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Targeting RNA binding protein in prostate cancer

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ABSTRACT
RNA binding protein (RBP) controls multiple aspects of RNA metabolism and plays crucial roles in many physiopathological contexts, including cancer. We recently identified an RBP HNRNPL as a novel prostate cancer dependency via regulation of RNA splicing, suggesting the potential to target RBP or RBP-RNA interaction to treat cancer.

The fate of RNA within the cell is exquisitely regulated by a plethora of RNA binding proteins (RBPs). Once an RNA is transcribed by RNA polymerase, it is rarely naked and usually bound by diverse classes of ribonucleoproteins (RNPs) or RBPs through the RNA lifetime, thereby orchestrating the RNA biogenesis, splicing, modification, transportation, translation and degradation. Alteration of RBP or RBP-RNA interaction may have detrimental effects on the cellular functions, thus underlying many pathological processes such as neurologic disorders, muscular atrophies and many types of cancers. For example, the loss-of-function of an RBP called FMRP, resulting from the genetic expansion of CGG triplet repeat within the FMR1 gene on the X chromosome, leads to a neurologic disease - Fragile X Syndrome. The loss of another RBP SMN, due to the genetic defects of SMN1 gene, affects the biogenesis of small nuclear RNPs in the motor neurons and consequently causes spinal muscular atrophy. Despite the continuing efforts to catalog pivotal RBPs among different diseases, the identity of key cancer-relevant RBPs and their roles during cancer development remain poorly understood.

Prostate cancer is a leading type of cancer incidence in men around the world. In addition to surgery and radiotherapy, the mainstream treatment of prostate cancer is androgen deprivation therapy targeting androgen receptor signaling, which has been shown to drive prostate cancer growth and progression. Whether certain RBPs could be implicated in prostate cancer development remains elusive and the possibility of targeting key prostate cancer-dependent RBP as novel therapeutics needs to be explored. In our recent studies, we used a genome-wide CRISPR/Cas9 knockout screen approach with a pooled lentiviral single guide RNA library targeting 19,050 genes in the human genome to identify essential genes, which are required for prostate cancer cell growth, in an unbiased and high throughput manner (Fig. 1). In addition to the known prostate cancer regulators such as AR and MYC, many of the top negatively selected essential genes encode core components for either the basic cellular apparatus or important biologic processes, such as ribosomal complex, spliceosome, proteasome, DNA replication and transcription initiation complex. Interestingly, when focusing on RBPs among the top prostate cancer dependency genes, we found that several heterogeneous nuclear RNP (hnRNP) family members emerge including HNRNPL, HNRNPC and FUS. There are around 30 members of HNRNP genes that are responsible for a variety of RNA processing steps, especially RNA splicing, acting in concert with the core spliceosomes and other splicing factors. Given our CRISPR screen results and the scattering reports that some HNRNP genes may be implicated in different types of cancer, it is worthy to systematically evaluate the function and mechanism of HNRNP family genes in prostate cancer.

In addition to CRISPR screen, we further surveyed the functional HNRNP genes in depth with a small scale of short interfering RNA (siRNA) screen especially targeting all the HNRNP family members. HNRNPL and HNRNPC were consistently identified as top hits by both approaches, with HNRNPL slightly performs better. We then continued to ask how HNRNPL regulates prostate cancer growth. Due to its nature to bind RNA via atypical RNA recognition motif, we first determined the HNRNPL-associated RNA landscape by RNA immunoprecipitation coupled with high-throughput sequencing (RIP-seq). Compared to ultraviolet crosslinking-based approaches such as CLIP-seq, our adapted RIP-seq method uses formaldehyde as crosslinker, which allows us to capture both the direct and indirect RBP-RNA interactions. In the scenario that an RBP plays a key role within the RNP but does not directly bind to all the RNAs that are bound and regulated by the RNP, our RIP-seq approach is superior to capture such functional indirect RBP-RNA interactions. HNRNPL preferentially binds to CA-repeat or CA-enriched regions of RNA as reported before, however, the identity of HNRNPL-associated RNA is not the same in prostate cancer as that in other contexts, possibly due to the different RNA
expression profiles per se. For instance, we observed that HNRNPL specifically binds to AR pre-mRNA, which translates into androgen receptor – the prominent driver and fuel for prostate cancer, thereby regulating the alternative splicing of AR and consequently the expression of different AR isoforms in prostate cancer cells.

The first-line functional consequence of HRNPL-RNA interaction is the coordination of RNA splicing, hinted by the significant intron-binding pattern of HNRNPL onto the RNA. Loss-of-function of HNRNPL influences the alternative splicing patterns of a set of RNAs that interact with HNRNPL, including AR. Moreover, HNRNRL also regulates the back splicing of its associated RNAs and thus are responsible for tuning the biogenesis of certain circular RNAs, the newly appreciated functional RNA species. It is likely that the interaction between HNRNPL and its RNA targets cannot only be functional to RNA splicing, but also to many other RNA processes such as RNA decay or translation etc., which we have not fully examined yet.

On the translational side, the expression level of both the HNRNPL and HNRNPL-regulated RNA targets, including both the alternatively spliced genes and circular RNA genes, are significantly associated with prostate cancer progression. The clinical relevance of HNRNPL expression to prostate cancer progression was also confirmed by another recent study, in which HNRNPL was indicated to drive prostate cancer progression by enhancing cell cycle and inhibiting apoptosis. Furthermore, HNRNPL is also involved in immune responses and breast cancer development by interaction with the pivotal long noncoding RNAs in those contexts.

In summary, the identification of a series of RBPs in mediating prostate cancer progression will elicit further explorations to evaluate the potential of targeting these RBPs or key RBP-RNA interactions for novel prostate cancer therapies (Fig. 1). Better characterization of the functional interface between critical RBPs and their interacting partners, either RNA or protein, may facilitate the development of appropriate targeting strategies, including small molecules, aptamers and antisense oligonucleotides approaches.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

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