



Genome-wide CRISPR screen identifies HNRNPL as a prostate cancer dependency regulating RNA splicing

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Which RBPs and their related RNA processing steps are functionally important, especially in prostate cancer, remains elusive.

The recent implementation of the clustered regularly interspaced short palindromic repeats (CRISPR)-associated nuclease Cas9 genome editing system has proved effective in high-throughput loss-of-function screens (12–14). Compared with RNA interfering (RNAi)-based gene knockdown, CRISPR/Cas9-based gene knockout confers a more thorough deletion of target gene expression and has less off-target effects when the guide RNA is appropriately designed (15, 16). The power of the pooled CRISPR screen has been demonstrated by several studies investigating the genes involved in drug and toxin resistance (13, 17), cancer metastasis (18), and immune response (19).

Here, by a genome-wide CRISPR screen and in depth mechanistic studies, we sought to systematically identify functional RBPs or RNA processing factors that are essential for prostate cancer growth and underlie pivotal cancer-related RNA processing steps, especially RNA splicing, thus potentially enabling the development of novel cancer therapeutics targeting RBPs or RBP–RNA interactions.

CRISPR screen | HNRNPL | prostate cancer | RNA binding protein | alternative splicing

Prostate cancer is among the most prevalent adult malignancies in developed countries. The principal treatment for prostate cancer once it is no longer amenable to surgery or radiation treatment is androgen deprivation therapy, which targets androgen or androgen receptor (AR) signaling. However, resistance to androgen deprivation therapy often develops and leads to a state termed “castration-resistant prostate cancer,” which still lacks an effective cure (1–3). Therefore, significant efforts have been devoted to better understand the mechanism of oncogenesis and to develop additional effective therapeutics targeting pivotal oncogenes, cancer-related signal transduction pathways, and epigenetic regulators (4, 5).

Alternative RNA splicing is a fundamental cellular process by which a single gene can give rise to multiple different transcripts and proteins. This process is tightly regulated by core spliceosomes and other splicing factors, such as the serine/arginine-rich family of proteins and heterogeneous nuclear ribonucleoproteins (hnRNPs) (6, 7). Multiple studies indicate that deregulation of alternative splicing is implicated in cancer progression and that the splicing machinery may be targeted therapeutically (8–10). In addition to RNA splicing, the physical interactions between RNAs and RNA binding proteins (RBPs) underlie multiple RNA processing steps, such as capping, polyadenylation, transport, localization, modification, and translation, thereby regulating many aspects of RNA fate (11).

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