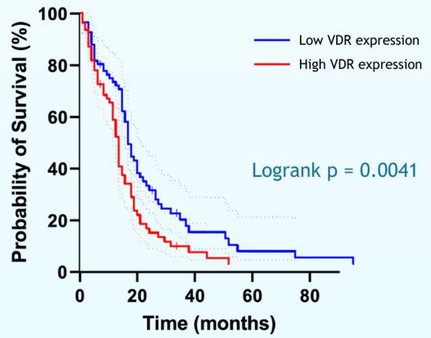
Unveiling a Novel Anti-tumor Mechanism: Vitamin D-driven Modulation of the Hippo Pathway in Glioblastoma

KH WONG, MY KIANG, GKK LEUNG
Department of Surgery, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong

Introduction

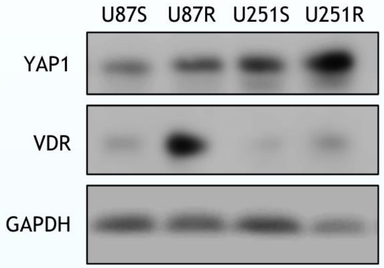
Glioblastoma (GBM) is the most malignant primary brain cancer. Vitamin D (VD) has been shown to exhibit anti-tumor effects on multiple cancers, including GBM. Hippo pathway has been involved in promoting the growth of numerous cancers including GBM, and is possibly involved in GBM resistance to temozolomide (TMZ). VD has been shown in previous literature to exhibit attenuating effects on Hippo pathway through activation of Vitamin D receptor (VDR) in metastatic neuroblastoma. Hence, this study aims to investigate whether VD can lessen TMZ chemoresistance in GBM through its interplay with VDR and the Hippo pathway.

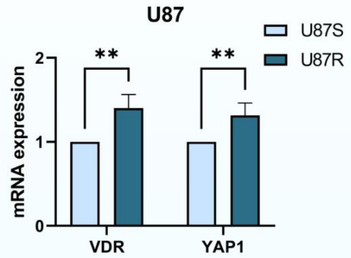
Methods / Results

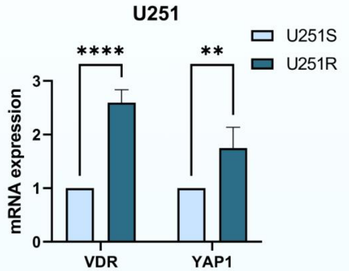


According to the TCGA databank, a higher expression of VDR in GBM is associated with poorer survival.

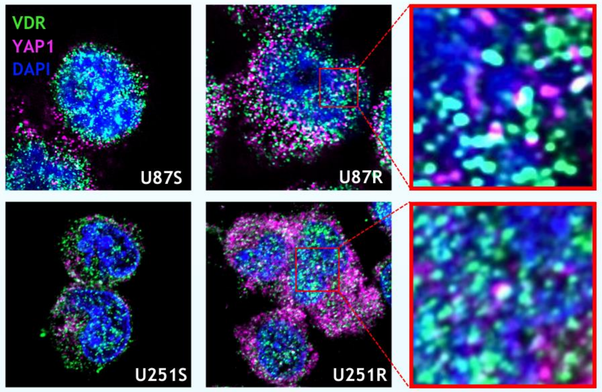
Methods / Results





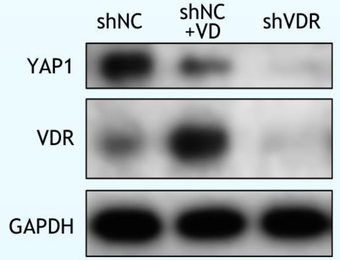


Western blot and quantitative PCR (qPCR) are conducted on chemosensitive (U87S and U251S) and chemoresistance (U87R and U251R) cell lines. Protein and mRNA expression analyses show that both VDR and YAP1 are over-expressed in chemoresistant cell lines.

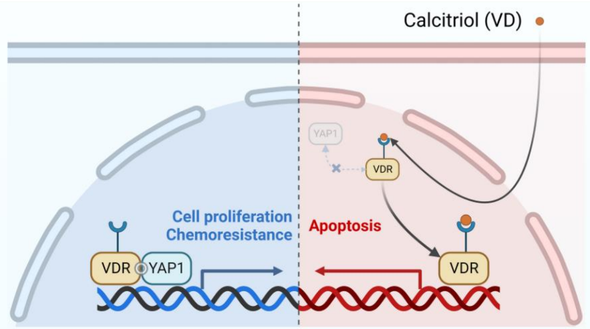


IF confocal imaging was used to examine the localization of VDR and YAP1 respectively. Representative images on the left show that VDR and YAP1 co-localize within the cell nucleus. Furthermore, the co-localization signals were more exaggerated in the chemoresistant cell lines in comparison with the chemosensitive cell lines

Short hairpin knockdown of VDR (shVDR) was acheived using lentiviral plasmids. Protein expression analysis shows that shVDR GBM cells express less YAP1, as compared to control (shNC). Besides, treating shNC cells with VD upregulates VDR while downregulating YAP1.



Discussion



We hypothesize a *novel intrinsic function of VDR*. Without activation by VD, VDR may serve as a coupling partner and stabilizer of transcriptional factors. As explained, the Hippo effector, YAP1, may be one of the transcriptional factor/activator that is stabilized via formation of transcriptional complexes with VDR, which then more readily upregulate genes that facilitate tumor growth and chemoresistance. In contrast, when extracellular VD increases, more VD binds to its nuclear VDR receptor, thus preventing the aforementioned interaction and reducing the VDR-YAP1 complex-medicated proliferation. Moreover, VD-activated VDR itself is a well-known transcriptional factor which upregulate genes that promote apoptosis and other cellular functions, thereby combating TMZ chemoresistance and tumor growth.

References

1. Ladumor, Y., Seong, B. K. A., Hallett, R., Valencia-Sama, I., Adderley, T., Wang, Y., Kee, L., Gont, A., Kaplan, D. R., & Irwin, M. S. (2022). Vitamin D Receptor Activation Attenuates Hippo Pathway Effectors and Cell Survival in Metastatic Neuroblastoma. Molecular cancer research : MCR, 20(6), 895-908.
2. Lo, C. S. C., Kiang, K. M. Y., & Leung, G. K. K. (2022). Anti-tumor effects of vitamin D in glioblastoma: mechanism and therapeutic implications. Laboratory Investigation, 102(2), 118-125.