Yes-Associated Protein (YAP) as a Target in Overcoming Glioblastoma Temozolomide Chemoresistance

WONG Cheuk Lun Ethan (MRes[Med] Student), KIANG MEI YEE KARRIE, LEUNG Ka Kit Gilberto Division of Neurosurgery, Department of Surgery, School of Clinical Medicine, HKU LKS Faculty of Medicine

1. INTRODUCTION

Glioblastoma (GBM) is the most lethal form of malignant brain cancer. Standard treatment for GBM is chemotherapy with temozolomide + radiotherapy, but chemoresistance is inevitable, which is the main reason of treatment failure. Overcoming chemoresistance would be the major breakthrough for the treatment of GBM.

2. YAP SIGNALING PATHWAY

Yes-associated protein (YAP) is a transcriptional co-activator and is implicated in promoting cancer growth.



Hippo signaling pathway is frequently suppressed in cancer cells, leading to overexpression of YAP and its nuclear translocation. Nuclear YAP (active state) regulates gene transcription that promotes cell growth and autophagy, which is favourable for GBM survival.

3. METHODOLOGY

TMZ-sensitive (S) and TMZ-resistant (R) U87 and U251 GBM cell lines were previously established. TMZ-R cells were maintained in low dose TMZ. Whether YAP contributes to TMZ chemoresistance is studied. YAP inhibitor verteporfin is also tested in *in vitro* models to investigate potential crosstalk with IGF1R.



resistant GBM cell lines as compared to TMZsensitive ones in Western Blot and qPCR.



YAP1 gene knockdown in U87 reduces cell viability and increases TMZ sensitivity.



YAP inhibitor verteporfin (VP) reduces cell viability in both U87 and U251 cell lines.



Verteporfin re-sensitizes GBM cells to high-dose temozolomide through YAP inhibition.

8. WHAT'S NEW

Our data suggest upregulation of YAP may contribute to TMZ chemoresistance.

- Targeting Hippo (YAP) signaling pathway might be able to re-sensitize GBM cells to temozolomide.
- This also provides evidence on repurposing verteporfin (FDA-approved drug) for treatment of glioblastoma, or combination therapy with TMZ.



