IGF-1-enhanced miR-513a-5p signaling modulates glioma cell sensitivity to temozolomide by targeting NEDD4L-inhibited Wnt/β-Catenin pathway

Kuo-Hao Ho¹,², Peng-Hsu Chen¹,², Chwen-Ming Shih¹,², Ku-Chung Chen¹,²

¹Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taiwan, ²Department of Biochemistry and Molecular Cell Biology, School of Medicine, College of Medicine, Taipei Medical University, Taiwan

Background: The insulin-like growth factor (IGF)-1 signaling is relevant in mediating glioblastomas progression. Micro (mi)RNAs are small noncoding RNAs that participates in glioma development. However, relationships between IGF-1 signaling and miRNAs in glioblastoma process are still unclear. Our aim was to identify the roles of IGF-1-mediated miRNA regulatory network in glioblastomas.

Methods and results: We found that IGF-1 treatment did not influence glioma cell growth, but significantly insensitized temozolomide cytotoxicity via WNT-β-catenin signaling. Neural precursor cell expressed developmentally downregulated 4-Like (NEDD4L), an E3 ubiquitin protein ligase, was recognized as a repressor in inhibiting WNT signaling. Lower NEDD4L levels were found in glioma cells compared with normal astrocytes, array, and RNA seq data of TCGA glioma patients. IGF-1 treatment significantly reduced NEDD4L levels. Overexpression of NEDD4L reduced glioma cell viability and attenuated IGF-1-insensitized temozolomide cytotoxicity. By conducting microRNA array analyses, we found that IGF-1 treatment induced 93 upregulated and 148 downregulated microRNAs in glioma cells. The miR-513a-5p, upregulated by IGF-1-mediated PI3K signaling, showed elevated levels in glioma cells compared with normal astrocytes, array data in TCGA, GSE61710, GSE37366, and GSE41032. Furthermore, a negative correlation was identified between miR-513a-5p and NEDD4L with TCGA glioma patients. NEDD4L was also validated as a direct target gene of miR-513a-5p. Overexpression of miR-513a-5p significantly affects NEDD4L-mediated IGF-1 signaling and temozolomide cytotoxicity.

Conclusions: These findings demonstrate a distinct role for IGF-1 signaling in temozolomide sensitivity for glioma therapy via miR-513a-5p/NEDD4L networks.