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Ganoderma lucidum extract and erlotinib synergistically reduce inflammatory breast cancer progression

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Small molecule tyrosine kinase inhibitors (TKIs) are among the current therapeutic strategies used to inhibit the epidermal growth factor receptor (EGFR). The high incidence of resistance to these therapies has greatly diminished their overall effectiveness, thus our objective is to investigate the efficacy of treatments that may be combined with TKI's to provide a sustained response for breast cancer (BC) patients. Here, we investigate the therapeutic potential of Ganoderma lucidum extract (GLE) in BC, focusing on the regulation of the EGFR signaling cascade when treated with the EGFR-TKI, erlotinib. SUM-149 inflammatory breast cancer (IBC) cells, intrinsic erlotinib resistant MDA-MB-231 non-IBC BC cells, and a successfully developed erlotinib resistant IBC cell line, rSUM-149, were treated with increasing concentrations of erlotinib, GLE, or their combination (erlotinib/GLE) for 72 h. Treatment effects were tested on cell viability, migration and invasion. To determine tumor progression, SUM-149 severe combined immunodeficient xenografts were treated with erlotinib/GLE or erlotinib for 13 weeks. We assessed the expression of extracellular signal-regulated kinase (ERK)-1/2 and serine/threonine-specific protein kinase (AKT) in vitro and in vivo. Our results show that GLE synergizes with erlotinib to sensitize SUM-149 cells to drug treatment, and overcomes intrinsic and acquired erlotinib resistance. Also, the combination of both drugs decreases SUM-149 cell viability, proliferation, migration and invasion. We show that GLE increases erlotinib sensitivity by inactivating AKT and ERK signaling pathways. We conclude that a combinatorial therapeutic approach might be an effective alternative to increase prognosis in breast cancer patients with EGFR overexpressing tumors.

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