a transcription factor that regulates p53 transcription, or whether Dronc has an unknown biochemical activity that alters transcription in a protease-independent manner. It is not clear what happens to caspase substrates in undead cells, and, if caspase substrates are cleaved, whether or not they are completely degraded. Do undead cells maintain epithelial structures such as cell polarity and cell junctions, and could the presence or absence of these characteristics contribute to their capacity to regenerate a tissue? It is curious that undead cells do not appear to be present at earlier stages in development even though the factors that promote their formation are expressed days earlier, suggesting that unknown mechanisms may exist to protect imaginal cells. Finally, it is important to determine the growth signal that is produced by undead cells. Recent work indicates that *wg* function is not required for tissue overgrowth [20], and, while Dpp induction occurs in *wg* mutant imaginal discs, Wells *et al.* [5] show that Wg and Dpp targets are downregulated in undead cells. Clearly, much work is required to understand how decisions of life and death are regulated in the context of animal development, but for now this study provides a significant advance by showing that killers can serve as guardian angels that facilitate the repair of damaged tissues.

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Nursing Behavior: Remembrance of Things Past

Successful suckling is vital to the survival of mammalian newborns. In many mammals, nursing behavior is triggered by maternally derived odors. Such odors may also promote the learned association of odorant cues present in the environment during nursing.

Nirao M. Shah

A mammalian newborn needs to nurse soon after birth, as it relies exclusively on milk from the mother for nourishment. In most mammals, the young navigate to the mammary glands without physical assistance from the mother and proceed to suckle effortlessly [1]. The complexity inherent in navigating to and grasping the nipple suggests that this innate response may benefit from learned associations that permit more efficient nursing [2]. Recent work in the rabbit [3,4], including work published in this issue of *Current Biology* [4], sheds light on learning promoted by cues that trigger suckling.

Newborns of many species display innate, species-specific behaviors to elicit food from the parents. For example, thrush nestlings present a wide open mouth — the gaping reaction — to their parent, who then deposits food into the oral cavity [5]. In this case, the nestlings gape in response to the particular visual profile displayed by adult thrushes. Mammalian newborns initiate suckling attempts in response to maternal cues. In many mammals, including rodents and rabbits, olfactory cues play an essential role in initiating nursing [1]. The response of the lactating mother is

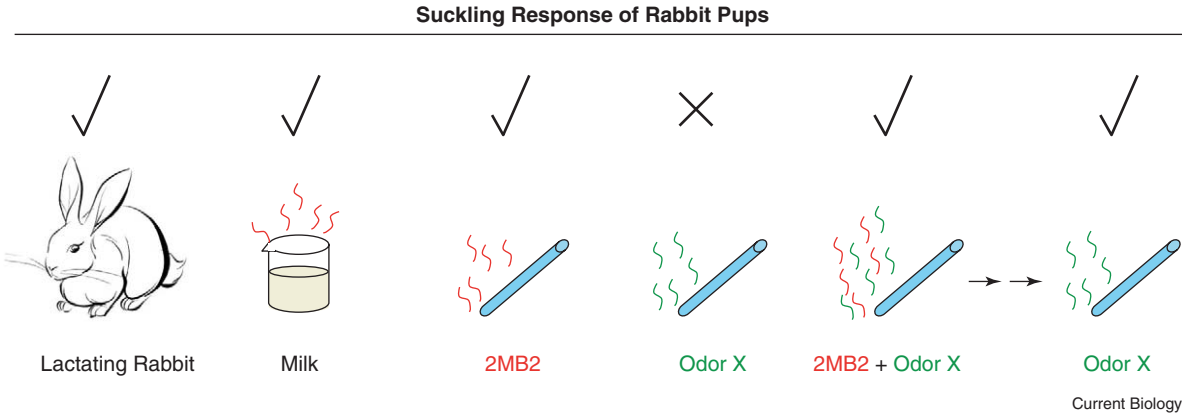

Figure 1. The rabbit suckling pheromone can effect learning of associated odors.

Rabbit pups efficiently locate the mother and initiate suckling within a few seconds. This suckling behavior is triggered by a volatile pheromone in milk, 2MB2 [3]. Remarkably, pups display the typical search and locate response to a glass rod when it is coated with 2MB2. Such a response is not displayed when irrelevant odors (Odor X) coat the glass rod. However, rabbit pups will respond to a paired presentation of Odor X (ethyl acetoacetate or furaneol in this particular case [4]) and 2MB2. Several hours after such a paired presentation, the pups will now also initiate the search and grasp response to Odor X alone [4]. In other words, 2MB2 can function as an unconditioned stimulus to elicit the suckling response from Odor X, the conditioned stimulus. (Schematic courtesy of Melody Wu.)

the milk ejection reflex or the milk let-down.

In most cases, the mother appears to be the sole source of odorants that trigger suckling. For example, washing the nipples of lactating rats abolishes the ability of pups to initiate nursing [1]. However, suckling is reinstated after the nipples have been painted with the wash distillate. Such olfactory signatures that communicate the social or reproductive status of an individual are called pheromones. Pheromones are thought to elicit innate behavioral or endocrinological responses in conspecifics [6–8]. In the case of nursing, it is mammary pheromones that enable the newborn to locate the nipple.

What is the chemical nature of pheromones? Despite the ubiquity of pheromonal communication in the animal kingdom, only a few pheromones have been purified to homogeneity. Even fewer have been demonstrated to be necessary and sufficient in recapitulating the response elicited by the source from which the putative pheromone was purified. Identified pheromones constitute a chemically diverse class of organic molecules, ranging from simple hydrocarbons to small peptides [9]. It is against this backdrop that Schaal *et al.* [3] in an elegant series of experiments, identified a mammary pheromone that triggers characteristic suckling responses in newborn rabbits.

Previous work had demonstrated that the rabbit mammary pheromone is a volatile present in the milk, and that it elicited a characteristic series of search movements of the head followed by nipple-grasping within a few seconds [10]. The rapidity of this search strategy is essential, as access to the nursing doe is limited to one contact per day, lasting about 5 minutes at most [11]. Using a combination of gas chromatography and mass spectrometry on milk volatiles, Schaal *et al.* [3] identified 2-methylbut-2-enal (2MB2) as the mammary pheromone, which effectively triggered the head searching and grasping movements of pups (Figure 1), [3]. Extraction of volatiles from milk abolished the search and grasp response, which was restored upon supplementing milk with 2MB2. The production of and response to 2MB2 is species-specific. Finally, 2MB2 can trigger the typical behavioral repertoire immediately from pups delivered by Caesarean section, demonstrating that the response to 2MB2 is innate and independent of postnatal experience.

Now a study by the same group provides a novel twist on our understanding of pheromonal action [4]. This work provides convincing evidence that 2MB2 can function as an unconditioned stimulus to trigger the search and grasp behavior in response to a conditioned stimulus. In other words, paired presentation of 2MB2 with a previously irrelevant odor (in this case, ethyl acetoacetate or furaneol) permits the activation of the head search and oral grasping response to subsequent presentation of the second odor alone (Figure 1). This response to the conditioned stimulus consolidates within 8 hours and persists for up to 72 hours after the initial pairing. Remarkably, the conditioned stimulus can be learned after just a single pairing with 2MB2 for 15 seconds. The association is specific to the odor paired with 2MB2, and the pups can learn to associate multiple odors with 2MB2 in successive trials. Learning of the conditioned stimulus can occur in the absence of prior nursing, providing evidence that 2MB2 may act as the primary reinforcer in this process.

The notion that a suckling pheromone can rapidly induce associative learning and impart salience to previously irrelevant odors makes intuitive sense. While pups may initially respond to 2MB2 emanating from the mother, it seems advantageous to rapidly associate other maternal cues with nursing as well. In real life, such conditioned stimuli could include not only odorants, but also tactile

cues such as the mother's fur. The authors demonstrate that pups that suckle mothers with odorants painted on the doe's belly subsequently perform search and grasp to the conditioned stimulus alone. Is 2MB2 as effective as nursing in promoting the learned association with the conditioned stimulus? This is difficult to answer because the authors employed concentrations of the conditioned stimuli at which the proportion of responding pups reaches saturation (~90%). It should be feasible to resolve this issue in future studies. In any event, these data provide strong evidence that the rabbit suckling pheromone can promote associative learning.

The present study demonstrates that suckling, an innate behavior, can be conditioned by a single pheromone. Previous work has demonstrated that, in many mammals, chemosensory neurons in the nose are segregated into the main olfactory epithelium and the vomeronasal organ. Activation of main olfactory epithelium neurons by odors is thought to elicit measured behavioral output, whereas the vomeronasal organ is thought to recognize pheromones which trigger innate, stereotypical responses [12]. Recent findings, however, suggest that this model is an oversimplification. For example, a putative pheromone in male mouse urine that serves as an attractant to females is likely recognized by sensory neurons in the main olfactory epithelium [13]. In addition, innate behaviors such as mating and aggression, which are thought to be triggered by pheromonal cues, appear to require a functional olfactory epithelium [14,15]. Finally, suckling requires a functional main olfactory epithelium but not an intact vomeronasal organ in many animals, including rabbits and mice [16,17]. Taken together, these data suggest that the strict segregation of function originally posited for the main olfactory epithelium and the vomeronasal organ may not be entirely accurate [18]. An interesting question for the future is whether associative learning can be promoted by all pheromones or whether this property is the exclusive domain of pheromones recognized by the main olfactory epithelium.

The study by Coureaud *et al.* [4] immediately suggests interesting directions for future research. What is the neural locus for learning the paired odor? The main olfactory epithelium expresses a large family of genes encoding G-protein coupled olfactory receptors [19]. Which olfactory receptors recognize 2MB2, and is the entire complement of receptors for 2MB2 required for learning the paired odor? Do human infants learn to pair other cues with nursing? Olfaction is thought to play a minor role in initiating suckling in human infants (cf. rooting reflex) [1]. However, this does not preclude associative learning of previously irrelevant cues with nursing in humans. After all, Romulus, the mythical founder of Rome, was said to have been nursed by a wolf and fed by Picus, a woodpecker.

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Replicative Helicases: A Staircase with a Twist

The first crystal structure of a ring helicase encircling single-stranded DNA reveals a mechanism for ATP-dependent DNA translocation.

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Following their elucidation of the structure of DNA, Watson and Crick were quick to realise its important implications for DNA replication. As they appreciated, replication of helically intertwined DNA strands represents a major topological challenge [1]. One problem is that the information to be copied is locked within