Dysregulation of HER2/HER3 signaling axis in Epstein-Barr virus-infected breast carcinoma cells

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摘要

Abstract

The role of Epstein-Barr virus (EBV) in the pathogenesis of breast cancer has been of long-standing interest to the field. Breast epithelial cells can be infected by EBV through direct contact with EBV-bearing lymphoblastoid cells, and EBV infection has recently been shown to confer breast cancer cells an increased resistance to chemotherapeutic drugs. In this study, we established EBV-infected breast cancer MCF7 and BT474 cells and demonstrated that EBV infection promotes tumorigenic activity of breast cancer cells. Firstly, we showed that the EBV-infected MCF7-A and BT474-A cells exhibited increased anchorage-independent growth in soft agar. The increased colony formation capacity in soft agar was associated with increased expression and activation of HER2/HER3 signaling cascades, as evidenced by the findings that the treatment of HER2 antibody trastuzumab (Herceptin), phosphatidylinositol 3-kinase inhibitor, or MEK inhibitor completely abolished the tumorigenic capacity. In the EBV-infected breast cancer cells, the expression of EBV latency genes including EBNA1, EBER1, and BARF0 was detected. We next showed that BARF0 alone was sufficient to efficiently up-regulate HER2/HER3 expression and promoted tumorigenic activity in MCF7 and BT474 cells by the use of both overexpression and small interfering RNA knock-down. Collectively, we demonstrated that EBV-encoded BARF0 promotes the tumorigenic activity of breast cancer cells through activation of HER2/HER3 signaling cascades.