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Mating induces developmental changes in the insect female reproductive tract

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In response to mating, the *Drosophila* female undergoes a series of rapid molecular, morphological, behavioral and physiological changes. Studies in *Drosophila* and other organisms have shown that stimuli received during courtship and copulation, sperm, and seminal fluid are needed for the full mating response and thus reproductive success. Very little is known, however, about how females respond to these male-derived stimuli/factors at the molecular level. More specifically, it is unclear what mechanisms regulate and mediate the mating response, how the signals received during mating are integrated and processed, and what network of molecules are essential for a successful mating response. Moreover, it is yet to be determined whether the rapid transition of the reproductive tract induced by mating is a general phenomenon in insects. This review highlights current knowledge and advances on the developmental switch that rapidly transitions the female from the 'unmated' to 'mated' state.

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Introduction

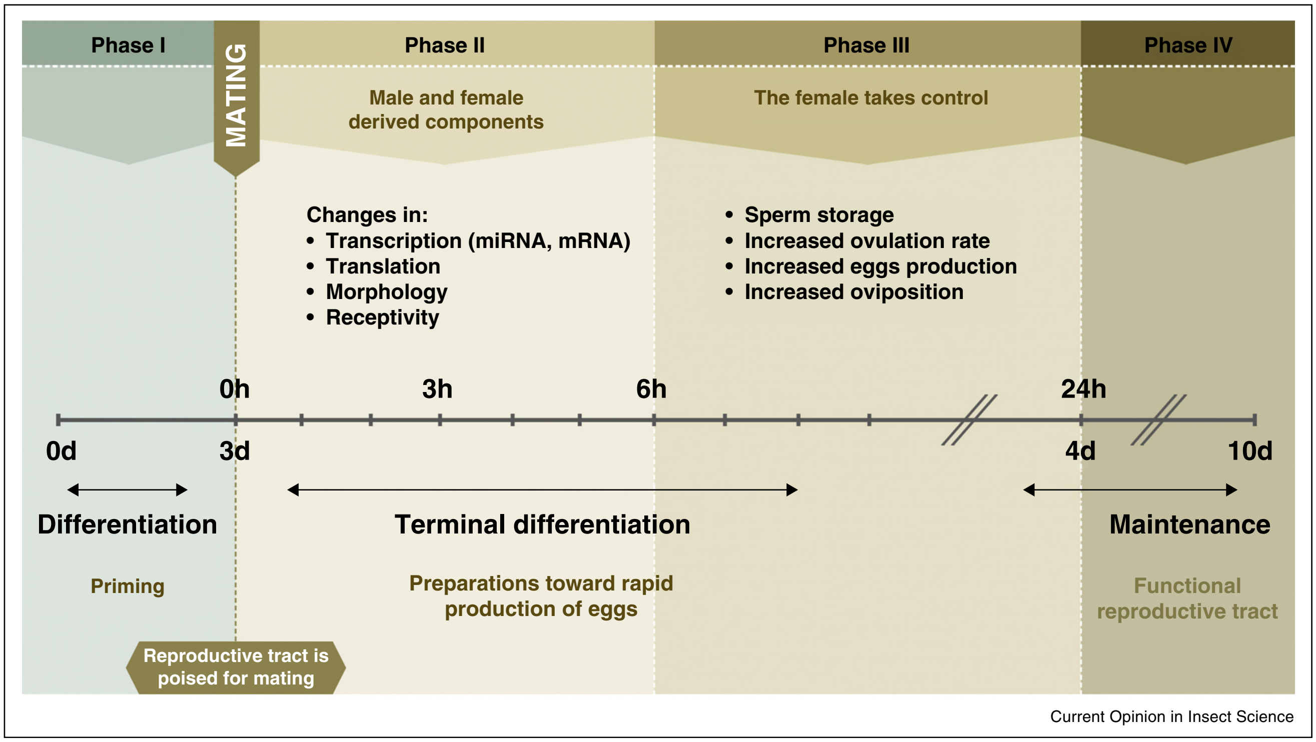
The female reproductive system plays several crucial roles in organisms with internal fertilization: it provides an environment the egg and sperm require for maturation prior to gamete fusion, facilitates fertilization, and supports embryo development [1–4]. *Drosophila melanogaster*, as a model system for studying how essential biological processes are regulated, has played a major role in unraveling the molecular mechanisms of development and physiology [5,6]. *Drosophila* remains the most important model system to study insect development and is the main reference species to which other emerging insect model organisms are compared [7,8]. Numerous studies in *Drosophila* and other organisms have shown that sperm, seminal fluid and other signals received during mating alter female behavior and physiology postmating, and that these changes increase the reproductive success of both the male and female [9–24]. Seminal fluid is composed of sperm and components secreted by the accessory glands, ejaculatory duct, and ejaculatory bulb of the male reproductive tract. Each of these seminal fluid components play an essential role in male and female reproductive success [10,23,25]. Despite this wealth of knowledge, little is known about how females respond to these male-derived stimuli/factors at the molecular level and more specifically what mechanisms regulate and mediate the mating response, how the signals received during mating are integrated and processed, and what network of molecules are essential for a successful mating response. In this review, we will focus on the female response in the first 24 hours postmating, highlighting the developmental switch that transitions the female from an 'unmated' to 'mated' state. We will discuss possible mechanisms through which external male-delivered signals modulate this developmental switch.

The mating response of *D. melanogaster*

In response to mating, the *Drosophila* female (Figure 1) exhibits an increase in ovulation and oviposition rate [26–29] a decrease in female receptivity to courting males [30]; storage of sperm [31,32]; and a decrease in female life span [26,33,34]. Many of the stimuli that initiate the female response are in the seminal fluid, a major component of which is the male accessory gland proteins (accessory glands proteins, Acps). While it is well-established that Acps are essential for triggering several postmating changes in the female [10,19,26,35], it is only recently, with the advent of cellular and molecular analyses of the female postmating, that we have begun to understand how these signals transform the female from an 'unmated' to 'mated' state.

At the morphological level, mating induces immediately after the start of copulation a series of conformational and size changes in the uterus and the oviduct which in part aid sperm to storage and allow the release and movement of oocytes through the tract [21,36•,37]. Additionally, mating induces tissue-wide differentiation in epithelia, muscle and nerve tissues. In many epithelia, one of the last steps of differentiation is the development of a layer of extracellular matrix (ECM) that covers the apical and/or basal membranes and the associated development of

Figure 1



Schematic model of the female *Drosophila* mating response. **Phase I** — the first few days post-eclosion, the reproductive system undergoes the first phase of differentiation, after which the reproductive tract is developmentally poised for a rapid response to an extrinsic cue (mating). **Phase II** — terminal differentiation is induced by stimuli (e.g. odorants, auditory, vision and tactile) perceived during courtship and largely by the transfer of seminal fluid proteins and sperm received during copulation. These stimuli and factors are necessary for the full female mating response [9–24]. In response to mating, the *Drosophila* female undergoes a series of rapid molecular, morphological, behavioral and physiological changes. During the initial phase, mating induces decrease or increase in the level of many miRNAs, mRNA transcripts and proteins. Other striking changes are also seen in reproductive tract morphology and female physiology. During this phase sperm reaches storage and ovulation begins. In addition, female receptivity to courting males decreases and persists for several days [9,17,19,21,37]. **Phase III** — a second switch point occurs at 6 hours postmating to sustain elevated fertilization and reproduction and is influenced by the female's regulatory and physiological responses to seminal fluid components and newly stored sperm. At this time the female starts to produce and deposit eggs at high rate [20,23,37]; terminal differentiation continues along with the onset of increased egg production and deposition and terminates during this phase. **Phase IV** — Maintenance the developmental program of the reproductive tract has ended and the organ is ready to support high fertility. Different colors represent different phases of the mating response. Note that the schematic presents a clear difference between the different phases (donated by the dashed line), but the exact duration of each phase is unknown.

hemi-adherens junctions (HAJs). HAJs connect the cell cytoskeleton with the ECM and are formed in all cell surfaces that contact an ECM [38,39]. In the oviduct epithelia of mated females, the apical ECM (AECM) and the thin layer of cuticle above it have a ruffled appearance, unlike unmated females, suggesting that the AECM and cuticle have increased in surface area. It is possible that mating enhances or modulates apical secretion via the AECM. Increased apical secretion and surface of the AECM is likely to be essential for ovulation, activation and movement of eggs along the duct. Mating also increases secretion and/or deposition of the ECM in the basolateral membrane at the oviduct and brings the ECM to a threshold concentration that can support the development of HAJs [37]. Another striking postmating change observed in the oviduct epithelia is the increase in the number of HAJs along the basolateral membrane in the upper oviduct. Because one function of the HAJ is to give shape and tension to cells and tissues [39], HAJs are particularly important in the upper oviduct, where the basolateral membrane is extensively infolded. Extensive infolding allows the expansion of epithelia during passage of an egg along the narrow duct. The infolded membrane also gives rise to a highly branched intercellular space that is filled with an ECM. The muscles of the upper oviduct appear more differentiated in mated than in unmated reproductive tracts; myofibrils and z-bodies are less dense, and there is little or no basal lamina. In addition, the number of nerve terminals or boutons innervating the lateral oviducts and the common oviduct increases ~70% postmating. Interestingly, the increase is in type II boutons, which cause vesicle release