Published OnlineFirst August 26, 2016; DOI: 10.1158/2159-8290.CD-RW2016-159

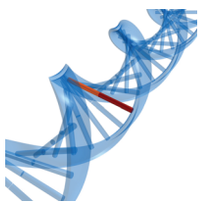
Prostate Cancer

Major finding: The prostate cancer risk SNP rs7463708 promotes transformation via upregulation of *PCAT1* lncRNA.

Mechanism: The T risk allele of rs7463708 enhances binding of ONECUT2 and AR to the *PCAT1* enhancer.

Impact: Prostate cancer risk–associated SNPs can promote prostate cancer via modulation of lncRNAs.

A PROSTATE CANCER RISK SNP UPREGULATES THE TUMORIGENIC lncRNA *PCAT1*



A number of SNPs are associated with predisposition to disease and the majority of these occur outside of protein coding exons, but the molecular mechanisms by which many cancer risk–associated noncoding SNPs contribute to tumorigenesis are unknown. Through analysis of GWAS data, Guo, Ahmed, and colleagues found that prostate cancer risk–associated SNPs were enriched in regulatory regions marked by DNase I–hypersensitive sites (DHS), androgen receptor (AR) and AR cofactor occupancy, and active histone marks. Risk-associated SNPs overlapped with DHSs near lncRNA genes, suggesting that these SNPs might increase prostate cancer risk through modulation of lncRNAs, many of which are expressed in cancer but not functionally characterized. Integrative analysis identified 45 candidate lncRNAs potentially regulated by noncoding risk-associated SNPs in prostate cancer, including *PCAT1*, which was overexpressed in prostate cancer. Consistent with these findings, depletion of *PCAT1* reduced prostate cancer cell growth *in vitro* and *in vivo*. The *PCAT1* promoter was predicted to interact with the rs7463708 risk locus, a region containing 3 SNPs and overlapping with a strong DHS downstream of the *PCAT1* transcription start site, which was bound by transcription factors including AR. Chromosome conformation capture confirmed that the *PCAT1* promoter strongly interacted with the T risk allele, but not the G non-risk allele, of rs7463708 upon androgen treatment, and CRISPR/Cas9-mediated disruption of the rs7463708 locus prevented the *PCAT1* promoter interaction and reduced *PCAT1* expression, suggesting that rs7463708 regulates the activity of a *PCAT1* enhancer. The T risk allele of rs7463708 exhibited increased occupancy by the transcription factors ONECUT2 and AR, which was further enhanced by androgen stimulation and resulted in increased *PCAT1* expression. Moreover, *PCAT1* recruited AR and LSD1 to the enhancers of two genes involved in prostate cancer, *GNMT* and *DHCR24*. In addition to identifying *PCAT1* as a prostate cancer–promoting lncRNA, these findings demonstrate that risk-associated SNPs can promote transformation through regulation of lncRNAs. ■

Guo H, Ahmed M, Zhang F, Yao CQ, Li S, Liang Y, et al. Modulation of long noncoding RNAs by risk SNPs underlying genetic predispositions to prostate cancer. Nat Genet 2016 Aug 15 [Epub ahead of print].

Drug Design

Major finding: The small molecule APS-2-79 stabilizes an inactive form of the MAPK scaffold KSR to repress RAS signaling.

Clinical relevance: APS-2-79 synergizes with MEK inhibitors to improve their efficacy in *KRAS* mutant cells.

Impact: Targeting both enzymatic and scaffolding activity in the RAS–MAPK pathway may inhibit RAS-driven tumors.

KSR MUTATIONS GUIDE DEVELOPMENT OF RAS PATHWAY ANTAGONISTS

RAS genes are frequently mutated in cancer, but therapeutic targeting of RAS has proven challenging, with drug development efforts largely focusing on the RAS effectors RAF, MEK, and ERK. A MAPK scaffolding protein, kinase suppressor of ras (KSR), which is a pseudokinase and noncatalytic regulator of the core RAS pathway signaling enzymes, has been suggested as an additional possible therapeutic target to disrupt RAS signaling. Dhawan, Scopton, and Dar noted *KSR* mutations that selectively inhibit mutant, but not wild-type, RAS from forward genetic screens in flies and worms and discovered that many of the mutations were adjacent to the KSR ATP-binding pocket, leading them to hypothesize that the interaction between KSR and RAF or MEK might be blocked by ligands that bind the KSR ATP-binding pocket. A collection of structurally diverse kinase inhibitors was screened to identify small molecules that bind the ATP-binding pocket of KSR2–MEK1 complexes, resulting in the identification of the quinazoline–biphenyl ether compound APS-1-68-2. Further optimization resulted in APS-2-79, a compound that potently reduced KSR-dependent MEK and ERK activation and mimicked the *KSR* mutant alleles that inhibit the oncogenic signaling of mutant *RAS*. Crystal structures indicated that APS-2-79 antagonized MEK phosphorylation by RAF by binding the KSR active site within the KSR2–MEK1 complex and stabilizing the inactive state of KSR2. Moreover, stabilization of the KSR inactive state with APS-2-79 enhanced the effects of MEK inhibitors in *KRAS*-mutant cells. The identification of an inactive form of KSR stabilized by a small molecule indicates that KSR targeting may indirectly suppress RAS signaling, and the combined effects of KSR and MEK inhibition suggest that dual targeting of enzymatic and scaffold proteins may improve RAS pathway suppression. ■

Dhawan NS, Scopton AP, Dar AC. Small molecule stabilization of the KSR inactive state antagonizes oncogenic Ras signalling. Nature 2016 Aug 24 [Epub ahead of print].

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AACR American Association for Cancer Research

CANCER DISCOVERY

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Cancer Discov 2016;6:1079. Published OnlineFirst August 26, 2016.