**Myoferlin is a Key Regulator of HER Receptor Family Function in Breast Cancer**

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Myoferlin is a member of the ferlin family of proteins that participate in plasma membrane fusion, repair and endocytosis events. Although few reports associate myoferlin with cancer, its actual role in tumor biology remains to date unveiled. Owing to a proteomic approach, we discovered myoferlin as an overexpressed cell membrane associated protein in human breast adenocarcinoma. We validated this observation in 150 breast cancer cases. We further investigated the biological role of myoferlin in breast cancer and found that it is a key functional regulator of HER receptor family. Myoferlin depletion blocked EGF-induced breast cancer cell migration and epithelial-to-mesenchymal transition. Mechanistically, lack of myoferlin led to impaired degradation of phosphorylated EGFR via dysfunctional caveolae. Inability to degrade pEGFR caused sustained activation and malfunction of downstream targets like AKT. NRG1 stimulation of myoferlin silenced, HER2 positive, breast cancer cells demonstrated similar dysfunctions of HER2 and HER3 activation. *U*sing two different animal models of breast cancer, we show that myoferlin depletion significantly suppressed the tumor development. Although the effects observed with different HER family members appear to involve distinct mechanisms, the data strongly evidence a paramount role of myoferlin in HER receptor function in cancer.

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