Abstract

CEACAM6 is a membrane-associated glycoprotein frequently overexpressed in cancer and has been widely associated with tumor progression, cancer signaling, and therapeutic resistance. However, its role in regulating the HER2 receptor stability and response towards HER2-targeted therapy remained unclear. This study aims to investigate the effect of CEACAM6 knockdown on HER2 and EGFR stability, as well as HER2-targeted therapy response in PC9 cells. The CEACAM6 knockdown PC9 cells were established using lentiviral-shRNA mediated silencing. EGFR and HER2 Receptor stability were evaluated using cycloheximide chase assay followed by western blot analysis. Lastly, cellular response towards HER2-targeted therapies, trastuzumab and trastuzumab-antibody-drug conjugates (ADCs) (Trastuzumab-MMAE and Enhertu) were assessed using proliferation assay and IC50 measurement. It was found that CEACAM6 knockdown accelerated the degradation of HER2 and EGFR compared to control cells, suggesting that CEACAM6 contributes to HER receptor stability. Despite statistical analysis was not able to be done, CEACAM6 depletion seems to reduce the early inhibitory effect of trastuzumab in some knockdown clones, while trastuzumab-ADCs largely retain their cytotoxic activity despite the presence of slight clone-dependent variability. Overall, the findings suggest that CEACAM6 may modulate HER2 receptor stability in PC9 cells, despite not being a suitable model for HER2 targeted-therapy response assessment.

Keywords: CEACAM6, HER2, EGFR, Receptor stability, PC9, Trastuzumab, Antibody-drug conjugates