Forgetting memories through distinct actin remodeling mechanisms

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After an event takes place, we may memorize different aspects of the experience, such as visual details or the general context. Empirically, these memory components appear to fade away at different rates, suggesting different cellular and/or molecular mechanisms underlying such memory decay. *Drosophila*, a pioneering animal model for discovering genetic components of forgetting, is known to form at least 2 different memory components after learning: anesthesia-sensitive memory (ASM) and anesthesia-resistant memory (ARM) (1). These 2 memory components are distinguishable from each other behaviorally and genetically (2–4), but both show decremental forgetting. Interestingly, the decay rates of ASM and ARM depend on 2 different Rho family proteins (5, 6). An important question is what signal cascades are downstream of these GTPases. Gao et al. (7) connect the dots by discovering distinct actin remodeling mechanisms for forgetting of ASM and ARM.

Forgetting opposes memory formation. Intuitively, people think that forgetting is a passive process—memory gradually fades away just as a rock is eroded over time and loses its shape. For an efficient information storage system to work properly, however, a dedicated "delete" function which removes unused or inappropriate information is required. From a molecular perspective, variant kinases and receptors are phosphorylated after learning, and the process is required for maintenance of labile memory (8). With time, basal activity of phosphatase within the neuron may counteract the learning-induced phosphorylation (9), thus "passively" returning phosphorylation to its baseline. In contrast, an active forgetting process recently has been proposed (10). Study of the fruit fly has identified Rac, a Rho family GTPase whose activity increases after learning to promote forgetting. Manipulating its activity bidirectionally affects forgetting but leaves learning intact (5). After a single training session during which odor and electric shock are paired, 2 distinct components of memory are formed, ASM and ARM, defined by their sensitivity to cold shock-induced anesthesia (1). These 2 types of memory differ from each other in their decay kinetics. In brief, ASM is labile and decays relatively fast, while ARM is more stable and can last more than 1 d. ASM and ARM also differ in terms of their molecular mechanisms and neuronal circuitry (2–4). Rac specifically is required for the decay of labile ASM, while Cdc42, another Rho family member, is required for the decay of ARM (6). Both Rho family members are well-known for their critical roles in cell migration via regulation of actin cytoskeleton assembly (11, 12). The downstream components of these signaling cascades, however, have been unclear.

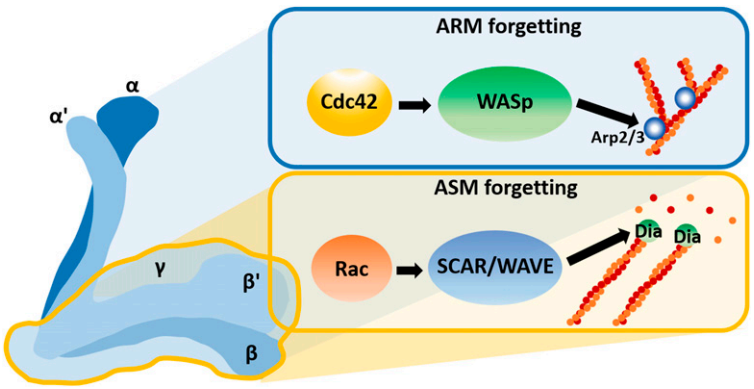

Fig. 1. Different actin remodeling pathways involved with ARM and ASM active decay. Forgetting of ASM requires Rac-SCAR/WAVE-Dia signaling and linear actin polymerization in γ KCs. Forgetting of ARM is dependent on Cdc42-WASp-Arp2/3 signaling and branched actin polymerization.

By adult-specific manipulation of genes, Gao et al. (7) found that the SCAR/WAVE complex is downstream of Rac1, while WASp is downstream of Cdc42 (Fig. 1). Previous studies have shown that Arp2/3 is downstream of SCAR and WASp (13), so Gao et al. also evaluated a role for Arp2/3 in forgetting. Surprisingly,

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they found that Arp2/3 is involved only in decay of ARM but not of ASM. Pharmacological inhibition of Arp2/3 not only specifically enhanced 6-h ARM in wild-type flies but also counteracted the increased decay rate caused by constitutive activation of Cdc42. Gao et al. (7) also discovered that formin (*Diaphanous*) is downstream of Rac and SCAR/WAVE. Feeding flies with SMIFH2, an inhibitor of formin-dependent actin polymerization, is sufficient to rescue the decreased ASM in flies with Rac or SCAR overexpression. The results clearly demonstrate 2 distinct molecular mechanisms of actin remodeling underlying the decays of ASM and ARM.

The implications of this study are profound. Arp2/3 and formin are well-known nucleators for branched and linear actin polymerization, respectively. That these 2 aspects of actin polymerization distinguish ASM from ARM raises intriguing questions about the synaptic morphologies presumably associated with these memory components. To address this question, however, we first need to know where to look.

Previous work has shown that Rac-dependent ASM forgetting and Cdc42-dependent ARM forgetting are located in the mushroom body (MB), a neuroanatomical structure of the adult brain composed of about 2,500 Kenyon cells (KCs) per hemisphere. Traditionally, MB neurons have been divided into 3 main subtypes: αβ, α′β′, and γ. In this study, Gao et al. (7) narrowed down and localized the ASM forgetting to γ neurons. However, they could not further localize ARM forgetting into specific KC subtypes (Fig. 1). By comparing the MB subtypes required for memory formation and forgetting, the results provide interesting insights into a fundamental question of forgetting: Does memory decay occur molecularly in the same neurons that encode the information or, alternatively, does forgetting involve other independent neurons which affect memory, maybe through neural competition or interference? Several pieces of evidence support the former notion. First, retrieval of ASM likely requires output from γ KCs (14), which is consistent with the location of Rac-dependent ASM decay. Second, both transgenic rescue experiments and manipulations that block neurotransmission show that ARM is encoded within all 3 different subtypes of KCs (4, 15, 16). This may be the reason why manipulating forgetting in a single type of KCs is not sufficient to enhance ARM. Future studies that connect these forgetting mechanisms with neuronal responses to the conditioned odor may distinguish these alternative models.

Extrapolating from the finding of Gao et al., we now might expect that all forms of memory (short-term memory, ASM, ARM, and long-term memory) will have different signal cascades associated with active memory decay in distinct underlying circuits.

ASM and ARM are likely located in the same set of KCs or in separate sets of KCs. If ASM and ARM decay occurs in the same KCs, then these 2 forgetting processes must be distinguished either temporally or spatially (or both). The signal cascade underlying ASM, for instance, may be induced during or soon after learning, while the signaling cascade underlying ARM may be induced more slowly. Alternatively, these signaling cascades might occur in the same neurons but in different subcellular locations. To that end, it is intriguing to speculate that these signaling cascades may parse into different synaptic fields associated with dopaminergic innervation of KCs (17). Importantly, we expect that superresolution microscopy might provide clarity to this issue (18). Extrapolating from the finding of Gao et al. (7), we now might expect that all forms of memory (short-term memory, ASM, ARM, and long-term memory) will have different signal cascades associated with active memory decay in distinct underlying circuits. By understanding the essential molecules involved in memory decay, we may be able to develop drugs targeting specific aspects of memory loss.

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