerythrine is a safe and effective therapeutic candidate for NPC is not supported if the main *in vitro* and *in vivo* efficacy data were generated using misidentified HeLa-derived or HeLa-contaminated cell lines.

Recommendations for Future Validation

To support relevance to NPC, the key experiments should be repeated in authenticated NPC models. Ideally, such validation should include both Epstein-Barr virus-positive and Epstein-Barr virus-negative systems, patient-derived NPC organoids or xenografts and orthotopic or metastatic models that better reflect the clinical biology of the disease.

This is particularly important because the study emphasizes NPC-specific issues, including metastasis, radioresistance, Epstein-Barr virus/LMP1 signaling and the miR-21/PTEN/PI3K/AKT axis. Without authenticated disease models, it is not possible to determine whether the observed effects of chelerythrine are relevant to NPC or merely reflect broader cytotoxic or signaling effects in a misidentified cellular background.

Conclusion

The study by Zhang et al. may provide preliminary evidence that chelerythrine affects proliferation, apoptosis, migration, epithelial-mesenchymal transition-associated markers and miR-21/PTEN/PI3K/AKT signaling in the tested cell system. However, because the central models used in the study, 5-8F and 6-10B, have been reported to be HeLa-derived, HeLa-contaminated or otherwise misidentified rather than authentic NPC cell lines, the data do not provide valid experimental evidence that chelerythrine is effective against NPC.

The continued use of misidentified cell lines remains a significant problem in NPC research and complicates the interpretation of experimental and translational findings [4,5]. Rigorous cell line authentication should therefore be considered an essential prerequisite for proposing disease-specific therapeutic conclusions.

Beyond the responsibility of authors to authenticate their experimental models, reviewers and editors also have an important responsibility to identify the use of misidentified or cross-contaminated cell lines and to prevent the publication of studies whose central conclusions depend on invalidated cellular models [6].

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The author is a member of the International Cell Line Authentication Committee (ICLAC; https://iclac.org/), which operates on a voluntary basis to prevent the use of misidentified or cross-contaminated cell lines in biomedical research.

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Authors' contributions

R.W. conceived and wrote the manuscript.

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