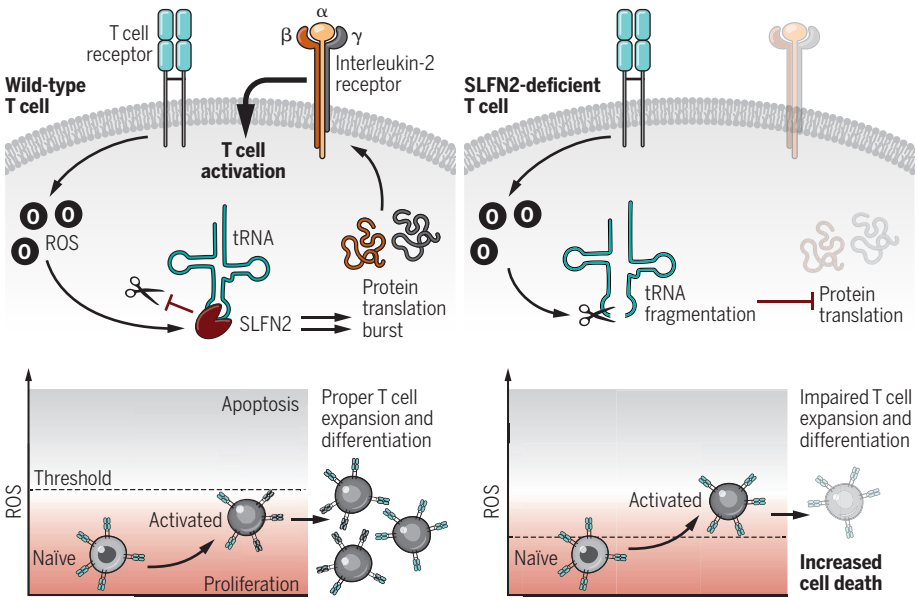
Protecting T cells from stress

T cell activation is accompanied by increased amounts of reactive oxygen species (ROS). Schlafen 2 (SLFN2) protects transfer RNAs (tRNAs) from ROS-induced cleavage to maintain the increased translation that is necessary for T cell activation. When SLFN2 is absent, this tRNA protection is removed, and T cells are more sensitive to ROS amounts and thus more likely to undergo cell death.



the stress response when the cells recognize antigen (see the figure).

Angiogenin (ANG) is a potent RNase that cleaves the tRNA anticodon loop to produce the half-molecule type of tRFs (*9*). Yue *et al.* found that SLFN2 protects tRNAs from ANG cleavage, and lower ANG expression restored tRNA amounts, protein translation, and cell proliferation of *Slfn2*-deficient T cells. *Ang* mRNA and protein expression are upregulated by T cell activation, which can be reversed by antioxidant. This represents a newly identified mechanism to trigger tRNA cleavage by directly regulating RNase expression. Further investigation is needed to understand whether the tRNA-protective function of SLFN2 also exists in other cell types.

The study by Yue *et al.* reveals an intricate regulation of ROS sensing and translation by SLFN2 during T cell activation. This mechanism may be relevant in autoimmunity because SLFN2 is important in a mouse model of multiple sclerosis (*2*). Notably, Schlafen family functions are not completely understood (*12*). This study opens several future directions in Schlafen family research. Is the regulation of RNA metabolism and translation a common theme of Schlafen function? It is unknown whether Schlafen proteins can bind to (and protect or cleave) other cellular RNAs or viral RNAs. Additionally, whether there is redundancy of function between members of the family awaits further research.

Growing evidence shows that tRNA fragments are not random degradation products, but rather they have biological functions (*9*). Because tRNA fragmentation can repress translation by decreasing the pool of tRNAs, or through direct inhibitory effects of tRNA fragments on the translation machinery through stress-granule formation or microRNA-like action, it will be interesting to determine which mechanism, if not all, are contributing to translation repression in SLFN2-deficient T cells. Additionally, RNases other than ANG mediate tRNA fragmentation (*9*), and in other contexts, tRNA fragments are generated efficiently even after *Ang* deletion (*13*). This suggests that although Yue *et al.* characterize ANG as the major tRNase during T cell activation, the mechanism may be generalizable to other RNases, whose activities could be regulated by other SLFN2-like tRNA-protective proteins in other biological contexts or cell lineages. ■

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NEUROSCIENCE

Neurobiology of novelty seeking

Neurons in the subthalamic "zone of uncertainty" assign intrinsic value to novel experiences

By **Zahra Z. Farahbakhsh** *and* **Cody A. Siciliano**

The human brain adapts with experience to learn and motivate future behaviors. But what drives motivation before learning? Attraction to the unknown, or curiosity, is a prerequisite for higher-order knowledge. Innate attraction to novelty is thought to be an evolutionary prerequisite for complex learning and guides organisms toward acquisition of adaptive behavioral repertoires (*1*). Indeed, heightened novelty exploration has been linked with augmented learning rates in mice and humans. Additionally, novel stimuli without any clear rewarding or biologically beneficial attributes can function as positive reinforcers, highlighting their powerful motivational properties (*2*). Heightened novelty-seeking phenotypes are premorbid risk factors for several neuropsychiatric disorders, such as addiction and bipolar disorder (*3*), relationships that are recapitulated in rodent models (*4*). On page 704 of this issue, Ahmadlou *et al.* (*5*) identify a population of neurons in the medial zona incerta (ZIm) that integrates arousal state and familiarity of stimuli in the environment to drive investigation of novelty in mice.

In search of explanations for innate motivations, psychologists at the turn of the 20th century developed methods for quantifying behaviors produced by physiological need states, such as hunger and thirst, in laboratory animals. Later formalized in "drive theory," these studies demonstrated that adaptive behaviors such as exploration and foraging could be predictably evoked regardless of prior experience (*6*). During these early investigations, researchers noted that similar behaviors occurred in novel contexts—for example, if animals were not habituated to the experimental apparatus. Initially noted as a confounding variable in hunger studies

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GRAPHIC: KELLIE HOLOSKI/*SCIENCE*

(*7*), later work demonstrated that attraction toward novelty can be strong enough to override hunger, thirst, and even pain (*8*, *9*).

Although the underlying psychological constructs are still debated, well-validated procedures have been developed for quantifying novelty-driven behaviors, such as exploratory activity in a novel arena, novelty-induced place preference, and novel-object investigation. Like other motivated behaviors, responses to novelty follow a temporal time course and can be satiated by exposure and augmented by deprivation (*10*, *11*). That said, precisely identifying the neurobiological substrates of novelty-driven behaviors separate from confounding motivational drives poses several challenges, and without tempered interpretation, spurious conclusions are common (*10*). Specifically, the structure of novelty assays makes it difficult to distinguish neural encoding of novelty as opposed to general locomotor activity, goal-based exploration, habituation, and other cooccurring processes (*12*). These limitations have made it difficult to uncover neurobiological substrates with specialized roles in novelty seeking.

Ahmadlou *et al.* used a free-access double-choice task in which mice were placed in an arena with a familiar and a novel object. Objects were sequentially replaced, so that novelty-induced investigation and subsequent habituation was observed many times throughout the session. Video analysis and statistical modeling revealed that animals interacted more with novel stimuli, and with stereotypic action sequences (such as bite, grab, and carry), which diverged on the basis of familiarity. When mice approached and sniffed objects, the probability of subsequently biting was greater when the object was novel, and the sniff-to-bite transition marked the onset of long bouts of continuous investigation. This allowed for interaction bouts to be separated into "deep" investigations, when sniff-bite was the first transition, or "shallow" when it was not. To parse novelty-induced investigation from general locomotion and interactions with familiar objects, the authors probed the neural mechanisms that allow novelty to briefly imbue otherwise neutral stimuli with positive reinforcing properties.

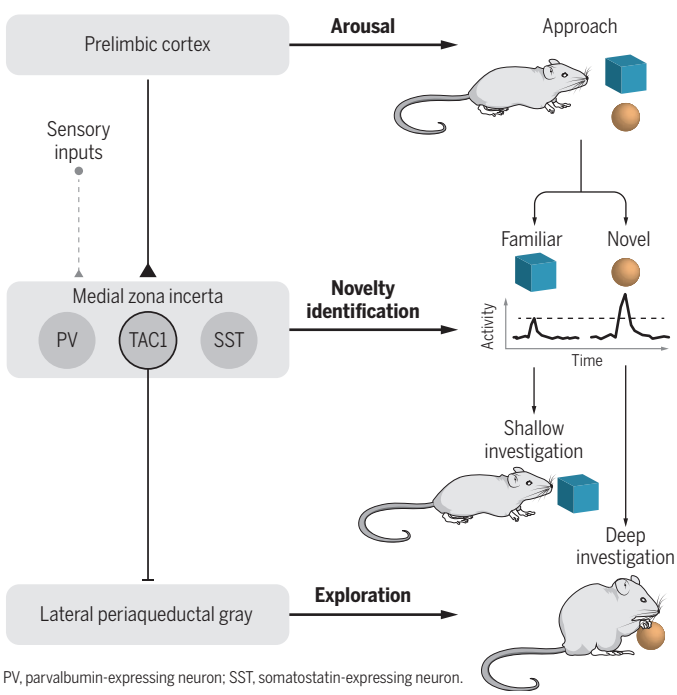
The zona incerta—Latin for "zone of uncertainty"—is a subthalamic nucleus with diverse connectivity throughout the brain and spinal cord that had been largely overlooked until recent years (*13*). Through innovative experiments, Ahmadlou *et al.* found that ZIm γ-aminobutyric acid (GABA) neurons are preferentially activated during deep investigation compared with shallow investigation, and that manipulating these neurons bidirectionally modulated time spent interacting with novel objects. Photoactivation of ZIm GABAergic neurons also acted as a positive reinforcer in an intercranial self-stimulation task, suggesting that endogenous activity observed during deep investigation may drive the reinforcing properties of novel stimuli.

Upstream projections from prelimbic cortex to ZIm were activated during both deep and shallow investigation, and their activity was highly correlated with arousal. Photoactivation of prelimbic inputs increased pupil diameter and downstream activity of GABAergic ZIm neurons, and inhibition of these synapses in ZIm attenuated novel object investigation. Together, this suggests that although prelimbic inputs to ZIm do not distinguish between novel and familiar stimuli, they provide excitatory drive necessary for novelty-induced increases in investigatory behavior. The authors speculate that sensory representations of stimuli converge with arousal-driven activity from prelimbic inputs within the ZIm to augment preference and depth of investigation when the stimulus is novel. They go on to show that modulation of investigation depth is mediated by a subset of ZIm neurons expressing tachykinin-1 (TAC1), a precursor of the neuropeptides substance P and neurokinin A. These TAC1-expressing neurons receive monosynaptic inputs from prelimbic cortex and send output projections to the lateral periaqueductal gray area. This implies a mechanism by which arousal-related information is transferred from cortex to the ZIm, where signals converge with encoding of stimulus features in TAC1^{+} ZIm neurons. In turn, these neuorns provide inhibitory drive to the lateral periaqueductal gray to determine whether a stimulus is treated as novel or familiar (see the figure).

Ahmadlou *et al.* detail a mechanism for assigning intrinsic reinforcing properties to novel stimuli. Further work will be required to understand how upstream sensory inputs identify novelty and how they interact with circuits involved in recall, reward, and fear to drive investigatory decision-making. Probing these systems may clarify the mechanisms that allow novelty encoding to influence learning and other motivated behaviors. The discovery of this cortico-subthalamic-hindbrain circuit may also reveal why novelty-seeking phenotypes confer neuropsychiatric disease vulnerability (*3*, *4*). The field is a step closer to understanding one of the most ubiquitous and influential innate drivers of human and animal behavior. ■

Circuitry involved in novelty-driven investigation

The prelimbic cortex carries motivational and arousal related information to the medial zona incerta (ZIm), which is putatively integrated with information from sensory inputs. Approaching an object or social target leads to activation of tachykinin-1 (TAC1)–expressing neurons in the ZIm, which scales with stimulus novelty. If sufficient activation of TAC1 neurons projecting to the lateral periaqueductal gray is reached, the object is treated as novel and investigated with specific behavioral sequences (sniffing and biting).



PV, parvalbumin-expressing neuron; SST, somatostatin-expressing neuron.

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