Distribution of hormone receptors (Estrogen Receptor, Progesterone Receptor and Androgen Receptor) in epithelial malignancies

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Abstract #3152

The importance of steroid hormone receptors to the biology of breast cancer was recognized over 40 years ago. New insights into hormone receptor biology and the increasing array of proteins that can modify their function have already translated into better therapies for breast cancer. The responsiveness of a tumor to hormone therapy is an important parameter in cancer management. Besides breast cancer, other cancers also express steroid hormone receptors. Hence, the purpose of this study was to capture the relative distribution of hormone receptors in all types of cancer including breast cancer.

In a total cohort of 9,491 patient samples, hormone receptors ER, PR and AR were assayed by immunohistochemistry on a Ventana platform using antibodies (ER (SP 1), PR (I E 2) and AR(AR 27). The slides were read manually by pathologists using the cutoff of (>=1+ and >=10% as positive) for AR, PR and ER. Based on these cutoffs, samples were deemed positive or negative.

Our preliminary observations indicate that the frequency of AR was highest in prostate (82%), followed by breast (45%), and ovary (25%). Low expression of AR was most often found in appendix (98.5%), colon-cecum (97%), colon-large intestine (95%), pancreas (95%), and gallbladder (95%). The frequency of ER was highest in fallopian tube (81%) followed by peritoneum (64%), uterus (56%), breast (52%) with marginal frequencies in lung (6.8%), small intestine(6.5%) and stomach (6%). The cancer types with negative ER expression were brain (99%), appendix (98.5%%), colon-large intestine (96%), and bones, joint & articular cartilage of other sites (96%). The frequency of PR was highest in adrenal gland (61%), uterus (51%), ovary (40%), bones, joints & articular cartilage of other sites (34%), and breast (33%). The cancer types in which PR was negatively expressed were appendix (96%), colon-cecum (92%), gallbladder (89%), bladder (88%), and small intestine (79%).

To our knowledge this is the first study involving a large patient pool in which hormone receptors have been investigated in a single clinical laboratory with standardized IHC. Cancer is a heterogeneous disease with different molecular drivers regulating its growth, survival and response to therapy. This study shows that hormone receptors are frequently expressed in cancer types outside of breast, which merits the inclusion of therapeutic strategies using hormone therapy in such tumors.

Introduction

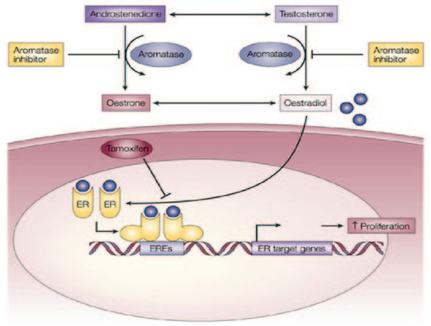
Steroid hormones are lipophilic molecules derived from cholesterol and synthesized in the adrenal cortex, the testis, the ovary and placenta. Steroid hormones reach their target cells via the blood, where they are bound to carrier proteins. Within the target cells steroid hormones bind to steroid hormone receptors which are the key mediators of steroid hormone action like cell proliferation, cell death, secretory activity and cellular mobility. This ability of steroid hormones is retained in many diseases including cancers originating in steroid hormone sensitive tissues including breast, genital tract, gastrointestinal tract, pancreas, lung and intracranial tumors.

The human estrogen receptor (ER) is a steroid hormone receptor which exists in the nucleus of the cells and is activated following the binding of a ligand (estrogen) and subsequently forms dimers within the nucleus at specific estrogen response elements in DNA upstream of estrogen regulated genes. Many of the genes regulated by estrogen are important for cell proliferation, survival, metastasis and angiogenesis. Tamoxifen, a selective estrogen receptor modulator (SERM) functions as a estrogen antagonist. Therapies designed to reduce the level of estrogen in patients such as ovarian ablation or aromatase inhibitors function by depriving the receptor of its ligand. Progesterone receptor (PR) is also a member of the steroid hormone family of receptors which is activated by progesterone and other steroid hormones.

Androgen exerts its biological effects through the Androgen Receptor(AR), a member of the nuclear receptor superfamily that acts as a ligand dependent transcription factor. Upon ligand binding, AR rapidly translocates to the nucleus where it binds to the androgen responsiveness element. The normal development and maintenance of the prostate is dependent on androgen acting through the androgen receptor. AR expression is maintained through prostate cancer progression and persists in majority of patients with hormone refractory disease.

The presence of steroid hormone receptors have been harnessed therapeutically, with drugs which modify the cellular levels or actions of steroid hormones being commonly used in the treatment of breast, endometrial and prostate cancer. The measurement of steroid hormone receptors is currently used diagnostically in several centers to identify potential endocrine responsiveness.

Classical model of estrogenic signaling and its deprivation by endocrine therapy



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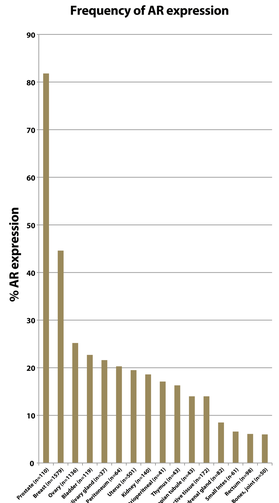
Estrogen binds to the estrogen receptor (ER), leading to dimerization, conformational change and binding to estrogen response elements (EREs) upstream of estrogen responsive genes including those responsible for proliferation. Tamoxifen competes with estrogen for ER binding whereas aromatase inhibitors reduce the synthesis of estrogens from their androgenic precursors. Johnston SRD et al. Aromatase inhibitors for breast cancer: lessons from the laboratory. Nature Rev Cancer. 2003; 3: 821-831.

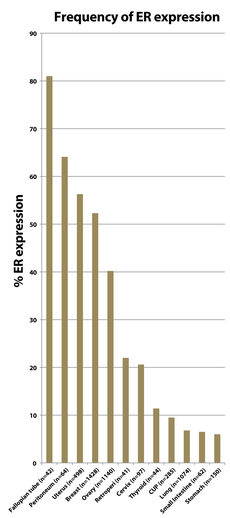
Results

Distribution of AR



Tumor type	Negative AR expression
Appendix(n=68)	98.50%
Colon-cecum(n=38)	97.40%
Colon-large intes(n=852)	95.40%
Pancreas(n=687)	95.20%
Gallbladder(n=61)	95.10%
Anus and anal cancer(n=38)	94.70%
Lymph node(n=56)	94.60%
Esophagus(n=135)	94.10%
Skin(n=272)	91.90%
Rectum(n=98)	91.80%
Bones, joint(n=50)	90%
Cervix(n=97)	89.70%
Intrahepatic bile duct(n=29)	89.70%
Lung(n=1073)	89.80%
Stomach(n=150)	89.30%
Small Intestine(n=61)	88.50%
Thyroid(n=44)	86.40%
Unknown prim site(n=285)	86.30%
Brain(n=97)	85.60%
Adrenal gland(n=82)	84.10%
Connective(n=172)	82%

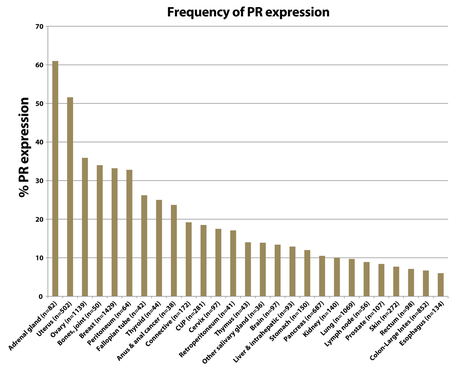
Distribution of ER



Tumor type	Negative ER expression
Brain(n=100)	99%
Appendix(n=68)	98.50%
Colon-large intes(n=852)	96%
Bones, joints(n=50)	96%
Rectum(n=98)	95.90%
Kidney(n=140)	95.70%
Adrenal gland(n=82)	95.10%
Esophagus(n=134)	95.50%
Gallbladder(n=62)	95.20%
Colon-cecum(n=38)	94.70%
Pancreas(n=685)	93.70%
Skin(n=272)	93.80%
Intrahepatic bile duct(n=29)	93.10%
Prostate(n=107)	90.70%
Connective(n=172)	90.10%
Bladder(n=120)	89.20%
Thymus(n=43)	88.40%
Lymph node(n=56)	87.50%
Anus & anal canal(n=38)	81.60%
Liver & intrahepatic(n=95)	78.90%

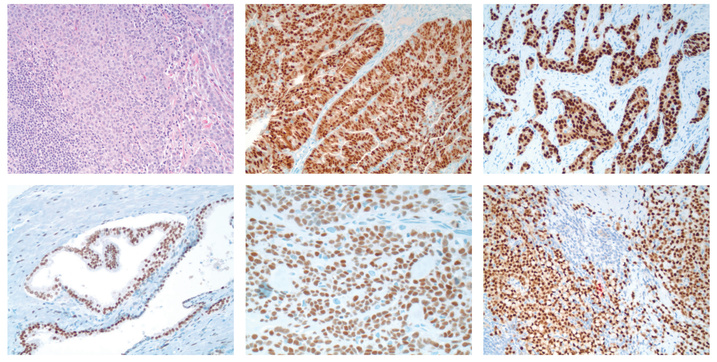
Results

Distribution of PR



Tumor type	Negative PR expression
Appendix(n=68)	95.60%
Colon-cecum(n=38)	92.10%
Gallbladder(n=62)	88.70%
Bladder(n=119)	88.20%
Small Intestine(n=62)	79%

Hormone receptor expression in epithelial cancers



Representative images of immunohistochemical staining of hormone receptor expression in breast, endometrioid, and head and neck cancers.

The top three panels show representative images of H & E in breast, ER expression in endometrioid cancer followed by PR expression in breast cancer. The bottom three panels show AR expression in normal prostate, followed by AR expression in head and neck carcinoma and breast cancer. Magnification 200x & 400x.

Conclusions

- The examination of steroid hormone receptors is pivotal to the understanding of endocrine sensitivity and therefore our study summarizes the frequency distribution of these biomarkers in a large cohort of different cancer lineages.
- Expression of AR was highest in prostate, breast, ovary, bladder and other major salivary gland tumors. The expression of AR was lowest in appendix, colorectal, pancreas, and gallbladder cancers.
- Expression of ER was highest in gynecologic cancers and breast cancer and was lowest in brain, appendix, colorectal, bones, joint and kidney cancers.
- Expression of PR was highest in cancers of the adrenal gland, uterus, ovary, bones & joint and breast. Expression of PR was lowest in appendix, colon, gallbladder, bladder and small intestinal cancers.
- Our study provides frequency distribution of hormone receptors in both expected and unexpected lineages which might be useful in evaluating new therapies, determining prognosis and assessing outcome of patients on endocrine therapy. Further, our data may be of value in exploring molecular target driven therapy in cancer particularly to research involving endocrine therapy and androgen deprivation therapy in non breast and non prostatic lineages.