WTAP weakens oxaliplatin chemosensitivity of colorectal cancer by preventing PANoptosis

Yue-Tao Tan, *et al. Cancer Letters* **604:** 217254, 2024

Presenter: Yi-Liam Chen **Date/Time:** 2025/11/27, 16:20 -17:10
Commentator: Dr. Li-Wha Wu **Location:** Room 601, Med College Building

Background: Chemotherapy is the most common treatment for cancer patients. Oxaliplatin-based chemotherapy is the standard treatment for patients with unresectable colorectal cancer (CRC). However, the intrinsic chemoresistance and acquired chemoresistance of tumors reduce the sensitivity of chemotherapy, therefore promoting tumor recurrence, progression, or distant metastasis, eventually leading to treatment failure. N^6-methyladenosine (m^6A), methylated adenosine(A) at the N^6 position, is the most abundant post-transcriptional modification in eukaryotes that relies on RNA methyltransferases, demethylases, and m^6A-binding protein. Recent studies have discovered a significant impact of m^6A RNA methylation in tumor proliferation, invasion as well as chemoresistance. However, the effect and downstream mechanism of m^6A methylation on oxaliplatin-based chemosensitivity in CRC remain largely unclear.

Objective: To investigate the function of m^6A methyl transferase Wilms tumor 1-associating protein (WTAP) in facilitating chemoresistance

Results: The authors first treated HCT116 and DLD1, two CRC cell lines, with control or oxaliplatin for 24 hours, and found out that m^6A methylation increased in the group treated with oxaliplatin. Next, the authors knockdown the expression of WTAP, the main regulator of m^6A methylation, and conducted m^6A-dot blot assays, qPCR analysis, immunoblotting, cell viability assay, LDH release assay, and xenograft transplantation in mice to further investigate its function under oxaliplatin treatment. They found that the CRC cells with WTAP depletion exhibited increased cell death, and the killing effect was more significant in the group with both WTAP knockdown and oxaliplatin treatment. They further showed that depletion of WTAP combined with oxaliplatin treatment also had greater anti-tumor effect on the xenograft animal model. The reduction of cell viability caused by WTAP inhibition combined with oxaliplatin treatment, was successfully reversed in HCT116 by using various inhibitors to block apoptosis, ferroptosis, neroptosis, or pyroptosis. Together, WTAP deficiency in combination with oxaliplatin leads to the activation of PANoptosis, a new type of cell death that cannot be explained by any of them alone. They later showed that WTAP inhibition induced PANoptosis under oxaliplatin treatment, possibly through regulating the stability of NRF2 mRNA in an m6A-dependent manner.

Conclusion: This study revealed that oxaliplatin treatment upregulated the expression of WTAP and increase the m^6A level, causing acquired chemoresistance. The depletion of WTAP also significantly enhanced the chemosensitivity of CRC cells by triggering m^6A-dependent PANoptosis through NRF2. These findings highlight the significance of WTAP-NRF2- PANoptosis axis as a prognostic indicator and a promising therapeutic target for chemoresistance in CRC treatment.