

CDK7 inhibition suppresses Castration-Resistant Prostate Cancer through MED1 inactivation

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Abstract:

Metastatic castration-resistant prostate cancer (CRPC) is an aggressive disease with high mortality rate, primarily resulting from the transcriptional addiction driven by Androgen Receptor (AR). First-line CRPC treatments typically target AR-signaling, but are rapidly bypassed, resulting in only a modest survival benefit with the FDA approved anti-androgen therapies such as abiraterone or enzalutamide. Therefore, molecular approaches that more effectively block the AR-transcriptional program are urgently needed. Here, we present evidence demonstrating that AR transcriptional signaling is activated through a

“phosphoswitch” catalyzed by cyclin-dependent-kinase 7 (CDK7). Specifically, CDK7 phosphorylates (*in vitro* and *in vivo*) the transcriptional co-activator MED1, a key subunit of Mediator complex, at Threonine 1457 to promote the formation of the AR-transcriptional complex at enhancers and super-enhancer (SE) sites. Furthermore, knockdown or inhibition of CDK7 with the recently developed covalent inhibitor THZ1 abolished T1457 phosphorylation that led to MED1 recruitment from the chromatin, attenuated AR-signaling and eliminated AR-addicted naïve or enzalutamide refractory prostate cancer cells. Interestingly, the reduced AR transcriptional output and cellular phenotypes associated with CDK7 knockdown or inhibition was reversed by T1457D phosphomimic suggesting MED1 as a major effector substrate of CDK7 transcription kinase. Finally, THZ1 demonstrated tumor regression in CRPC xenograft models *in vivo*. In summary, our identification of MED1 T1457 as a novel CDK7 substrate, which is essential for driving AR-mediated transcription, makes CDK7 a potential “non-oncogene dependency” in AR addicted advanced prostate cancer. Taken together, we will present data that strongly support the clinical evaluation of CDK7 specific inhibitors as a monotherapy or in combination with second generation anti-androgens in refractory castration-resistant prostate cancer.

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