Illuminating the Neuronal Architecture Underlying Context in Fear Memory

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Context plays a foundational role in determining how to interpret potentially fear-producing stimuli, yet the precise neurobiological substrates of context are poorly understood. In this issue of *Cell*, Xu et al. elegantly show that parallel neuronal circuits are necessary for two distinct roles of context in fear conditioning.

A traditional Scottish poem requests deliverance "From ghoulies and ghosties…and things that go bump in the night" (Hardy, 1895). In life, there are Things that intrinsically drive fear, as well as correlates of these Things that may be feared by association. For example, if we have encountered a scary Thing that goes bump in the night, our fear of the Thing may lead us also to fear bumps and nights. Learned fear is a complex emotion, shaped by our memories of aversive occurrences (Things), as well as by associated discrete cues (bumps) and general contexts (nights).

In this issue of *Cell*, Xu and colleagues examined the neural architecture required for context-dependent fear memory. Context can play many roles in the establishment and retrieval of fearful experiences (Maren et al., 2013) (Figure 1). For example, a silent ghouly appearing one night may cause the next night to be fraught with fear. Here, the nighttime context alone is sufficient to evoke the fear memory of the previous night. Another night, a ghost emerges with a bump. A reoccurrence of that same bump might again produce fear, whether heard in the night or the day. However, if many bumps are later heard in the daylight without the manifestation of a ghost, it may be that the bump need only be feared if arriving at night. Here, the nighttime context effectively gates the retrieval of fear memory associated with the bump cue.

As context plays a key role in fear memory, the brain must have ways that it can represent and convey these contextual elements. A variety of work has broadly implicated signaling from the hippocampus to the amygdala to be important for contextual elements of fear conditioning (Maren, 2001). Here, Xu et al. (2016) (this issue of *Cell*) explored the intriguing possibility that distinct subcircuits, emanating from the same location in the ventral hippocampus (vHC) and projecting to different regions of the amygdala, may mediate disparate aspects of context in fear memory.

Xu and colleagues began by using state-of-the-art viral circuit mapping to characterize anatomical projections from the vHC to the central amygdala (CEA) and the basal amygdala (BA). As each of these amygdalar regions plays roles in fear behavior (Gross and Canteras, 2012; Maren et al., 2013), a key question was whether vHC neurons conveyed a generalized contextual signal by projecting to both regions. Strikingly, the authors found that the vHC → BA projection emanated from an almost entirely different population than the vHC → CEA projection, illustrating parallel circuitry that might subserve distinct contextual modalities.

The authors then examined whether these structurally segregated pathways could produce different contextual dependencies in fear memory. In a laboratory

Figure 1. The Role of Context in Fear
The growl of a tiger elicits profoundly different reactions in distinct contexts.

setting, fear can be induced using an aversive shock (the "Thing"), presented in conjunction with a tone cue (the "bump") and/or an environmental context (the "night") (LeDoux, 2000). This approach causes the tone cue and/or environmental context to be associated with the aversive shock. Later, re-exposure to these associated stimuli alone can be sufficient to cause the animal to cease movement ("freeze"), an innate fear behavior that indicates a fear memory has been formed. Fear memory can then be studied by measuring this freezing in response to combinations of fear-associated stimuli.

Using variants of this general approach, Xu et al. (2016) subjected mice to two canonical fear conditioning paradigms. First, the authors studied contextual fear conditioning. Here, animals received foot shocks in a given context, resulting in freezing upon reintroduction to the associated context the following day (an experimental analog of the "silent ghoul" memory). Second, the authors examined context-dependent retrieval of cued fear memory (akin to the nighttime gating of the "bumpy ghost" memory). Using optogenetics to selectively silence individual pathways during fear memory retrieval, dissociable context-dependent roles for the two vHC → amygdala circuits were identified. Specifically, the vHC → BA pathway was selectively necessary for fear responses driven by conditioned context, whereas the context-dependent retrieval of the cued fear memory selectively required the vHC → CEA projection. Taking these two experiments together, Xu et al. (2016) demonstrated the remarkable finding that the brain uses structurally and functionally segregated parallel circuits to relay contextual information during fear memory.

Context plays a critical role in fear memory, but it also shapes our interpretation of the world in many other ways (Urcelay and Miller, 2014). Recent work has shown that vHC projection neurons are involved in many complex behaviors (e.g., social memory) that could be shaped by context (Ciocchi et al., 2015; Okuyama et al., 2016). As the vHC→ BA pathway examined here exhibits a reciprocal projection back to the vHC (Pitkänen et al., 2000; Xu et al., 2016), this work suggests an anatomical substrate that could project contextual elements of fear back onto other vHC-dependent behaviors. Identifying whether this pathway generally shapes vHC processing will be central for building a unified framework of the neural architecture of context. The work of Xu et al. (2016), shedding light on the darkness associated with fearful Things, contributes a key element to this framework.

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MIS12/MIND Control at the Kinetochore

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Kinetochores are complex multiprotein machines that link chromosomes to dynamic microtubules for chromosome segregation. Two studies in *Cell* reveal the structure of the human MIS12 and budding yeast MIND kinetochore complexes and the regulatory mechanisms that enable them to link chromosomes to microtubules during mitosis.

The equal segregation of chromosomes during cell division in eukaryotes is controlled by the kinetochore, a multiprotein complex that links chromosomes to the microtubules of the mitotic spindle. The formation of the kinetochore is a multistep process in which the site of kinetochore formation is first determined by a specialized chromatin domain at the chromosomal centromere. This chromatin promotes the assembly of a set of centromere-specific proteins (CENPs) that bind centromeres throughout the cell cycle and serve as the platform on which complex kinetochores are built.