**TIAM1 promotes chemoresistance and tumor invasiveness**

**in colorectal cancer**

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 **Presenter:** Yi-Fan Chiu 　　 　　 **Date/Time:** 2020/03/19, 15:10 -16:00

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**Background**

Misregulation of the Wnt pathway is one of the causes of colorectal cancer (CRC), and it is also related to stemness and resistance. Although there are many drugs commonly used in clinical treatment of CRC, most patients finally develop acquired resistance to these chemotherapeutic. Recurrence and metastatic transmission of the disease remain the leading causes of death from the disease. T-lymphoma invasion, and metastasis-inducing protein-1 (TIAM1) is one of the Wnt-responsive genes and has recently been identified as an oncogene. It was reported that the suppression of TIAM1 retards cell growth, colony formation, invasion, and migration potential in CRC. Interestingly, TIAM1, cancer stem cells, and CRC have been studied in association with Wnt signaling pathway, respectively. Cancer stem cells are closely related to resistance. Therefore, it is necessary to understand the underlying mechanisms by which drug resistance develops in CRC, in order to develop effective therapeutic strategies for CRC patients.

**Objective/Hypothesis**

The authors aimed to elucidate the relationship between TIAM1 and chemoresistance in CRC.

**Results**

In the beginning, the authors found that TIAM1 as an oncogenic factor was overexpressed in CRC tissues derived from patients who did not respond to chemotherapy and was associated with poor prognosis. They demonstrated that knockdown of TIAM1 could enhance the sensitivity to chemotherapy drugs and reduce the invasion capacity of CRC cells*.* The invasion capacity of cancer cells was related to chemoresistance, and the preliminary results showed that TIAM1 could initiate cell resistance. Further, the expression of stemness-related genes and tumorsphere formation assay confirmed that resistance was regulated by stemness. Next, the effect of TIAM1 on mice was confirmed by xenograft. It was consistent with the results *in vitro*. When TIAM1 was inhibited, resistance to chemotherapeutics agents was weakened by suppressing stemness, and the chemosensitivity of mice tumors to the drug was increased. Finally, they demonstrated that colorectal cancer-associated fibroblasts (CAFs)-derived conditioned medium overexpressed TIAM1 expression and enhanced resistance to chemotherapeutic agents in the CRC cell and inhibition of TIAM1 expression in CAFs could weaken this process. It was also found that Wnt-related genes were also involved in regulation. It suggested that CAFs promoted chemoresistance by enhancing stemness and activating Wnt signaling pathway.

**Conclusion**

The results displayed that TIAM1 regulates CRC chemosensitivity through stemness and Wnt signaling pathway. Therefore, TIAM1 may be an important therapeutic target. Further understanding of mechanisms could lead to new therapeutic strategies for CRC treatment.

**Reference**

1. B Wang, *et al.*, miR-29b suppresses tumor growth and metastasis in colorectal cancer via downregulating Tiam1 expression and inhibiting epithelial–mesenchymal transition. *Cell Death & Disease* **5**, page1335 (2014).