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Tracking progesterone receptor-mediated actions in breast cancer ☆

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ABSTRACT

Ovarian steroid hormones contribute to breast cancer initiation and progression primarily through the actions of their nuclear transcription factors, the estrogen receptor alpha (ERα) and progesterone receptors (PRs). These receptors are important drivers of the luminal A and B subtypes of breast cancer, where estrogen-blocking drugs have been effective endocrine therapies for patients with these tumors. However, many patients do not respond, or become resistant to treatment. When endocrine therapies fail, the luminal subtypes of breast cancer are more difficult to treat because these subtypes are among the most heterogeneous in terms of mutation diversity and gene expression profiles. Recent evidence suggests that progestin and PR actions may be important drivers of luminal breast cancers. Clinical trial data has demonstrated that hormone replacement therapy with progestins drives invasive breast cancer and results in greater mortality. PR transcriptional activity is dependent upon cross-talk with growth factor signaling pathways that alter PR phosphorylation, acetylation, or SUMOylation as mechanisms for regulating PR target gene selection required for increased cell proliferation and survival. Site-specific PR phosphorylation is the primary driver of gene-selective PR transcriptional activity. However, PR phosphorylation and heightened transcriptional activity is coupled to rapid PR protein degradation; the range of active PR detected in tumors is likely to be dynamic. Thus, PR target gene signatures may provide a more accurate means of tracking PR's contribution to tumor progression rather than standard clinical protein-based (IHC) assays. Further development of antiprogestin therapies should be considered alongside antiestrogens and aromatase inhibitors.

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Abbreviations: AF, activation function; AP-1, activator protein 1; CD, common docking; CDK2, cyclin dependent kinase 2; CK2, casein kinase II; DUSP6/MKP3, dual specificity phosphatase 6/MAPK phosphatase 3; EGF, epidermal growth factor; ER, estrogen receptor alpha; GR, glucocorticoid receptor; HER2, human epidermal growth factor receptor 2; HRT, hormone replacement therapy; IHC, immunohistochemistry; JAK, janus kinase; MAPK, mitogen activated protein kinase; PR, progesterone receptor; PRM, progesterone receptor modulator; RT-qPCR, reverse transcription quantitative polymerase chain reaction; SERM, selective estrogen receptor modulator; Sp1, specificity protein 1; SR, steroid hormone receptor; STAT, signal transducers and activators of transcription; SUMO, small ubiquitin-like modifier; WHI, World Health Initiative; WT, wild type.

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1. Introduction

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related death in women. In 2013, it is estimated that 232,000 women will be diagnosed with breast cancer and 39,000 women will die from the disease (Siegel et al., 2013). Clinically, protein expression levels for estrogen receptor alpha (ERα), progesterone receptor (PR), and HER2 are the primary biomarkers used to inform breast cancer treatment strategies. Breast cancers are characterized into three main groups: ER-positive, HER2-amplified, and triple negative tumors, which are negative for ER, PR, and HER2. Up to 70% percent of breast tumors express ER or PR upon biopsy, and these tumors are associated with greater overall survival and decreased metastasis (Bardou et al., 2003; McGuire, 1978). Tumors that express high levels of HER2, primarily through genomic amplification of the *ERBB2* locus, are associated with worse outcomes (Slamon et al., 1987).

In addition to testing for ER, PR, and HER2 protein expression levels, many other molecular tests have begun to be used clinically to assess breast tumor aggressiveness, risk of relapse, and optimal treatment strategies. A recent collaborative study characterized untreated primary breast tumors by integrating data from multiple high-throughput genomic technologies including DNA copy number arrays, exome sequencing, mRNA expression, microRNA sequencing, and reverse-phase protein arrays. This comprehensive analysis identified four major subtypes of breast cancer with unique molecular drivers: luminal A, luminal B, HER2-enriched, and basal-like (Table 1) (Cancer Genome Atlas Network, 2012). Luminal A tumors typically expressed high levels of ER and PR, whereas luminal B tumors usually expressed high levels of ER but reduced levels of PR. Nearly 75% of all breast tumors were identified as luminal A or luminal B, and these tumors were the most heterogeneous and had the least prominent molecular drivers. HER2-enriched tumors were generally driven by amplification of the *ERBB2* locus, and basal-like tumors rarely expressed ER, PR, or HER2 and were driven by PI3K pathway mutation. These data indicate that distinct treatment strategies must be developed that target the molecular drivers specific to each breast cancer subtype; however, additional research is needed to characterize the molecular heterogeneity identified among the four breast cancer subtypes, especially the most abundant luminal subtypes.

Antiestrogen therapy targeting ER is the primary treatment strategy for the luminal subtypes of breast cancer. Although this treatment strategy has been very successful, approximately 40% of patients eventually relapse. To improve treatment outcomes, it must be appreciated that breast cancer is a hormonally driven disease that should be analyzed in the context of steroid hormone receptor transcriptional activity in addition to common mutations (Brisken, 2013). Thus, a deeper investigation into the molecular signaling within the luminal subtypes will greatly enhance our understanding of disease biology and improve treatment strategies for patients bearing these tumors. In this review, we discuss how progestins are critical for mammary gland development and increase breast cancer risk in post-menopausal women. Recent advances surrounding PR and its post-translational modifications that mediate breast cancer cell proliferation and survival are presented. The last decade of molecular research has provided a powerful rationale for targeting PR in a subset of breast cancer patients. The potential for clinical antiprogestin therapies is discussed. We propose that PR transcriptional signatures will provide more reliable tumor biomarkers that accurately track activated PR relative to total PR levels as measured by protein-based assays.

Table 1
Molecular subtypes of breast cancer.
Data derived from a comprehensive breast cancer study (Cancer Genome Atlas Network, 2012).

Molecular subtype	Clinically reported status (% within subtype)	Common mutations (% within subtype)	Common copy number amplifications	Common copy number deletions	Average mutations per Mb
Luminal A	ER+ (96), ER− (3) PR+ (90), PR− (8) HER2+ (6), HER2− (90)	*PIK3CA* (45), *TP53* (12), *GATA3* (14), *MAP3K1* (13)			0.84
Luminal B	ER+ (99), ER− (1) PR+ (77), PR− (23) HER2+ (16), HER2− (80)	*PIK3CA* (29), *TP53* (29), *GATA3* (15), *MLL3* (6)		*TP53*, *MAP2K4*, *CDKN2A*	1.38
HER2-enriched	ER+ (53), ER− (43) PR+ (36), PR− (64) HER2+ (67), HER2− (28)	*PIK3CA* (39), *TP53* (72)	*ERBB2*	*TP53*, *MAP2K4*	2.05
Basal-like	ER+ (14), ER− (84) PR+ (9), PR− (88) HER2+ (2), HER2− (95)	*TP53* (80), *PIK3CA* (9)	*PIK3CA*	*PTEN*	1.68
All Tumors	ER+ (76), ER− (22) PR+ (65), PR− (33) HER2+ (15), HER2− (82)	*TP53* (37), *PIK3CA* (36), *GATA3* (11), *MAP3K1* (8)			

2. Steroid hormones influence breast cancer risk

Steroid hormones are associated with many empirically identified breast cancer risk factors. Heritable mutations in the *BRCA1* or *BRCA2* DNA repair genes disproportionally increase a woman's risk of breast (45–65%) and ovarian (11–39%) cancer compared to other cancers (Antoniou et al., 2003). The organ-specific cancer penetrance for these mutations has been difficult to understand, but a recent finding that women with *BRCA1/2* mutations had significantly higher levels of estradiol, increased PR expression, and higher circulating progesterone levels during the luteal phase of the menstrual cycle may suggest a possible link to increased cancer risk (Widschwendter et al., 2013). In a related translational study, nulliparous *BRCA1/p53* deficient mice displayed increased epithelial cell proliferation and differentiation, which normally is only induced during pregnancy, that could be blocked by a PR antagonist (Poole et al., 2006). These data suggest that rapid cell proliferation in the breast may be synergized through *BRCA1/2* deficiency and increased estrogen and progesterone exposure may party explain the organ-specific cancer risk of these mutations.

Lifetime exposure to elevated levels of steroid hormones, including estrogens and progestins, increases the relative risk of breast cancer incidence in pre- and post-menopausal women (Clemons & Goss, 2001; Key et al., 2002). Multiple epidemiological studies link hormonal contraceptive use in pre-menopausal women with increased breast cancer risk. Progestin-only depot-medroxyprogesterone acetate (DMPA) usage for greater than 12 months was shown to increase breast cancer risk by 2.2 fold (Li et al., 2012). A pooled analysis found that young women currently using combined oral contraceptives have a 24% increased breast cancer risk than nonusers, but the risk decreases over 10 years of non-use (Collaborative Group on Hormonal Factors in Breast, 1996). A recent study confirmed the elevated risk for any current oral contraceptive use but revealed that triphasic preparations containing a progestin, levonorgestrel, account for most of the elevated breast cancer risk in pre-menopausal women (3.05 relative risk compared to nonusers) (Hunter et al., 2010). In a different cohort of pre-menopausal women,