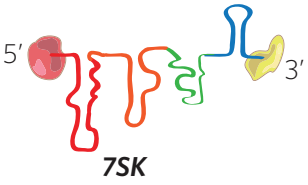
TRANSCRIPTION

7SK's enhanced roles

Nat. Struct. Mol. Biol. doi:10.1038/nsmb.3176



NAT. STRUCT. MOL. BIOL.

7SK is a small nuclear RNA (snRNA) that, as part of a specific small nuclear ribonucleoprotein (snRNP) complex, regulates promoter-proximal pausing during transcription. Using a series of genome-wide RNA profiling technologies, Flynn *et al.* now identify an additional role for 7SK in controlling transcription at enhancer elements. Using chromatin-RNA pulldown and sequencing techniques, the authors showed that 7SK RNA is associated with active RNA polymerase II transcription sites in diverse mammalian cell types. Distinct profiles of proteins are associated with 7SK at promoters, typical enhancer (TE) and super enhancer (SE) elements. 7SK depletion experiments highlighted 7SK's role in regulating transcriptional abundance and preventing DNA damage at SEs, and chromatin isolation by RNA purification mass spectrometry (ChIRP-MS) revealed that 7SK forms a cellular complex with BAF, a well-characterized SWI/SNF family chromatin-remodeling factor. *In vivo* click-selective 2′-hydroxyl acylation and profiling experiments (icSHAPE) demonstrated that 7SK adopts a distinct RNA secondary structure that enables its specific binding to BAF. Further experiments showed that the 7SK-BAF snRNP is localized at enhancers by an acetyllysine-bromodomain interaction, where BAF exerts its transcriptionally repressive effects by nucleosome repositioning. Taken together, the study highlights that 7SK snRNA (and likely other snRNAs) may provide versatile scaffolds for targeting regulatory proteins to distinct chromatin sites in the genome. *TLS*

SIGNAL TRANSDUCTION

Lowered exchange rates

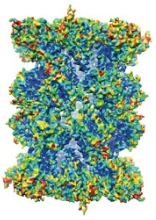
Science **351**, 604–608 (2016)

Ras is a small GTPase that cycles between an active GTP-bound and an inactive GDP-bound state in response to upstream signaling effectors. GTPases promote the hydrolysis of GTP, whereas nucleotide exchange factors (GEFs) mediate the exchange of GTP for GDP. Oncogenic forms of Ras such as $KRAS^{G12C}$ have constitutive activity presumably due to an inability to undergo GTP hydrolysis. Previous small-molecule screening efforts had identified ARS-853 as a specific inhibitor of $KRAS^{G12C}$ but without revealing the exact mechanism. Lito *et al.* observed that ARS-853 selectively decreased KRAS-GTP levels in $KRAS^{G12C}$ mutant lung cancer cells and this correlated with inhibition of Ras effector activation and reduced cell proliferation. Differential scanning fluorimetry analysis revealed that ARS-853 bound specifically to the inactive GDP form of $KRAS^{G12C}$. Genetic and biochemical studies determined that $KRAS^{G12C}$ retained basal GTPase activity to cycle from the GTP- to the GDP-bound state and that ARS-853 binding to KRAS-GDP trapped it in the inactive state by preventing its interaction with exchange factors. Inhibition of receptor tyrosine kinases that drive nucleotide exchange shortened the time required for ARS-853 to work and enhanced its potency, suggesting that a combination therapy of ARS-853 with inhibitors of nucleotide exchange could be effective in patients with $KRAS^{G12C}$ lung cancers. *GM*

DRUG DISCOVERY

One without the other

Nature **530**, 233–236 (2016)



NATURE

Inhibition of the proteasome has been shown to be toxic for the malaria parasite *Plasmodium falciparum*. Although inhibitors of the *P. falciparum* proteasome exist, they have limited utility as therapeutics because they target the human proteasome as well. To find selective inhibitors of the *P. falciparum* proteasome, Li *et al.* first compared the substrate specificities of *P. falciparum* and human 20S proteasomes by testing their activities against 228 diverse synthetic tetradecapeptides and found that *P. falciparum* exhibited a selective preference for cleaving tryptophan at positions 1 and 3. The authors then modified the canonical trileucine scaffold found in common proteasome inhibitors with tryptophan at the first and third positions to generate three new inhibitor compounds. One, WLW-vs, was highly selective for the parasite proteasome β2-subunit over its β5 subunit and over the human proteasome. A comparison of a cryo-EM structure of WLW-vs bound to the malarial proteasome to that of the human apo proteasome core explains the specificity towards the former over the latter. A second parasite-selective inhibitor identified here had a large therapeutic window against the *P. falciparum* proteasome and was efficacious in a rodent infection model without toxicity. These proteasome inhibitors were also active against parasites resistant to artemisinin, the current standard of treatment. These results suggest that antimalarial drugs could be made to exclusively target the malarial proteasome. *MB*

HOST-MICROBE INTERACTIONS

Intake control

Cell Metab. **23**, 324–334 (2016)

The gut microbiota is important in the metabolism of nutrients consumed by the host organism. It is thought that these bacteria can also influence host feeding behavior through the regulation of neuronal pathways responsible for appetite control and satiety. Several potential mechanisms for controlling food uptake exist, but it has not been known if bacterial-derived proteins could influence appetite-controlling pathways. Breton *et al.* first determined that the growth dynamics of regularly fed *Escherichia coli* K12 cells are associated with the host prandial and postprandial phases in rats and then used a proteomics approach to identify differences between proteins secreted by the bacteria after ten minutes (exponential phase of growth, Exp) and two hours (stationary phase, Stat). They found 20 differentially expressed membrane proteins and 20 differentially expressed cytoplasmic proteins, most of which have been implicated in anabolic or catabolic processes. One specific *E. coli* protein, ClpB, known to cause release of the satietogenic hormones GLP-1 and PYY, was increased in the Stat growth phase. The authors next introduced the *E. coli* proteins secreted during Exp- and Stat-phase growth into rats by colonic infusion and found that the Exp proteins increased plasma GLP-1 levels, whereas the Stat proteins increased plasma PYY as well as ClpB in the colonic mucosa. These results, as well as a set of electrophysiology experiments, suggest that bacterial proteins produced during nutrient-induced bacterial growth may control appetite via stimulation of satiety hormones locally in the gut and, after they reach the systemic circulation, via activation of central anorexigenic circuitries. *MB*

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