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RESEARCH TOPIC:

G-Protein coupled Estrogen Receptor as a harbinger of breast cancer prognosis and metastasis: A dual investigation into its use as prognostic marker and driver of cellular migration.

RESEARCH PROPOSAL ABSTRACT

Estrogen binds to the classical estrogen receptors ERα and ERβ leading to their translocation to the nucleus. They bind to DNA elements regulating the expression of target genes involved in cell growth and survival. Estrogens can also induce rapid non-genomic responses that do not depend on gene regulation. Non-genomic estrogen effects include increased migration and invasion of cancer cells and effects on cell growth and cell cycle progression. These non-genomic effects are thought to be mediated not only by the classical ER but mainly by newly discovered truncated forms of ERα such as ERα46 and ERα36 and more interestingly by the G-coupled protein receptor protein, GPER.

GPER is activated by 17β-estradiol but it can also recognise xenoestrogens including bisphenol A and selective estrogen receptor modulators (SERM) including tamoxifen. Of concern is that SERMs like tamoxifen that inhibit ERα and ERβ function can activate GPER. GPER activation has been linked to neoplastic transformation of estrogen-dependent cancers. It is also becoming clear that long-term use of tamoxifen in breast cancer patients and in healthy women undergoing chemo-preventative tamoxifen trials leads to increased risks of endometrial cancer. Interestingly, a Swedish study showed that the lack of plasmamembrane localised GPER expression was a good predictor of positive tamoxifen response and increased long-term disease free survival in hormone receptor positive tumours. Together, these data suggest that the cellular response to estrogen is more complex than initially thought and more importantly that the treatment with SERMs may not always have the desired effects in such tumours due to opposing effects on alternative estrogen receptors such as GPER.

There is a dearth of knowledge regarding GPER expression and localisation in breast tumours within cancer patients from African origin. It is also clear that the regulation of GPER and its effects on cancer characteristics such as metastatic potential are not understood yet.

This project aims to explore the potential use of GPER as a marker for breast cancer prognosis and as a potential therapeutic target itself.

GPER activation can lead to changes in cell migration and adhesion which are linked to metastasis in vivo. Using a newly developed agonist with a high predicted binding affinity for GPER we will delineate the cellular signalling pathways that emanate from GPER and converge on the focal adhesions responsible for cell adhesion and the actin cytoskeleton which is responsible for cellular tension to understand how GPER functions during metastasis.

To determine if GPER is a useful stratification marker for sensitivity to tamoxifen in ER positive breast tumours a prospective trial will be initiated to assess GPER expression and localisation in primary ER positive tumours and through follow-up of these patients, link GPER expression and therapy response.