

AR Condensates Promote Malignant Progression in Castration-Resistant Prostate Cancer

Shabnam Massah¹, Nicholas C. Pinette¹, Emirhan Tekoglu², Rafailia Beta¹, Vanessa C. Arianto¹, Jane Foo¹, Sumanjit Datta¹, Meiyun Guo¹, Robert Bell¹, Anne Haegert¹, Maily Terrado¹, Stanislav Volik¹, Stephane Le Bihan¹, Jennifer M. Bui³, Martin E. Gleave¹, Suhan K. Rhie⁴, Colin C. Collins¹, Nathan A. Lack^{1,2}, Jörg Gsponer^{3*}, and Nada Lallous^{1*}

1. Vancouver Prostate Centre, University of British Columbia, Vancouver, BC, V6H 3Z6, Canada.
2. Department of Medical Pharmacology, School of Medicine, Koç University, Istanbul, 34450, Turkey.
3. Michael Smith Laboratories, University of British Columbia, Vancouver, BC, V6T 1Z4, Canada.
4. Department of Cancer Biology and the Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA.

*Co-corresponding authors.

Background: In castration-resistant prostate cancer (CRPC), androgen receptor (AR) signaling is restored despite androgen deprivation therapy through mechanisms including AR overexpression and expression of constitutively active splice variants such as AR-V7. How AR-V7 promotes resistance and disease aggressiveness remains unclear. We previously showed that full-length AR forms nuclear condensates to activate transcription. Here, we investigated whether AR-V7 similarly forms condensates and whether condensate formation shapes a distinct transcriptional program linked to malignant progression in CRPC.

Methods: We used confocal microscopy to visualize condensates formed by endogenous and exogenous AR-V7 in CRPC and non-CRPC models. Using a condensate-deficient AR-V7 mutant, we defined condensate-dependent and -independent transcriptional programs by RNA-seq and related them to AR-binding site density and expression dose-response. We assessed the contribution of condensate-associated transcription to proliferation and migration using the Incucyte live-cell imaging system and siRNA knockdown of condensate-dependent genes. We evaluated the clinical relevance of the condensate-associated gene signature by correlating it with proliferative and metastatic phenotypes in CRPC patient datasets.

Results: AR-V7 spontaneously formed nuclear condensates independent of full-length AR in CRPC models, with markedly reduced condensate formation in a non-CRPC model. Using the condensate-deficient mutant, we identified two AR-V7-driven transcriptional programs, one of which was preferentially sensitive to disruption of condensate formation. These condensate-associated genes were enriched for promoters with higher densities of AR-binding sites and showed exponential activation with increasing AR-V7 expression, contrasting with the linear response of less-sensitive genes. Condensate-associated transcription enhanced proliferation and migration in CRPC models, and the corresponding gene signature correlated with highly proliferative and metastatic phenotypes in CRPC patients.

Conclusions: AR-V7 condensates enable activation of a specific transcriptional program that promotes malignant progression in CRPC, independent of full-length AR. These findings identify condensate formation as a potential therapeutic vulnerability in AR-V7-driven CRPC.

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