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Commentary

FEN1 drives small cell neuroendocrine carcinoma of the cervix progression and holds promise as a therapeutic target

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Abstract

Small cell neuroendocrine carcinoma of the cervix (SCNECC) is a rare and clinically aggressive subtype of cervical cancer associated with a poor prognosis. To investigate its underlying pathological mechanisms and identify potential therapeutic targets, researchers have increasingly employed single-omics or multi-omics integrated analysis, including single-cell transcriptome sequencing, proteomics, whole-exome sequencing, and genomics. In a study by Jianbing Liu *et al.*, proteomic profiling of SCNECC tumor tissues and adjacent non-tumor tissues revealed that FEN1 drives disease progression by modulating PCNA expression. FEN1 shows promise as a novel therapeutic target for SCNECC. This commentary emphasizes that omics technology is an effective research approach for investigating the pathological mechanisms of SCNECC, and FEN1 shows potential as a novel therapeutic target for SCNECC. However, further experiments are required to elucidate its mechanisms of action.

Keywords: Small cell neuroendocrine carcinoma of the cervix, SCNECC, Proteomics, FEN1, Targeted therapy

Commentary

Small cell neuroendocrine carcinoma of the cervix (SCNECC) represents a clinically uncommon and poorly prognostic variant of cervical cancer. Currently, both its underlying pathological mechanisms remain elusive, and there is a lack of specific therapeutic drugs. Through a systematic research process involving proteomic screening, validation of pivotal molecules, functional assays, and investigation into molecular mechanisms, the recently published study has demonstrated that flap structure-specific endonuclease 1 (FEN1) exhibits aberrant overexpression in SCNECC and actively contributes to its initiation and progression [1]. These findings not only furnish a scientific foundation for molecular pathology research on SCNECC but also identify a novel target for the development of targeted therapeutic agents.

Omics Technology: Lighting the Way to Uncover SCNECC Pathological Mechanism

Single-cell transcriptome sequencing, proteomics, whole exome sequencing, and genomics, either individually or combined, are widely used to study the pathological mechanism of SCNECC [2–7]. Proteins serve as vital biological macromolecules that carry out diverse functional activities within cells. Proteomics, a technology dedicated to the "large-scale analysis of protein characteristics, encompassing expression levels, post-translational modifications, and protein-protein interactions", offers a panoramic perspective for interpreting diseases at the protein level. This approach perfectly addresses the research challenges associated with SCNECC: given its rarity, traditional molecular

mechanism studies are hindered by a scarcity of data. In contrast, proteomics enables the efficient identification of differentially expressed proteins by comparing the protein landscapes of cancerous tissues with those of their para-carcinoma tissues, thereby providing a "top-down" scientific screening pathway for pinpointing key driver targets. It constitutes a pivotal technological underpinning for exploring therapeutic targets in SCNECC. Integrated with subsequent GO and KEGG analyses, along with validation experiments, the authors of this study have successfully executed a sequential research paradigm of "screening-enrichment-validation." The research maintains a coherent and logical framework while closely adhering to the fundamental characteristics of the disease, thereby offering a robust scientific foundation for unraveling the molecular mechanisms of SCNECC, facilitating early detection, and enabling precise therapeutic interventions.

Leveraging omics research techniques, a comparative analysis of protein expression profiles was performed between SCNECC tumor tissues and their para-carcinoma tissues. This endeavor led to the identification of 2,333 differentially expressed proteins, comprising 2,168 upregulated and 165 downregulated proteins in the tumor tissues. Through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses, the researchers found that these differentially expressed proteins could be enriched in the pathway of DNA replication, a characteristic feature aligned with the high proliferative potential of tumors. These proteins might constitute a crucial regulatory node in SCNECC. This observation is in close concordance with the rapid proliferative phenotype exhibited by SCNECC.

FEN1: A Promising Novel Therapeutic Target for SCNECC

FEN1, a divalent metal-dependent protein endowed with both exonuclease and endonuclease activities, plays a pivotal role in the base excision repair (BER) pathway and is involved in Okazaki fragment maturation during DNA replication [8]. FEN1 was identified and subsequently recognized for its intimate involvement in DNA metabolism and genome stability [9,10]. The aberrant expression of FEN1 has been documented across a spectrum of cancers, for example cervical cancer and cholangiocarcinoma [11,12]. Based on the proteomic comparative analysis of cancer tissues and adjacent normal tissues in SCNECC, the authors focused on FEN1 as a candidate molecule for in-depth exploration. Through a series of cell-based assays (including CCK-8 assays, colony formation assays, and cell cycle/apoptosis analyses) and *in vivo* animal experiments, the authors have delineated the advantageous impact of FEN1 overexpression on the survival and proliferation of SCNECC cells, as well as its pivotal role in driving tumor formation. Furthermore, molecular biology experiments have revealed that FEN1 propels SCNECC progression by modulating PCNA expression, while concurrently influencing the expression levels of PIK3CA, BCL-2, and Caspase-9. This offers a molecular-level explanation for the pathological and biological hallmarks of SCNECC, namely its "high proliferative rate and apoptosis resistance," and sheds light on the underlying mechanisms contributing to its rapid progression. These findings furnish novel scientific evidence for a deeper comprehension of the pathological characteristics of SCNECC.

FEN1 holds promise as a novel and promising therapeutic target for SCNECC. Presently, there are no tailored pharmacological treatments specifically designed for SCNECC, and its management predominantly relies on treatment protocols adapted from small cell lung cancer. This approach may partially account for its unfavorable prognosis. In other types of cancers, several researchers have emphasized the promising therapeutic potential of FEN1 inhibitors for cancer treatment, highlighting FEN1 as a viable target for cancer therapy [13–15]. In this research, the authors not only comprehensively elucidate the overexpression of FEN1 in SCNECC and its pivotal role in disease progression but also employ the FEN1 inhibitor SC13 to modulate FEN1 expression *in vivo*. The findings reveal that silencing FEN1 exerts a potent anticancer effect on SCNECC. These results underscore the feasibility of "targeting FEN1" as a therapeutic strategy for SCNECC, providing compelling preliminary evidence for the development of targeted drugs. This advancement carries significant implications for addressing the clinical challenges of SCNECC, which are currently marked by "limited treatment modalities and a poor prognosis."

Given the rarity of SCNECC, this study initially validated FEN1 expression with a limited clinical sample set. Further validation using an expanded immunohistochemistry (IHC) cohort, along with medical record analysis, is needed to explore FEN1's links to disease progression, treatment, and prognosis, aiding the shift of FEN1-targeted strategies to clinical use. The abnormal expression of FEN1 in SCNECC suggests that it might be utilized as a marker for the diagnosis of SCNECC. However, its presence in multiple cancers prevents it from being a specific marker, which is disappointing. Future research will seek molecules uniquely abnormally expressed in SCNECC, integrating them with traditional pathology and IHC markers to improve diagnostic accuracy and offer new insights into SCNECC's distinct traits.

In general, this study, guided by clinical needs, used proteomics to identify FEN1 as a key molecule in SCNECC, verified its feasibility as a target, and advanced specific drug development. It provides vital data for molecular research and actionable targets for precision treatment. Combining targeted and traditional therapies may improve prognosis, underscoring the study's timeliness and practicality.

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