Abstract citation ID: bvac150.1804

Tumor Biology

ODP551

Halting ErbB-2 Isoforms Retrograde Transport to the Nucleus as a New Theragnostic Approach for Triple Negative Breast Cancer

Patricia Virginia Elizalde, PhD, Franco Izzo, PhD, Maria Florencia Chervo, PhD, Sharon Salma Merin, Ms, Agustina Dupont, MD, Violeta Chiauzzi, MSc, Sofia Bruni, MSc, Ezequiel Petrillo, PhD, Diego Montero, MD, Maria Florencia Mercogliano, PhD, Cecilia Jazmin Proietti, PhD, Roxana Schillaci, PhD, Santiago Madera, MSc, and Rosalia Ines Cordo Russo, PhD

Triple negative breast cancer (TNBC) is clinically defined by the absence of estrogen and progesterone receptors and the lack of membrane overexpression or gene amplification of the receptor tyrosine kinase ErbB-2/HER2. Due to its heterogeneity, clinical biomarkers and targeted therapies for this disease remain elusive, and chemotherapy has been the standard of care for TNBC. ErbB-2 is classically located at the membrane of BC cells, where it triggers signaling cascades and promotes oncogenesis. We previously demonstrated that ErbB-2 is also localized in the nucleus (NErbB-2) of TNBC cells, from where it drives growth (1). We also discovered that TNBC expresses both wild-type ErbB-2 (WTErbB-2) and alternative ErbB-2 isoform c (ErbB-2c) (1). ErbB-2 migrates to the nucleus via retrograde transport. Here, we revealed that Retro-2, an inhibitor of retrograde transport that protects cells form the deleterious effects of toxins and viruses, evicts both WTErbB-2 and ErbB-2c from the nucleus of BC cells. Using BC models from several molecular subtypes, as well as normal breast cells, we demonstrated that Retro-2 specifically halts the proliferation of cells expressing NErbB-2. Moreover, Retro-2 decreased the expression of genes induced by NErbB-2 (i. e. cyclin D1 and Erk5) and promoted cell cycle arrest at G0/G1 phase and apoptosis. In addition to R2 growth inhibitory activity in vitro, we here also demonstrated that its optimized cyclic derivative Retro-2.1 (in particular the (S)-enantiomer) showed improved efficacy both to evict ErbB-2 isoforms from the nucleus and to inhibit proliferation in vitro. Importantly, Retro-2 eviction of both ErbB-2 isoforms from the nucleus resulted in a striking growth abrogation in multiple TNBC preclinical models, including xenografts and tumor explants). Our mechanistic studies demonstrated that Retro-2 induces a differential accumulation of WTErbB-2 at the early endosomes and plasma membrane, and of ErbB-2c at the Golgi, shedding light both on Retro-2 action on endogenous protein cargoes undergoing retrograde transport and on the biology of ErbB-2 splicing variants. Compelling evidence demonstrated that mRNAs 5' and 3' untranslated regions (UTRs) mediate post-transcriptional regulation of gene expression and determine protein levels and fate. While both T1 and T3 have different 5' but the same 3' UTRs sequences, our in silico studies showed that T1 and T3 RNA secondary structures vary in the region containing both their 5' and 3' UTRs. These findings suggest that T3 secondary structure impacts in its cell specific localization. Together, our present discoveries identify R2 as a precision oncology tool to target NErbB-2 retrograde transport. This novel theragnostic approach could greatly improve the outcome of TNBC patients. (1) Chervo MF et al, Oncogene 2020: 39: 6245-62.

Presentation: No date and time listed