

CONTRIBUTION OF ABERRANT ANDROGEN RECEPTOR SIGNALING TO PROSTATE TUMORIGENESIS

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Prostate cancer is a major public health issue in developed countries and ranks first in incidence and second in mortality among all types of cancer affecting Australian men. The androgen receptor (AR), a nuclear transcription factor, is required for the growth and survival of prostate cancer cells. Alterations in the androgen-signaling axis, including increased expression of the AR, amplification of the receptor, gain of function AR gene mutations and altered cofactor interactions, have been implicated in the failure of androgen ablation therapy and the development of castration-resistant prostate cancer. Recently, we reported collocation of AR gene mutations to discrete regions of the ligand binding and amino terminal (NTD) domains of the receptor. To assess the functional consequence of these AR variants, we have utilised prostate specific over expression in a murine model. Enforced expression of one AR-NTD variant (i.e. AR-E231G) resulted in 100% of transgenic mice developing prostate cancer and lung metastases by 50 weeks of age. The AR-E231G mouse model offers a unique opportunity to define global gene expression patterns well before prostate tumors arise, and to identify the pivotal genes capable of mediating oncogenic transformation of the prostate as a result of aberrant AR signaling. Although the AR is now accepted as the major determinant of prostate cancer cell survival, it is currently unclear how the receptor sustains genomic signaling under conditions of systemic androgen ablation. We have recently demonstrated that the evolutionarily conserved Hsp70/Hsp90 cochaperone, small glutamine-rich tetratricopeptide repeat containing protein alpha (α SGT), acts to (a) promote cytoplasmic compartmentalization of the AR, thereby silencing the basal/ligand-independent transcriptional activity of the receptor, (b) regulate the sensitivity of AR signaling by androgens, and (c) limit the capacity of noncanonical ligands to induce AR agonist activity. Quantitative immunohistochemical analysis of α SGT and AR levels in a cohort of 32 primary and 64 metastatic human prostate cancers revealed dysregulation in the level of both proteins during disease progression. The significantly higher AR/ α SGT ratio in metastatic samples is consistent with sensitization of prostate tumor cells to androgen signaling during disease progression, particularly in a low-hormone environment. These findings implicate α SGT as a molecular rheostat of signaling competence by the AR *in vivo* and provide new insight into the determinants of androgen sensitivity during prostate cancer progression.