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REST mediates androgen receptor actions on gene repression and predicts early recurrence in prostate cancer

Charlotte Lavallee[1], **Jens Ceder**[2], **Diego Iglesias-Gato**[1], **Anders Bjartell**[2], **Colin Collins**[3] and **Amilcar Flores-Morales**[1]
[1]University of Copenhagen, København
[2]University of Lund, Sweden
[3]Department of Urologic Science, Canada

The Androgen Receptor (AR) is a key regulator of prostate differentiation as well as prostate tumorgenesis in all stages, including the growth of castration resistant tumors. The actions of the AR in the prostate are complex and include induction and repression of transcription. The mechanisms mediating AR repression of gene expression and their significance in prostate cancer carcinogenesis are poorly understood. Sequence analysis of androgen receptor occupied regions suggests a number of possible interactors with the AR, including the repressor element-1 silencing transcription factor (REST/NRSF). REST has a proposed role as a tumor suppressor and represses neuronal gene expression. Chromatin immunoprecipitation showed that AR binds chromatin regions containing well characterized cis-elements known to mediate REST transcriptional repression, while cell imaging studies confirmed that REST and AR closely co-localize *in vivo*. Androgen-induced gene repression also involves modulation of REST protein turnover through actions on the ubiquitin ligase β-TRCP. Gene expression profiling revealed that REST not only acts to repress neuronal genes but also genes involved in cell cycle progression, including Aurora Kinase A, that has previously been implicated in the growth of neuroendocrine-like castration-resistant tumors. The analysis of prostate cancer tissue microarrays revealed that tumors with reduced expression of REST have higher probability of early recurrence, independently of their Gleason score.

charlotte.lavallee@sund.ku.dk

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