cell malignancy, including normal prostatic epithelium, benign prostatic hypertrophy, and metastatic prostate cancer. Using ERK activation as a read-out, we show that NE promotes ERK phosphorylation in a dose dependent manner, and time course study further reveals a sustained ERK activation upon NE treatment. Western blot evaluation demonstrates strong EGFR expression in cell lines derived from normal and benign prostatic gland, and preferential expression in hormone resistant versus hormone responsive cells. In agreement with EGFR-dependent mitogenic signaling, activation of ERK is abrogated by siRNA-mediated EGFR knockdown, as well as by pretreatment of cells with irreversible EGFR inhibitor AG1478. Importantly, NE evokes cancer cell migration at a lower range of NE concentrations relative to nonneoplastic cells. In prostate cells, from a total of seven EGFR ligands, amphiregulin (AREG) is predominantly expressed, and the addition of NE results in the release of AREG. Moreover, AREG gene silencing by siRNA or inhibition of AREG biological activity by neutralizing antibody, prevents NE-induced ERK phosphorylation and cell migration. Together, our study reveals a distinct and essential role of AREG-EGFR signaling axis in NE-triggered prostatic cellular response.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Androgen Activity in the Primary and Metastatic Prostate Cancer Microenvironments Influences Disease Progression and Patient Outcomes.

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Background: Cancers do not exist in isolation, surrounding tumours are supportive cells, which create the microenvironment in which cancer cells reside. In the prostate cancer (PCa), androgen receptor (AR) signalling in the surrounding fibroblasts is strikingly distinct from that within PCa cells, and has specific functions to produce, maintain, and modulate the extracellular matrix (ECM) which surrounds and interacts with PCa cells. The supportive cells of metastatic sites differ from those in the primary site and produce different types of cellular microenvironments. Since the advent of second generation anti-androgen therapy there has been an increase in the presence of liver metastasis. This project investigates how AR and anti-androgen therapy affect the prostate liver microenvironment and the subsequent effects on cancer.

Results: Analysis of microenvironment of primary and metastatic sites indicates transcriptional responses distinct from that seen in PCa cells. This is exemplified by proliferation responses to androgen and anti-androgens in microenvironment cells being the reverse to that seen in Pca cells. Dichotomising microdissected PCa patient material of matched cancer and stromal tissue, based on stromal AR level shows distinct transcriptional profiles in the matched cancer cells. From previous studies, we know AR status in cancer adjacent fibroblasts (CAFs) of the primary tumor inversely associates with patient outcomes. Analysis of single cell CAFs and microdissected stromal samples points to a potential sub population of CAFs with this AR status. Conditioned media from liver and prostate fibroblast cells suggests that inactivation of AR signalling produces proliferative paracrine signals that can affect cancer cell growth. AR in primary site fibroblast and liver stellate cells regulates secretome and ECP production in the primary and metastatic site. Prostates and livers from enzalutamide treated mice showed changes in collagen fibres compared to control mice, as visualised by picro-direct-red staining. We cultured PCa cells within 3D-ECM microenvironments created in vitro from prostate fibroblasts or liver cells. The different 3D-ECM were able to produce changes in PCa cells, including gene transcription, intracellular signalling pathways, and proliferation and apoptotic responses. These data suggest that the responses of primary and metastatic microenvironments to androgens and anti-androgens can influence phosphorylation of intracellular pathways leading to alterations in gene transcription. Furthermore, the transcriptional responses of cancer cells in vitro to changes in microenvironmental AR signalling can be used to predict patient outcomes.

Conclusions: Our data suggests that anti-AR therapy produces organ microenvironment-specific signals that influence the response of prostate cancer to treatments and affects patient outcomes.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Antagonism of Growth Hormone Receptor Suppresses Cancer Growth and Drug Resistance in Mice

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Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) play important roles in different stages of progression and drug resistance in many types of cancers, including breast, colon, endometrial, liver cancer and melanoma. GH receptor (GHR) is highly expressed in melanoma and promotes cancer proliferation and multidrug efflux pumps mediated drug resistance. Knockdown of GHR in melanoma cells significantly increased their drug sensitivity in vitro. Thus, a GHR antagonist could become a therapeutic molecule in suppressing melanoma cancer growth and sensitizing the tumor to chemotherapy in vivo. Here, we used GHR antagonist (GHA) transgenic mice which constitutively express a GHA to specifically suppress GH/IGF-1 axis. We found have circulating IGF-1 level was significantly lowered in these mice as a result of GHR antagonism. Furthermore, the sera