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Emerging developmental genetic model systems in holometabolous insects

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The number of insect species that are amenable to functional genetic studies is growing rapidly and provides many new research opportunities in developmental and evolutionary biology. The holometabolous insects represent a disproportionate percentage of animal diversity and are thus well positioned to provide model species for a wide variety of developmental processes. Here we discuss emerging holometabolous models, and review some recent breakthroughs. For example, flies and midges were found to use structurally unrelated long-range pattern organizers, butterflies and moths revealed extensive pattern formation during oogenesis, new imaging possibilities in the flour beetle *Tribolium castaneum* showed how embryos break free of their extraembryonic membranes, and the complex genetics governing interspecies difference in head shape were revealed in *Nasonia* wasps.

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Introduction

The breakthrough in developmental genetics in the late 1970s and 1980s was to a large extent driven by research on a single holometabolous insect, the 'fruit fly' (vinegar fly) *Drosophila melanogaster* [1]. With the discovery of the homeobox, research in this species also inaugurated the molecular phase of evolutionary developmental biology [2,3], which remains a thriving field in the 21st century [4]. In the 1990s, results obtained in *Drosophila* became the starting point for systematically exploring the developmental gene network in other insects and beyond [5–9].

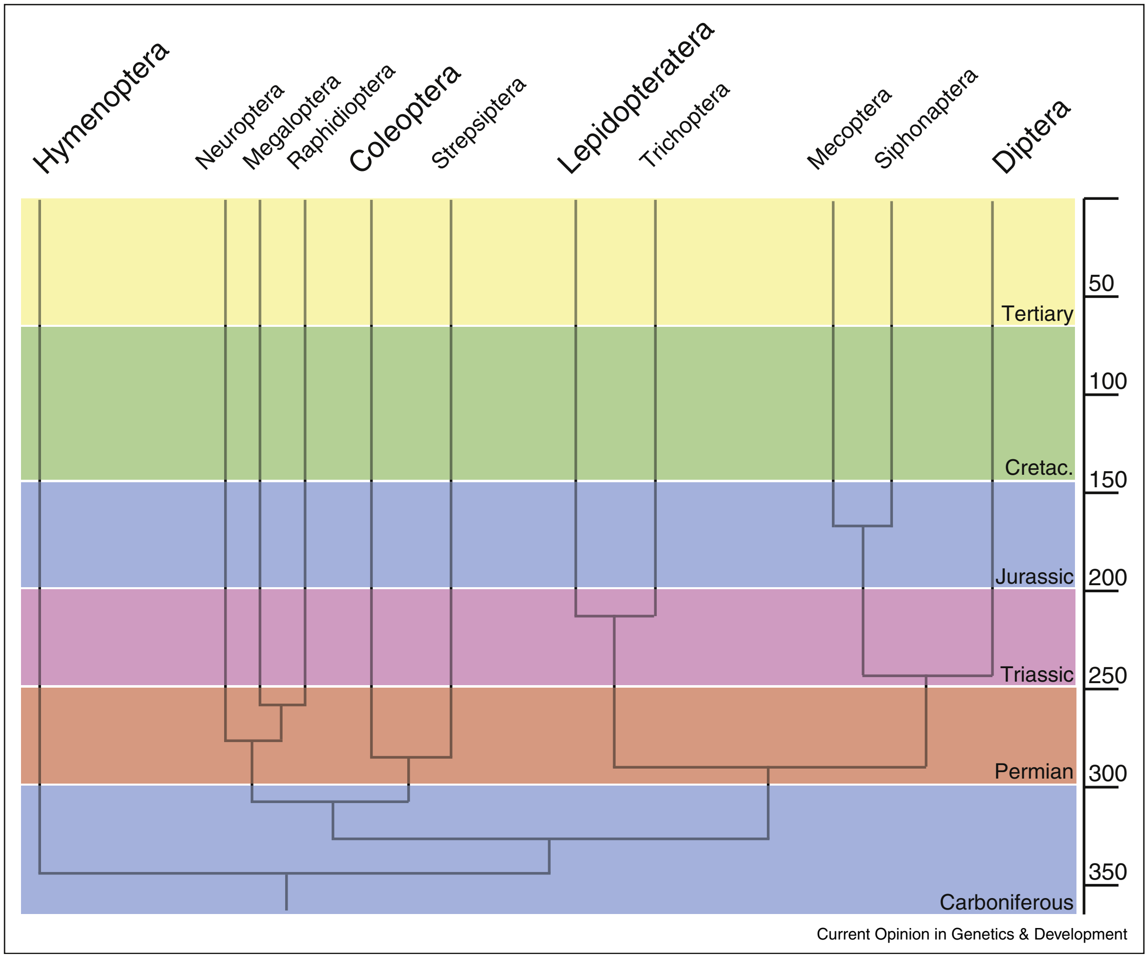
The pace with which new experimental insect systems and research questions have been added to the rapidly growing field of comparative developmental genetics has been accelerating in the last 20 years, owing to important technological advances, such as RNA interference (RNAi) [10,11], next-generation sequencing (NGS) [12], and genome editing technology [13,14]. But, owing to other challenges such as culture techniques, access to embryos, sample transparency, eggshell removal, or delivery of nucleic acids or proteins to the tissues of interest, the number of insect species in which developmental gene networks have been examined with functional approaches is still rather small. Here, we review progress with experimental systems that belong to the extremely large group of holometabolous insects, which make up roughly half of all animal and plant species described and about 83% of the insects [15]. The Holometabola form a monophyletic group [16] whose defining developmental feature is the specialized larva, which is probably homologous to the less-specialized nymph of hemimetabolous insects [17–20]. Comparative developmental genetic studies have been carried out on all life stages but mostly on embryos. As embryologists, we focus here on species that are suitable for functional genetic analysis in embryos. The examples that we choose to highlight belong to the four dominant holometabolous insect orders Diptera (midges, flies), Lepidoptera (moths, butterflies), Coleoptera (beetles), and Hymenoptera (sawflies, wasps, bees, ants).

Diptera

The Diptera include approximately 152,000 named species of midges and flies that evolved through several episodes of accelerated radiation since their late Permian origin around 250 million years ago (Figure 1, [21]). With the 'fruit fly' *D. melanogaster*, the dipterans also include one of the most studied genetic model organisms of animal development (http://flybase.org/). They are therefore exceptionally well suited for studying the evolution of developmental mechanisms at the molecular level. This has long been recognized in the *Drosophila* field where, by exploiting genetic hybridization approaches and germ line transformation technology, multiple *Drosophila* species have played an important role in understanding the genetic basis of evolutionary parallelisms and novelties (e.g. [22–26,27•,28,29•]).

Additional dipteran species have been developed as developmental genetic models because they promise insights into the evolutionary origin of *Drosophila* traits,

Figure 1



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Phylogeny of Holometabola. Branch points and divergence times are based [16]. Note that the divergence times are subject to ongoing debate and the fossil record of some groups (e.g. Hymenoptera) begins much later [15].

are interesting in their own right, or have translational potential in applied entomology. Here, we focus on distant relatives of *Drosophila* that have been shown to be amenable to developmental genetic studies at the functional level and review some of the reasons for which they have caught the eye of evolutionary developmental biologists.

Nematocera

The midges ('Nematocera') represent multiple basal lineages of dipterans that originated early in the Triassic (247-208 MYA). Best known among them are the mosquitoes, which belong to the monophyletic Culicomorpha, one of the four major branches of lower dipterans. Work on the developmental gene network in mosquito embryos has high translational potential (e.g. [30–32]), but is difficult because the pigmented eggshell of the most important disease vectors in this group is difficult to remove and poses a significant obstacle to embryological work.

Nevertheless, the developmental gene network of a malaria vector, *Anopheles gambiae*, has been examined in a series of gene expression studies [33–37]. More recently, *Aedes agypti*, a vector of Dengue, Yellow fever and Zika, has emerged as one of the first mosquito models in which the embryonic gene network has been probed, not only at the level of gene expression, but also at the level of gene function, using gene knockdown through RNA interference [38–42]. The potential of *A. aegypti* as a developmental genetic model organism was recently demonstrated in an impressive study that combined expression profiling, germ line transformation, genome editing, and genetic approaches to identify a dominant male-determining factor in this species [43••].

The non-biting chironomids are distant relatives of mosquitoes on the Culicomorpha branch that are more closely related to the disease-transmitting black flies (Simulium). Chironomids have a long history in developmental biology. We owe to this group the first detailed description of