Abstract:
The majority of breast cancers express estrogen receptor alpha (ER) and are estrogen-dependent. In ER-positive breast cancer, ER antagonists decrease cell proliferation and tumor growth. Tamoxifen (Tam), an ER antagonist in breast cancer cells, is the most widely used adjuvant therapy for patients diagnosed with ER-positive breast cancer. While Tam treatment is effective for most patients, innate Tam resistance is observed in some patients and the development of Tam resistance after long-term treatment remains a clinically relevant outcome. The molecular mechanisms that underlie Tam resistance are not well understood. While Tam action is often attributed entirely to ER antagonism, Tam sensitivity has been observed in breast cancer cells that lack ER suggesting alternative mechanisms of Tam action. We have shown that GPER1 mediates Tam action in breast cancer cells via induction of IGFBP-1 expression and subsequent inhibition of IGF-1R-dependent cell signaling. Additionally, our data indicate that this GPER1-mediated mechanism of Tam action inhibits IGF-1-stimulated ER phosphorylation and the accumulation of IGFBP-1 is sufficient for the development of Tam resistance in breast cancer cells. GPER1-mediated mechanisms of Tam action in breast cancer cells modulate IGF-1R activity and inhibit phosphorylation-dependent ER signaling. Data supporting the central role that for GPER and regulation of IGF-1R-dependent cell signaling in Tam-treated breast cancer cells will be presented.