Press Release

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An unexpected chemosensor pathway for innate fear behavior against predator odor

Innate fear is an essential emotion for animals to avoid danger in a natural environment. Rodents kept in a laboratory also show instinctive fear behavior against the smell of predators such as foxes, cats or snakes despite having never seen them before. This innate fear represents an evolutionarily conserved and genetically encoded survival mechanism. However, the molecular basis of innate behaviors is largely unknown. Scientists at the International Institute for Integrative Sleep Medicine (WPI-IIIS) at the University of Tsukuba in Japan hypothesized that it might be feasible to investigate the molecular mechanism of innate fear using a forward genetics approach.

The researchers used chemical mutagenesis to introduce random mutations into mice. The mutant mice are screened for abnormal fear responses against a potent derivative of fox odorant, 2MT, which was discovered by co-authors Ko and Reiko Kobayakawa at Kansai Medical University. The screen identified a mutant pedigree, named fearless, showing markedly attenuated freezing response (typical fear behavior in mice) against the odorant. The fearless pedigree carried a mutation in the Trpa1 gene, which function as a pungency/irritancy receptor.

Loss of Trpa1 in mice diminished predator odor-evoked innate fear behaviors, although they exhibit a normal sense of smell. The research team then found that Trpa1 acts as a chemosensor to detect

predator odors. Trpa1 is highly expressed in the trigeminal somatosensory system, which plays a crucial role in nociception, sensing harmful and potentially painful chemicals. They showed that Trpa1-expressed trigeminal neurons contribute critically to fear odor-evoked innate freezing behavior.

"Surprisingly, the trigeminal system, but the not the traditional olfactory system, triggers instinctive fear responses," says the senior author Qinguha Liu. "Predator odor-mediated activation of the Trpa1 nociceptive pathway should instinctively warn the mice of imminent dangers and trigger emergency responses to promote survival. Our studies provide a compelling molecular logic to explain how predator odor-evoked innate fear/defensive behaviors are genetically hardwired."

Furthermore, this study represents the first forward genetics screen on emotion. Understating basic mechanism of fear is important for therapeutics of human anxiety disorders. According to the National Institute of Mental Health (NIMH), approximately 40 million of Americans are affected by a spectrum of fear/anxiety disorders, including general anxiety disorder, panic disorder, social and specific phobia, obsessive compulsive disorder (OCD), and post-traumatic stress disorder (PTSD).

"We hope that identification of core fear genes, together with the use of "fearful" mice as animal models, should facilitate our understanding of the genetic origins and development of novel and effective therapeutics for human anxiety disorders," says a co-author Masashi Yanagisawa.

The article, “Large-scale forward genetics screening identifies Trpa1 as a chemosensor for predator-evoked innate fear behaviors” was published online in Nature Communications on May 23, 2018.

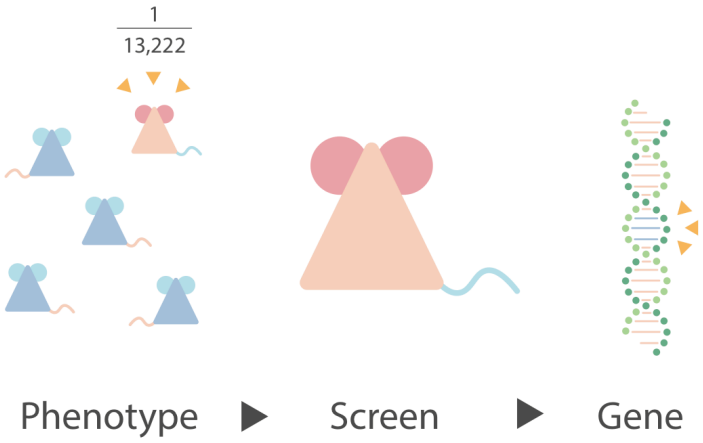

Fig1. The researchers used a forward genetics approach to determine the genetic basis responsible for a particular phenotype among mutagenized mice.

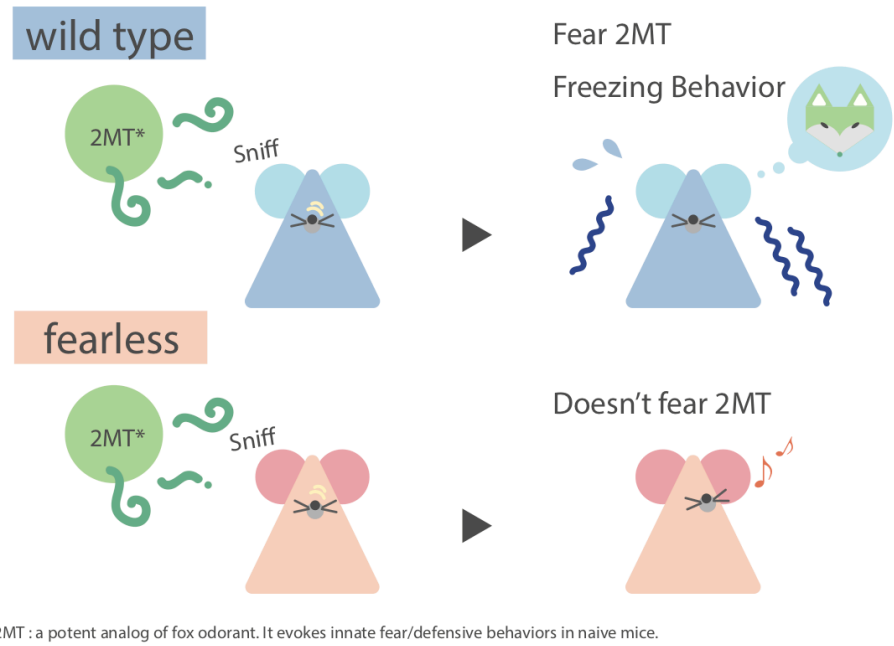

Fig2. WT and Fearless are screened for abnormal fear responses against a potent derivative of fox odorant. Fearless showed markedly attenuated freezing response.

Bibliographic information
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