Estrogen-related receptor alpha (ERRα): from an orphan receptor to a crucial pivot in cancer progression

by Marco Fiorillo

Breast cancer (BC), a leading cause of cancer-related death in women, often exhibits resistance to conventional treatments. Here, we investigated the roles of cholesterol and mevalonate in breast cancer progression and therapy resistance. Our recent findings have revealed that these compounds activate the estrogen-related receptor alpha (ERRα) pathway, leading to increased expression of key proteins associated with tumor aggressiveness and drug resistance. Furthermore, cholesterol-induced activation of ERRα promotes epithelial-mesenchymal transition (EMT) and inflammatory responses in breast cancer cells, shaping the tumor microenvironment. Additionally, high cholesterol levels enhance macrophage infiltration, angiogenesis, and cancer-associated fibroblasts (CAFs) phenotype. Clinically, these findings have important implications for understanding treatment failure and cancer dissemination. We have defined estrogen-related receptor alpha gene (ESRRA) signature in multiple types of breast cancer, using bioinformatic analysis of patient samples. Importantly, ESRRA expression correlates with poor prognosis, suggesting it as a potential therapeutic target. In addition, ERRα protein expression has been validated through immunohistochemistry in female patients diagnosed with invasive BC, including Luminal ER(+) BC, TNBC and metastatic lesions, as well as in the tissue surrounding the tumor. Overall, targeting the cholesterol-ERRα axis may offer novel strategies for combating breast cancer progression and resistance to therapy.