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abstract

Enhancing Chemosensitivity in Pediatric Cancers: Investigating the Role of SLFN11 in Response to DNA-Damaging Agents and PARP Inhibitors

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Enhancing Chemosensitivity in Pediatric Cancers: Investigating the Role of SLFN11 in Response to DNA-Damaging Agents and PARP Inhibitors

Author: *Christophe Raynaud [1], Ayesha Jabeen, Dina Awartani, Eiman Ahmed, Shimaa Sherif, Apryl Sanchez, Wouter Hendrickx*

Affiliation: [1] *Sidra Medicine, Doha, Qatar*

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Introduction: Schlafen family member 11 (SLFN11) plays a critical role in inducing irreversible cell cycle arrest in response to DNA damage. Recently, SLFN11 has emerged as a predictive biomarker for sensitivity to DNA-damaging agents (DDA). Previous studies by our group demonstrated that increased SLFN11 expression enhances chemosensitivity in breast cancer cell lines, prompting us to explore its functionality in pediatric cancers. Our initial findings revealed varying SLFN11 expression levels and inconsistent survival outcomes across different pediatric tumor types, leading us to investigate SLFN11's mechanism of action in three distinct pediatric cancers.

Methodology: We employed the CRISPR activation (CRISPRa) system to assess the effects of enhanced SLFN11 expression in pediatric cancer cell lines. Specifically, we focused on PDM-182 (Wilms tumor), CRL-1544 (osteosarcoma), and HTB-186 (medulloblastoma) to evaluate their sensitivity to DNA-damaging agents such as Cisplatin and PARP inhibitors, including Talazoparib.

Results: We screened 13 pediatric cell lines for SLFN11 expression and promoter methylation. Our data showed an expected correlation between SLFN11 promoter methylation and its expression levels. Using the CRISPR- UNISAM system, we achieved a stable, specific upregulation of SLFN11, resulting in up to a 7-fold increase in expression across the three pediatric cell lines. This upregulation significantly enhanced the sensitivity of these cell lines to Cisplatin and Talazoparib, as compared to their unmodified counterparts.

Conclusion: Our results demonstrate that upregulating SLFN11 expression sensitizes pediatric cancer cells to both DNA-damaging agents and PARP inhibitors, mirroring the effects observed in adult cancers. Ongoing research aims to elucidate the precise mechanisms through which SLFN11 mediates its effects in pediatric cancers, furthering its potential as a therapeutic target.