Still no evidence for transgenerational inheritance or absence of epigenetic reprogramming in the honey bee

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In multicellular organisms, cell identity can be maintained through DNA methylation patterns that control gene expression (1). These and other epigenetic marks installed during development require erasure to facilitate zygote totipotency (2). Otherwise, epigenetic information may be transferred, at least transiently, across generations (1, 2). In mammals, epigenetic reprogramming during germ-cell formation and early embryogenesis ensures zygote totipotency (2, 3). Yet-to-be-explored mechanisms appear to exist in other groups (2). This is expected given that zygote totipotency is a general phenomenon (4). In addition, Weismann's germ–soma divide, manifest in vertebrate animals (1, 2) and subtly recognized for other groups (5, 6), offers substantial, though not impregnable, protection to the germline, from the soma's lifetime experience. Apparently, natural selection prioritized a "fresh start" for zygote genomes, zealously protecting them from mutations and acquired epigenetic marks (2).

A recent study reports intergenerational transfer of DNA methylation patterns in honey bees (7). The authors found greater similarity of methylomes within patrilines (a drone, its semen, and its daughters) than between patrilines and interpreted these findings as an indication of the absence of DNA-methylation reprogramming. Thus, they conclude that, in honey bees, methylation marks are stably transferred across generations in both germline and somatic tissues and that this process (i.e., transgenerational inheritance) could be widespread and important for producing adaptive change (7).

Care should be taken when interpreting these findings as proof for transgenerational inheritance serving an adaptive role in evolution. Stable inheritance of epimutations still awaits robust demonstration, even for acclaimed naturally occurring epimutants (see refs. 2 and 8 on toadflax's *Lcyc* locus). To bring about evolutionary change, the transmission of environmentally induced epigenetic marks would require high fidelity and consistency. Otherwise, the so-called epialleles would disappear in the following generations, even when selectively favored, simply because the mechanism failed to reproduce the epigenetic mark. If in ref. 7 the methylomes were transferred as non-DNA information via the sperm, the process lacked the necessary fidelity for stable transmission. Epigenetic marks could come from either parent, and the authors estimated that the proportion of methylated CpGs that were inherited specifically from fathers to daughters was between 18 and 29%. Only a fraction of the methylated regions was considered to have been thus transferred to the following generation. If this fraction corresponds to different genome regions in each generation, then the inheritance pattern would be quickly lost.

Also, epigenetic marks respond to both environmental and genetic factors (1, 2), so that greater methylome similarity within patrilines is also expected from sequence-based heredity. Indeed, sequence polymorphism is thought to be a major contributor to DNA methylation patterns in honey bees (9, 10). Thus, evidence of methylomes grouping nicely according to genetic relatedness (i.e., patrilines) does not imply direct transfer of methylomes, as the authors suggest. Finally, claims for true transgenerational inheritance require examination of F2 and subsequent generations (2, 3), which was not performed in the honey-bee study.

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