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Targeting Protein Interactions: A Novel Therapeutic Strategy against Prostate Cancer

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Editorial

The expression and signaling of Androgen Receptor (AR) is necessary for the development of prostate cancer, and hence, is a major target for pharmaceutical drug development against the disease. AR, which is predominantly present in the cytoplasm when inactive, is activated by the binding of androgens resulting in its translocation to the nucleus. Once in the nucleus, AR modulates the expression of target genes by binding to androgen-responsive elements (ARE) on their promoter/enhancer regions and recruiting coregulators and other proteins of the transcriptional machinery.

A critical locus of AR function is its binding to coregulators that serve as platforms for interactions with other proteins involved in various cellular functions including transcription, signaling and cell cycle regulation. Increase in the expression of these coregulator proteins and their activation of AR signaling in the absence of hormones in prostate cancer are evidences of their role in the disease [1]. Consequently, disrupting AR interactions with its coregulators by mimicking interacting 'protuberances' or 'sockets' within the binding regions using small molecules or peptidomimetics could serve as a strategy to block AR function.

Mimicking a-helical secondary structures to block protein interactions has an immense potential owing to their prevalence in the interacting motifs of many therapeutically relevant proteins. The 10-12 amino acids that comprise an a-helix rotate in such a way that the side chains of i, i+3 and i+4th amino acids project out from the helix and are available for interactions with other proteins. A major subset of AR coregulators interact with the ligand binding domain in AR through their signature a-helical LXXLL motif (X is any amino acid). Peptides mimicking LXXLL motif have previously been used to successfully block AR-coregulator interactions [2]. However, their use as drugs is limited due to their low cell permeability and stability.

In our paper in Nature Communications [3], we reported the use of oligo-benzamide scaffolds to mimic a-helical LXXLL motif. The conformationally constrained oligo-benzamide, named D2, projects its side chains to emulate the position and angular orientation of i and i+4 amino acid side chains of the LXXLL motif, thereby, disrupting AR interactions with LXXLL-motif containing coregulator, Proline-, glutamic acid- and leucine-rich protein 1 (PELP1). The critical role of coregulator PELP1 in AR-mediated signaling in prostate cancer was recently demonstrated by Yang et al. [4]. The LXXLL-mimetic D2 was able to disrupt AR-PELP1 interactions and AR-transcriptional function in the nM range, and its effect overcome by an overexpression of either AR or PELP1, suggesting its role as a competitive inhibitor in AR-PELP1 binding. Another convincing proof of the mimetic blocking AR signaling is that while it suppressed the growth of AR-positive cells in vitro, it had no growth-inhibitory effect on AR-negative prostate cancer cells.

Experiments done in vivo in mouse xenografts and human tumor explant models highlight the clinical translatability of D2. Notably, intratumoral and intraperitoneal administration of D2 significantly blocked the growth of tumor in subcutaneous C4-2 cell xenografts in SCID mice. Also, no toxicity or changes in weight were observed in these D2-administered mice. Additionally, our co-immunoprecipitation assays revealed a decrease in interaction between AR and PELP1 in human prostate tumor explants cultured with D2, demonstrating the ability of the mimetic to function on prostate cancer cells in their native environment.

Although D2 can potentially inhibit a wide array of protein interactions involving LXXLL motif, its binding specificity could be improved by using larger oligo-benzamide scaffolds that present more binding groups from the a-helical secondary structure. A major advantage of using small mimetics to block protein interactions is that while they can be designed to selectively bind to specific binding pockets in target proteins, they are less prone to proteolytic cleavage and have higher bioavailability compared to peptide mimics. Also, the ease of synthesis of these oligo-benzamide-based mimetics using simple chemical reactions makes them very attractive from a pharmaceutical point of view [5].

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