



ANIMAL BEHAVIOR

Culture and conformity shape fruitfly mating

Potent social learning sustains the inheritance of mating preferences over generations

By **Andrew Whiten**

Culture pervades every aspect of human lives, its achievements providing a compelling explanation for our species' domination of the planet (1). Defined as the matrix of traditions built by previous generations and inherited by social learning, culture was long thought to be uniquely human. In recent decades, however, mounting evidence for culture defined in this way has accumulated for numerous vertebrate species and an expanding diversity of behaviors (2). Examples include migratory knowledge in bighorn sheep (3); foraging techniques in humpback whales (4), great tits (5), and bumble bees (6); and tool use in apes (2). These discoveries suggest that although human culture has developed unprecedented complexities, it evolved from more elementary forms shared with other species. On page 1025 of this issue, Danchin *et al.* (7) offer evidence that a species that may surprise many should be added to this growing animal "culture club": the humble fruitfly.

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They show that the mating preferences of female fruitflies are strongly influenced by the existing preferences they observe in other females, generating traditions that are repeatedly passed on to others and spread in the population. Animal culture may be a much more widespread phenomenon than hitherto acknowledged.

The study of Danchin *et al.* offers further surprises. The most notable concerns conformity—the tendency to copy whatever a majority of one's companions are seen to do, which has long been known to take extreme forms in our own hypercultural species. In a classic human experiment, individuals were invited to judge which of several lines matched the length of a target line (8). Although the answer was perceptually obvious, the experimenter arranged that before the subjects voiced their judgment, several stooges placed by the experimenter said it was a different line. Many subjects then conformed in echoing this blatantly false opinion. We humans are prone to conform to many well-established customs, a motivation often interpreted as an adaptive element of our deeply cultural natures (1, 9).

To test for conformity in fruitflies, Danchin *et al.* placed female fruitflies in a hexagonal

Virgin female fruitflies' choice of mating partner is strongly biased toward the characteristics of males that a majority of already-mating females prefer, sustaining mate-choice "cultures."

chamber, encircled by six compartments in each of which they could observe a female fly mating with a male dusted with either pink or green coloring, while the male of the alternative color merely stood by. For some females, all six mating males were pink; for others, all were green. Other females experienced displays with varying proportions of pink versus green males mating, or a neutral experience with equal proportions.

Females were then tested for their mating preferences. As expected, those exposed to the neutral case chose at random, whereas if they had seen mating exclusively with pink males they tended to choose pink, and similarly for those that had seen mating with only green males. Remarkably, however, the relationship between mating preferences witnessed and mating preferences subsequently enacted was far from linear, for as soon as the deviation from equality was as little as 60:40, females echoed that bias in their mate choices as much as if it were 100:0. The intensity of this effect exceeds any in the limited, and debated (10), studies reporting such conformist transmission in birds (6) and fish (11).

Such an exaggerated copying bias has been called "hyperconformity" (12). Its occurrence, as earlier demonstrated conceptually and mathematically for humans (9), is of considerable importance for cultural evolutionary theory, because it has the potential to maintain traditional preferences across generations (9, 12). In the case of genetically inherited traits, Fisher (13) showed that sexual selection, in which females prefer one male characteristic over another, can lead to a runaway evolutionary spiral as the favored male characteristic becomes increasingly common in subsequent generations, along with female preferences for it. Hyperconformity could generate an equivalent runaway cultural effect. If female preferences are selected culturally, along with genetic selection associated with the preferred male characteristic, then genetic and cultural inheritance might interact; this is a question for future research.

To empirically explore the scope for transmission across cultural generations in the fruitflies, Danchin *et al.* used the hexagonal chamber in a different way. This time, a dozen virgin females were placed in the central arena and could observe six males all of the same color, each mating with a female in the surrounding compartments. The first six of the observer females to successfully mate with a male, whether pink or green, then became the "demonstrators" for a further dozen

virgin females in the central arena. Repeating this process created a “cultural transmission chain” between “cultural generations,” which showed that the original color bias was sustained for an average of about eight cultural generations before it faded. This effect exceeded what would be expected if preferences occurred by chance. However, it seems far from the long-term stability that hyperconformity might predict.

The authors suggest that this is because, given copying errors, a population of just six per generation is insufficient for cultural stability. A mathematical model incorporating their findings predicted outcomes in larger populations, which in nature may number in the hundreds. Even with just 30 to 40 individuals, the number of generations the model predicted to display stable preferences rose exponentially into the hundreds and even thousands.

Like all models, these results depend on an array of assumptions and inputs. They await further empirical testing. Experiments directly testing the effect of group sizes greater than 10 on conformity have been rare even for human subjects, and are yet to be explored in animal studies (6, 11). Just one study of primates, focused on transmission of large, group-wide preferences, reported a strong conformity effect (14). Danchin *et al.* offer their model in lieu of empirical studies, which are considered impractical with large fruitfly populations. But the short generation time of these tiny flies permits evolution to be traced over scores of generations (15). If founder populations similar to but larger than those created for the present study's transmission chains are created and allowed to reproduce, perhaps cultural transmission may be tracked across biological generations, as the population rapidly expands. The potential for examining interactions between the effects of genetic and cultural selection and inheritance in this classic model species is exciting indeed. ■

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CANCER BIOLOGY

Metastases go with the flow

Blood flow mechanics influence metastatic efficiency

By Jacky G. Goetz^{1,2,3}

To colonize distant organs and thus disseminate throughout the body, cancer cells and associated factors exploit several fluids for transport. Recently, circulating tumor cells (CTCs) were found to survive and exploit the inner biomechanics of the bloodstream to foster tumor metastasis (1, 2). Thus, in addition to using both the blood and lymphatic circulation as a means to travel throughout the body (3–5), the underlying forces allow CTCs to seed distant metastases. The contribution of fluids, particularly vascular flow mechanics, and physical constraints raises interesting questions about the biology of metastasis.

According to the “seed and soil” theory of metastasis, CTCs survive and establish growing colonies in distant organs within environments that are compatible with their growth. Successful metastatic outgrowth involves several steps, including organ infiltration, immune escape, growth, and survival in supportive niches (6). The metastatic potential of tumor cells is also tightly linked to body fluids that favor their journey to distant organs (1, 2). CTCs disseminate early through the lymphatic circulation to spread to tumor-draining lymph nodes, which often correlates with reduced survival. Although removal of these metastatic lymph nodes has shown no benefit on overall survival of patients with, for example, melanoma (7), as well as other types of cancer, lymph nodes were recently demonstrated to be intermediate steps for metastases in mice (3–5). Efficient CTC colonization of distant organs occurs mostly via the blood circulation (6) (see the figure).

On their way to blood vessels (intravasation), invading tumor cells encounter mechanical pressures imposed by architectural constraints of tissues. In particular, space constraints induce nuclear squeezing, which challenges the integrity of the nucleus and triggers genomic rearrangements that might foster metastatic potential (8). It is likely that such pressure also applies to CTCs during arrest in distant sites, extravasation (exiting vessels), and metastatic outgrowth.

Both individual and rare groups of invasive carcinoma cells enter the tumor-

associated vasculature (9, 10). Although it is unclear whether clusters of CTCs can transfer from the lymphatic to the blood circulation (4, 5), a mixture of single and clumps of CTCs disseminate throughout the body before they reach a distant organ (10). In the circulation, CTCs face multiple physical constraints that will directly affect successful seeding. Single CTCs need to overcome the mechanical stress imposed by shear forces, likely to induce apoptosis (programmed cell death), before they lodge in a capillary in a distant organ. This mechanical stress can considerably reduce the ability of CTCs to successfully initiate the growth of a metastatic colony. When shed as clumps and traveling as clusters, CTCs are more resistant to shear forces and cytotoxic immune cells (10). They are also more likely to become lodged in microvessels in distant organs before seeding metastatic colonies (10). Indeed, mechanical constraints imposed by vessel architecture and size contribute to the intravascular arrest of CTCs (11), and clusters of CTCs are rapidly trapped in tiny capillaries. Intravital imaging in living mice recently demonstrated that CTC clusters could also form mechanically, as a consequence of the initial arrest of a single CTC (12). Nevertheless, some clusters of CTCs avoid lodging and are capable of squeezing through capillary-sized vessels as a group (13). Such clusters reduce their hydrodynamic resistance by forming single-file structures that rely on intercellular adhesive interactions. However, whether extravasation from blood vessels of clusters of CTCs is more efficient than single CTCs remains to be demonstrated.

In addition to mechanical trapping imposed by vessel architecture and size, single or clusters of CTCs also rely on blood flow, their adhesive potential, and blood components (such as platelets) to arrest successfully at distant sites (2). Indeed, although physical restriction can explain how CTCs become lodged in a capillary bed downstream of the tumor along the anatomical route of the blood circulation, it does not explain the sites of metastasis, which are specific for each cancer type (organotropism). Recent observations demonstrate that both the efficiency and location of CTCs becoming lodged in distant sites correlate with the presence of permissive flow regimes in some vascular regions (2). The transit of CTCs in the blood circulation is stopped when their adhesive capacity overcomes the shear forces imposed

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