CS-37. DUAL FUNCTIONS OF EFEMP1 IN MALIGNANT GLIOMA IN RESPECT TO REGULATION OF EGFR AND NOTCH SIGNALING PATHWAYS

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EFEMP1 exerts both tumor suppressive and oncogenic effects in glioma. EFEMP1’s binding to EGFR accounts for its suppression of the intracranial (i.c.) tumorigenicity of glioma cells expressing high levels of EGFR. This finding is consistent with an overall favorable prognosis value of EFEMP1 expression in gliomas, specifically high EGFR-expression ones. We also found that in gliomas without EGFR overexpression, heightened levels of EFEMP1 expression were associated with unfavorable patient outcomes in prognosis models. To delineate the cell context-dependent function of EFEMP1 in glioma, we compared the effect of EFEMP1 to EGFR and NOTCH signaling activities in different glioma cell lines/primary cultures and their derived subpopulation lines. The results showed a common effect of EFEMP1 on blocking EGFR signaling, but variations on NOTCH signaling. In U87 glioma cell line, EFEMP1 blocked EGFR while activated NOTCH, with overall suppression of i.c. tumorigenicity. In U251 glioma cell line, EFEMP1 blocked EGFR but no effect on NOTCH signaling, and overall suppression of i.c. tumorigenicity. In U251-derived subculture (U251-NS) which was enriched with stem-like tumor initiating cells where EGFR expression level was low, EFEMP1 up-regulated NOTCH1, HES1, and HEY1 gene expressions. The effect of EFEMP1 to U251-NS i.c. tumorigenicity was contradictory. It changes the effect of tumor promoting to tumor suppressing by increasing inoculum size. With increase of inoculum size in i.c. xenograft model or exposing cells to serum in in vitro culture, there was an increase of chromosome 7 copy score (total chromosome 7 number per cell in xenografts/cell culture) and increase of EGFR expression. EFEMP1 changed pro-invasion function to anti-growth, hence reduced the alteration on equilibrium of tumor heterogeneity in responding to changes of tumor microenvironment. In conclusion, the effect of EFEMP1 up or down-regulation in malignant glioma needs to be studied in respect to the status of EGFR and NOTCH signaling activities.