Estrogen-related receptor alpha: an orphan finds a family

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Abstract
Identification of molecules and their effectors has led to new therapies designed to specifically inhibit pathways in molecularly defined breast cancer subtypes. An orphan nuclear receptor, estrogen-related receptor alpha, has been shown to be a downstream target of two tyrosine kinase growth factor receptors: human epidermal growth factor receptor 2 and the type I insulin-like growth factor receptor. Identifying the mechanistic actions of orphan nuclear receptors could lead to new biomarkers and molecular targets in malignancy.

Background
Nuclear receptors (NRs) are well accepted as critical mediators in many aspects of breast cancer pathogenesis. Molecular cloning of estrogen receptor alpha (ERα) has demonstrated how molecular targeting of specific domains of a single protein can improve outcomes. Molecular cloning techniques have revealed receptors related to ERα, including the ‘estrogen-related receptor’ (ERR) family.

Recent prognostic studies have demonstrated that overexpression of one of these family members, ERRα, is associated with a poor outcome in patients with ER− breast cancer [1], yet the transcriptional regulation of the orphan receptor ERRα is still not well known. Overexpression of ERRα has been shown to be associated with elevated human epidermal growth factor 2 (HER2) expression [2], and ERRα can interact with the co-regulators PGC-1α and β (peroxisome proliferator-activated gamma co-activator-1 alpha and beta) [3,4] in addition to a number of p160 co-activators [5,6]. Interestingly, ERRα displays distinct subtype transcriptional activation that is not similarly identified by ER [7]. Unlike ERα, which has been targeted by ligand deprivation (oophorectomy and aromatase inhibitors) and selective estrogen receptor modulators (tamoxifen and fulvestrant), ERRα has no known ligand and therefore is not amenable to drug inhibition in the same fashion.

If ERRα regulates breast cancer cells, then we need to understand its mechanism of action. Since there are no known ways to target ERRα+ ER− breast cancers, molecular techniques could be used (a) to gain an understanding of how ERRα modulates gene expression in breast cancer subtypes [8-11] and (b) to develop potential therapeutic approaches to target ERRα-driven tumors [12].

The article
Chang and colleagues [12] created normal human mammary epithelial cell lines overexpressing ERRα to better understand its transcriptional targets. Since no ligand exists for ERRα, overexpression of the well-characterized co-regulator of ERRα, PGC-1α, was used to activate transcription [3]. Unsupervised gene clustering analysis and binary regression modeling defined transcriptional programs associated with ‘low or high ERRα activity’. When applied to seven clinical breast cancer microarray gene sets, high ERRα activity was shown to be associated with poorer prognosis. Experiments using an ERRα antagonist in normal human mammary epithelial cells that ranged in low, medium, and high ERRα expression showed a positive correlation between an intrinsic ERRα gene expression signature and breast cancer growth.

The authors further identified a relationship between increased ERRα activity via the upregulation of the ERRα co-activator PGC-1β. Inhibitors of the type I insulin-like growth factor receptor (IGF-1R) and HER2 receptors or PI3K/AKT pathway blocked this upregulation whereas mitogen-activated protein kinase inhibitors did not. Lastly, it was identified that heregulin and IGF-1 treatment led to increased C-MYC protein expression or recruitment to intron 1 of the PGC-1β gene (or both) to stimulate expression. The authors of another recent paper [13] have identified a similar dual relationship between androgen-dependent, androgen receptor (AR) signaling, and tumor growth in the molecular apocrine...
subtype of breast cancer (that is, ER-/AR+) by the upstream actions of WNT and HER2/HER3 signaling pathways [14]. Collectively, these findings identify a new role for the ‘orphan’ ERRα as a transcriptional regulator of PI3K and growth factor signaling via C-MYC activation of the PGC-1β promoter and invite new cellular strategies to be tested in specific molecular subtypes of breast cancer.

The viewpoint
Breast cancer treatment would be simpler if a single protein regulated a single pathway in all cancer cells, yet this is never the case. Moreover, the orchestrated interplay of tyrosine kinase growth factor signaling pathways reveals complex interconnected pathways relevant to tumor biology. Furthermore, it is now evident that, in order to accurately assess and target NR activity in breast cancer, both the upstream and downstream modulators associated with aspects of NR gene regulation need to be appreciated. This group has previously shown a role for ERRα in cancer cell motility [15], and it would be important to know whether the gene signatures for ERRα in cancer cell motility are the same.

Chang and colleagues [12] have furthered the idea that ‘orphans’ are regulated in a coordinated manner to affect breast cancer biology. Upstream activation of cell signaling is necessary to fully reveal the biology mediated by ERRα. Given this complex system, it is evident that measurement of ERRα alone will reveal very little about its activation state; deeper investigation into signaling molecules, adaptor proteins, and gene signatures will be required to fully assess its biological significance. Understanding these molecular interactions is necessary to answer important clinical questions. How do we use our current understanding of the interplay of growth factor and NR signaling to design the most effective clinical treatments for breast cancer? Is it better to target the downstream targets or the upstream drivers of cancer-promoting growth factor intracellular signaling pathways or both? How do we find the key nodes regulated by these molecular signaling systems to exploit as therapies?

There are clearly multiple upstream drivers of a single downstream mediator and vice versa. Thus, future clinical trials must be carefully designed to identify the key convergence sites and to employ appropriate therapies designed to adequately impinge on their downstream effectors. Chang and colleagues have shown that just because you’re an orphan doesn’t mean that you’re not important! By revealing functions for ERRα, these authors have suggested how future therapeutic treatment strategies need to reflect and complement the continually evolving molecular complexity of breast cancer.

Abbreviations
AR, androgen receptor; ER, estrogen receptor; ERR, estrogen-related receptor; IGF-1, type I insulin-like growth factor; NR, nuclear receptor; PGC, peroxisome proliferator-activated gamma co-activator-1.

Competing interests
The authors declare that they have no competing interests.

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