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Review

Sex-specific regulation of development, growth and metabolism

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ABSTRACT

Adult females and males of most species differ in many aspects of their morphology, physiology and behavior, in response to sex-specific selective pressures that maximize fitness. While we have an increasingly good understanding of the genetic mechanisms that initiate these differences, the sex-specific developmental trajectories that generate them are much less well understood. Here we review recent advances in the sex-specific regulation of development focusing on two models where this development is increasingly well understood: Sexual dimorphism of body size in the fruit fly *Drosophila melanogaster* and sexual dimorphism of horns in the horned beetle *Onthophagus taurus*. Because growth and development are also supported by metabolism, the regulation of sex-specific metabolism during and after development is an important aspect of the generation of female and male phenotypes. Hitherto, the study of sex-specific development has largely been independent of the study of sex-specific metabolism. Nevertheless, as we discuss in this review, recent research has begun to reveal considerable overlap in the cellular and physiological mechanisms that regulate sex-specific development and metabolism.

1. Introduction

Males and females are different. At the most elementary level, males and females differ in the size of their gametes: few large gametes in females and many small gametes in males. These differences in gamete size, however, result in fundamental differences in the reproductive strategies that optimize fitness in each sex and that are favored by selection. This in turn impacts myriad aspects of biology, resulting in sex-specific differences in adult morphology, behavior and physiology. There has been more than a century of research describing the nature of these differences in male and female form and function, and into the selective pressures that ultimately generate them. What is much less well understood, however, is how these differences arise during development and what effect they have on adult physiology and metabolism.

The goal of this paper is to review recent advances in our understanding of sex-specific development, growth and metabolism. Sex-specific development requires differences in gene expression between males and females, while sex-specific growth also implicates differences in the metabolic process that drive growth. This review will explore both the developmental-genetic and metabolic processes that generate male and female phenotype, with a particular focus on body and trait size. Rather than attempt a broad overview of these processes in all animals, however, we will largely restrict our focus to holometabolous insects, which have become primary models in the study of sex-specific development, growth and metabolism. As will become clear, many of the developmental and physiological mechanisms employed to generate female and male phenotype in holometabolous insects are extremely evolutionarily conserved, so discoveries made in these species facilitates discoveries made in other species, including our own. We will consider two exemplars of sex-specific development and growth in insects: The developmental regulation of sexual size dimorphism of body size *Drosophila* and of horn size in horned beetle (Scarabaeidae). We will then turn our attention to sex-specific differences in metabolism in *Drosophila*, particularly as it pertains to the generation and maintenance of the female versus the male body.

2. The genetics of sex-determination

In order to understand the cellular and physiological mechanisms of sex-specific development and metabolism, it is first necessary to briefly review the mechanisms underlying sex determination. Since this review is focusing primarily on sex-specific development, growth and metabolism in holometabolous insects, we will only consider these mechanisms here. Readers interested in sex determination mechanisms in other animals, particularly vertebrates, should read [1–4] for comprehensive reviews.

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The mechanisms of genotypic sex determination (GSD) in insects have been best established in *Drosophila* (Fig. 1) [5–8]. Canonically, *Drosophila* GSD is regulated by the X-chromosome to autosome ratio (X:A ratio model) [9], although more recent evidence suggests that it is regulated by the number of X chromosomes (X-counting model) in diploid cells [10]. Possession of two X chromosomes leads to the synthesis of the RNA binding protein Sex-lethal (Sxl) in females only [6,11–13]. Sxl controls both dosage compensation, through suppression of *male-specific-lethal-2* (*msl-2*) [5,14,15], and sex-specific phenotypic differentiation [12,16]. The latter is achieved by the splicing of *transformer* (*tra*) transcripts into the female form by Sxl in females only, generating functional Transformer [17–20]. Tra in turn regulates the alternative splicing of *doublesex* (*dsx*) transcripts to produce the female isoform of Dsx protein [21], which controls development of the female phenotype [22–24]. In males, where there is no Sxl and the default splicing of *tra* results in a non-functional protein, *dsx* is spliced into the male isoform, which directs development of the male phenotype [22,25,26]. The absence of Tra in males also results in the default splicing of *fruitless (fru)* pre-mRNA into a male-specific isoform, which is translated into protein and functions in the CNS to regulate male-specific behavior [27–29]. In females, Tra splices *fru* into a female-specific isoform that is not translated (although see [30] for the effect of non-sex specific isoforms of *fru* on female behavior) [28,31]. While most sex-specific development appears to be regulated via Tra, there is also increasing evidence that Sxl also directly regulates sexual dimorphism independent of Tra, including behavior [32] and body size [33]. GSD mechanisms in other insects are similar but not identical to the mechanisms in *Drosophila* [6]. In all holometabolous insects, however, *tra* is alternatively spliced to produce functional protein only in females, and its presence or absence controls alternate sex-specific splicing of *dsx* [34,35]. (The one exception to the conservation of the Tra-Dsx splicing cascade is in Lepidoptera, where *tra* has been lost and dsx splicing is regulated by a male-specific protein and a female-specific piRNA [36]).

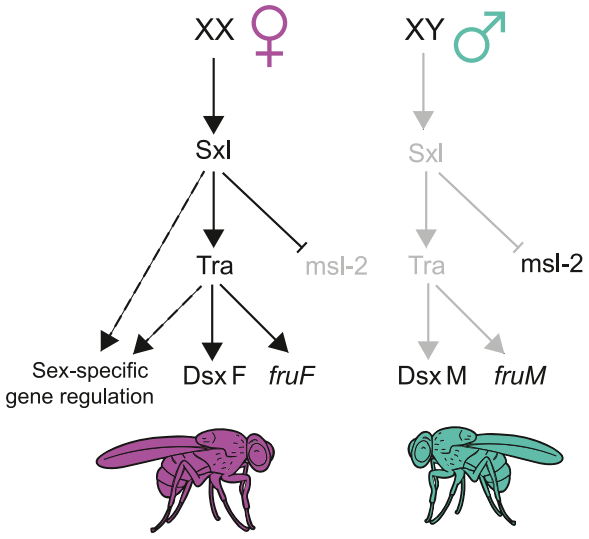

Fig. 1. Genetic sex determination cascade in *Drosophlia*. Functional parts of the cascade are shown in black, non-functional parts are shown in gray. The possession of two X chromosomes leads to the synthesis of Sxl, which splices *tra* pre-mRNA to generate a functional protein in females only. Functional Tra in turn splices *dsx* pre-mRNA to generate the female isoform of Dsx (DsxF). In males, in the absence of Sxl and functional Tra, *dsx* pre-mRNA is spliced to generate the male isoform of Dsx (DsxM. Functional Tra also directs the splicing of *fru* pre-mRNAinto a female isoform (*fruF*) that is not translated, while the absence of functional Tra in males results in the default splicing of *fru*pre-mRNA into a male isoform (*fruM*) that is translated into functional protein. Active Sxl also suppresses the synthesis of the dosage compensation protein msl-2 in females, which otherwise heightens the activity of the single X chromosomes in males. Here and in all other figures, female is purple an male is green. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

3. Sex-specific regulation of growth: an overview

Perhaps the most obvious phenotypic difference between females and males is body size, a phenomenon referred to as sexual size dimorphism (SSD) (Fig. 2A). SSD varies in both direction and degree among even closely related species. There are some general trends, however: In mammals and birds, the male is usually the larger sex, while in invertebrates the female is usually the larger sex. For male-biased SSD, the increase in male body size is generally thought to reflect sexual selection on males for their ability to compete for and/or attract mates. For female-biased SSD, the increase in female body size appears to reflect fecundity selection on females, where reproductive success is typically limited by the production of large gametes and therefore correlates with body size. In addition to differences in overall body size, however, males and females may also differ in body proportion; that is, the relative size of different organs. This is most apparent for exaggerated secondary sexual characteristics, such as horns and antlers, used by males to attract or compete for females.

In order to generate sex-specific differences in body size, males and females must necessarily differ either in initial body (egg) size, the rate and duration of body growth, or the rate and duration of subsequent body degradation (Fig. 2B). All of these mechanisms are utilized to generate and modify sexual size dimorphism, and often more than one is used within a species. Perhaps the least common mechanism generating SSD is variation in initial body size, although there is sexual size dimorphism of egg size in some birds [37,38] and at least one insect [39]. Much more typical are sex-specific differences in the rate and duration of growth. Sex-specific differences in growth rate are seen to generate SSD in both insects [39–44] and vertebrates [45–49], as do differences in growth duration (bimaturism) [40,49–53]. Finally, sex-specific differences in post-growth mass reduction can also influence SSD. In holometabolous insects, for example, metamorphosis imposes a delay between the cessation of overall growth and adult emergence, during which non-feeding larvae and pupae lose mass. If this mass loss is sex-specific, this can also generate or modify SSD [40,41].

The same mechanisms can generate sexual dimorphism in the size of individual traits, particularly exaggerated secondary sexual characteristics used by males to compete for or attract females. (Here we restrict the term SSD to refer to sexual dimorphism of overall body size, rather than sexual dimorphism in the size of individual traits). For example, in horned *Onthophagus* beetle, males grow large head- or thoracic-horns that are typically reduced or absent in females. These horns grow from a patch of epidermal cells that rapidly proliferate at the end of larval development, and fold in upon themselves to form a disc [54]. This disc then unfurls during pupation to form a horn, that may be subsequently modified by apoptosis to its final size and shape. Different species modify different parts of this developmental program to generate sexual dimorphism in horn size and shape. For example, in *O. nigriventris*, sexual dimorphism arises primarily due to differential growth of the thoracic horn in the pre-pupal period, with moderate differential resorption of horn tissue during pupation to further refine the sexual dimorphism [55]. In *O. binodis* in contrast, larval growth of the thoracic horns is the same in males and females, which are sexually monomorphic at the beginning of pupation. However, substantial sex-specific resorption of horn tissue during pupation results in the sexual dimorphism in thoracic horn length observed in adults [55]. Similar developmental mechanisms generate other sexually dimorphic traits, such as antlers in male deer [56], asymmetrical claws in male fiddler crabs [57], and the exaggerated third legs in male water striders (*Microvelia longipes*) [58].

Perhaps the most obvious form of sexual dimorphism is of the reproductive organs themselves, including ovaries, testis, and the internal and external genitalia. Much has been written on the

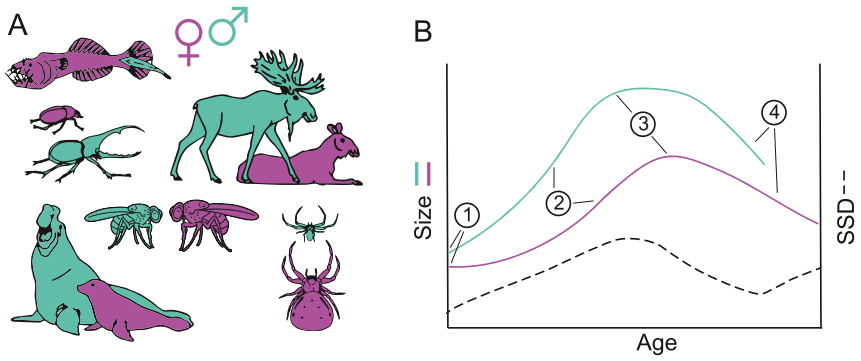

Fig. 2. Sexual size dimorphism (SSD) in animals. (A) The direction and extent of SSD varies extensively among species. (B) SSD can be generated by sex-specific differences in (1) initial body size, (2) growth rate, (3) growth duration, and (4) mass loss. Adapted from [159].

developmental processes that generate male versus female reproductive systems, and of oogenesis and spermatogenesis, and we will not detail these processes here. However, in most animals, including *Drosophila* [59,60] and humans [61], the male and female gonads and genitalia originate through differential growth, and apoptosis, of different parts of the same primordia.

With the exception of initial body/trait size, the mechanisms that generate sexual dimorphism – either of the whole body or individual traits – are therefore dynamic (Fig. 2B). Consequently, sexual dimorphism is not a static state but one that changes as individuals in a population develop and mature (Fig. 2B).

4. Sex-specific growth in *Drosophila*

Of all animals, the regulation of body size at the developmental-genetic and physiological level is perhaps best understood in the fruit fly *Drosophila melanogaster*. Fruit flies are holometabolous insects and so molt through three larval instars before pupating and metamorphosing into their final adult form. Growth of the body as a whole is restricted to the larval period, and final body size is more-or-less fixed by the size of the larval body at pupation. Growth of external body parts of the adult fly (the wing, legs, eyes, genitalia, etc) also takes place primarily during the last larval instar, where they grow internally as imaginal discs before differentiating during metamorphosis into their adult structures. The discs do, however, continue some growth at the beginning of the pupal period, relying on stored nutrients to fuel cell proliferation.

Broadly speaking, the size of the larva at pupation, and hence final body size, is regulated by four developmental phenomena [62]. The *first* phenomenon is attainment of critical size, the point in development when the larvae initiates the synthesis and release of ecdysone, a steroid hormone. Ecdysone titers then fluctuate in series of ever-increasing pulses, each of which drives a developmental event that prepares the larva for pupariation and metamorphosis. Whole body growth stops when a pulse of ecdysone initiates larval wandering, at which point the larva stops feeding and searches for a pupariation site. The *second* phenomenon that regulates final body size is therefore the length of time between attainment of critical size and larval wandering, called the terminal growth period (TGP), and the *third* phenomenon is the rate of growth during the TGP. Finally, larvae lose mass during non-feeding wandering phase before pupariation, which reduces final body size. This is therefore the *fourth* phenomenon that regulates adult body size in *Drosophila*. Of these, sex-specific critical size, growth rate and mass loss appear to be the primary regulators of SSD in *Drosophila*.

4.1. Sex-specific critical size in Drosophila

Males and females differ in their critical size and so initiate the hormonal cascade that ends body growth at a smaller size in males than in females (Fig. 3A) [41]. Although its mechanisms have not been completely elucidated, evidence suggests that critical size is attained when ecdysone biosynthesis switches from non-autonomous to autonomous regulation [63]. Prior to attainment of critical size, ecdysone

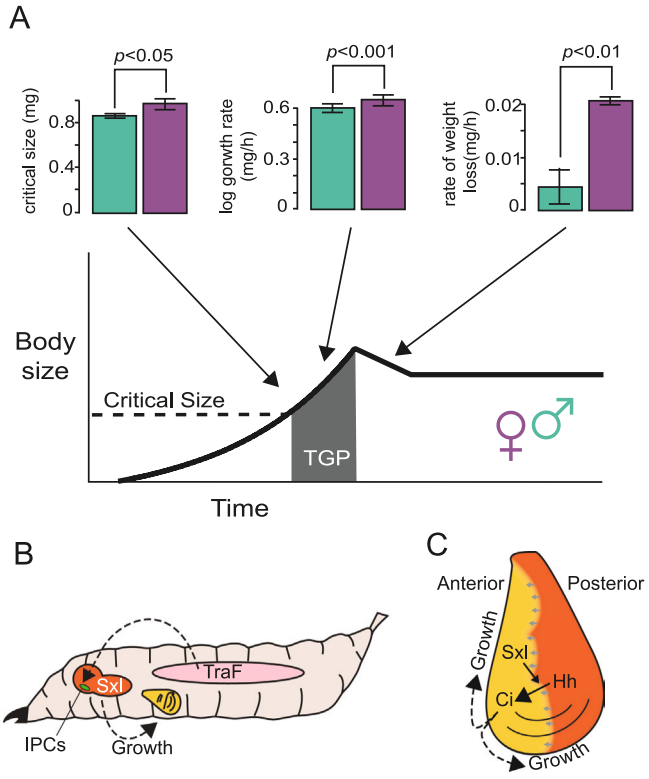

Fig. 3. Development of sexual size dimorphism in *Drosophila*. (A) SSD is generated by an increase in critical weight and growth rate in females, and is maximal at peak larval mass. Higher mass loss in females versus males during larval wandering, however, reduces SSD prior to adult eclosion. TGP: terminal growth period. Data from [41](B) The systemic regulation of SSD appears to be regulated by two mechanisms. The activity of Sxl in the female brain (red), including in the insulin-producing cells (IPCs, green) increases female growth of the body and the imaginal discs (yellow), seemingly independent of dILPs. Further, the activity of Tra in the female fat body (pink) also increases female growth, ostensibly through the release of dILP2 from the IPCs. (C) The trait-autonomous regulation of SSD in the wing imaginal disc appears to be regulated by the elevated activation of Hh by Sxl. Hh is a morphogen that is synthesized in the posterior compartment of the wing imaginal disc, and spreads to the anterior compartment. Sxl in the anterior compartment increases the levels and rate of nuclear entry of Cubitus interruptus (Ci), the Hh signaling target, which then acts indirectly across the whole disc to enhance growth.

synthesis by the prothoracic gland is regulated by a number of factors. These include nutritional signaling via the insulin/insulin-like growth factor signaling (IIS) and Target of Rapamycin (TOR) pathways [63], as well as signaling via prothoracicotropic hormone (PTTH) [64], which is in turn regulated by a number of external and internal stimuli such as photoperiod [65] and signals from damaged imaginal discs [66,67]. Collectively, these factors cause a gradual rise in ecdysone biosynthesis early in the third larval instar that correlates with an increase in body size [63]. Once ecdysone reaches a particular threshold, however, it begins to regulate its own biosynthesis via positive and negative feedback loops, which generate the pulses of ecdysone responsible for larval wandering and pupariation [68]. It is this threshold that appears to correspond to the critical size. Why male critical size is smaller than female critical size presumably reflects differences in when this threshold is achieved relative to body size. One possibility is that levels of circulating ecdysone are lower in females than males of the same size. If the critical size ecdysone threshold were the same in both sexes, then females would therefore achieve critical size at a larger size than males. Alternatively, if the critical size ecdysone threshold were higher in females than males, this would also result in females having a larger critical size. Detailed studies of the differences in ecdysone synthesis and circulation in the two sexes would help separate these two hypotheses.

4.2. Sex-specific growth rate in Drosophila

Males and females also differ in the amount of growth achieved during the TGP [41]. This is not due to differences in the duration of the TGP but in the rate of growth during the TGP (Fig. 3A) [41]. A primary regulator of growth rate during the TGP, and of final body size, is nutritional signaling via the IIS pathway: low nutrition during the TGP reduces systemic IIS, slows body growth rate and reduces final body size [69]. Intriguingly, low nutrition also reduces or eliminates SSD [70,71], while direct suppression of IIS activity through mutation of the insulin receptor (InR) has the same effect [41]. Consequently, changes in nutrition and IIS activity have more of an effect on female body size than male body size, and suggests that IIS activity is higher in well-fed females than well-fed males. This hypothesis is supported by a number of observations (Fig. 3B). First, females appear to secrete higher levels of *Drosophila* insulin-like peptide 2 (dILP2) from the insulin-producing cells (IPCs) in the brain than males, and have correspondingly higher levels of IIS activity in the mid-third larval instar [70]. Second, knockout of the different *dILPs* (with the exception of *dILP6,* see below) reduce body size more in females than males, while activation of IIS increases body size in males more than females [72,73]. Third, increases in dietary protein have a more potent effect activating the IIS pathway in females than in males, corresponding to an increase in SSD on higher protein diets [74]. This effect is also dILP2 dependent and involves the female-specific transcriptional upregulation of *stunted* (*sun*) [74], a circulating insulinotropic peptide produced by the fat body (the *Drosophila* equivalent of the liver and adipose tissue) in response to dietary protein [75]. The regulation of sex-specific growth in turn appears to be controlled by the activity of Tra in the female fat body.

Collectively, these data present a relatively simple model of sex-specific growth rate in *Drosophila*: females grow faster than males in a nutrient-dependent manner due to increased levels of circulating dILP2 and IIS-activity on high quality diets. Some details remain equivocal, however. A second study failed to detect any sex-specific differences in IIS activity in the mid-second and early third larval instars [33], when SSD is already apparent. This study also found that, while loss of dILP2 reduced larval body size, it did not affect SSD in wandering third larval instar [33], when SSD is greatest in *Drosophila* [41]. Intriguingly, however, loss of dILP2 did affect SSD of the growing wing imaginal discs at the same stage [33], suggesting that dILP2 is necessary to generate SSD of the imaginal tissue but not of the body as a whole. Further, expression of the female-specific gene *Sexlethal* (*Sxl)* in the IPCs was necessary for normal whole-body SSD in wandering third larvae, but overexpression of either *dILP2* or *dILP5* did not affect SSD [33]. This suggests that the IPCs may affect SSD of the larval body independent of IPC-secreted dILPs (Fig. 3B). While these observations may be difficult to reconcile with earlier studies [70], they may reflect differences in the regulation of SSD under different dietary conditions. Studies looking at the effect of diet quality on SSD indicate a complex relationship between carbohydrate and protein level, SSD, dILP expression and dILP peptide levels in the brain [71,76]. Further, as noted above, dILP2 appears to have a particularly potent effect on SSD when larvae are fed a high protein diet [74]. Thus differences in diet between studies may impact the outcome of ostensibly identical experiments.

4.3. Sex-specific mass loss in Drosophila

The final mechanism through which SSD can be generated in *Drosophila* is through sex-specific mass loss during the non-feeding wandering stage, between the end of the TGP and pupariation (Fig. 3A). This has a considerable influence on male and female body size, with females losing more mass than males. Since females are larger than males at the beginning of larval wandering, this has the effect of reducing the SSD index (*female mass/male mass – 1* [77]) from about 0.3 at the beginning of larval wandering to 0.15 at pupariation [41]. How mass loss is regulated is poorly understood, but it presumably reflects metabolic activity as the non-feeding larvae prepares for metamorphosis. One possible candidate is dILP6, which regulates the growth of adult-specific tissues during the post-feeding period and is expressed by the fat body. Knockdown/out of *dILP6* reduces the growth of adult-specific tissues, lowering adult body mass and increasing excretion of unused materials during wandering and after adult eclosion [78,79]. While the effect of *dILP6* knockout on adult body mass is the same in both sexes [78], it reduces pupal size in males but not females, relative to controls [72]. If, during normal development, the greater mass loss in female larvae is due to lower levels of *dILP6* expression, then this may explain why loss of *dILP6* has a greater effect on male pupal size than female pupal size.

4.4. Trait-autonomous regulation of SSD in Drosophila

The mechanisms that regulate SSD discussed above are systemic: that is they affect overall body size through sex-specific differences in the hormones that regulate growth rate and duration. However, the size of individual traits in the body is also regulated by trait-autonomous factors. These factors generate the characteristic shape of a trait, and ensure , for example, that our feet are bigger than our hands, or that a *Drosophila's* wings are bigger than its halteres. Trait-autonomous factors include genes that specify cell fate during development; that is patterning genes. Gynandormorphs in *Drosophila* and other insects, which are a mosaic of female and male cells within a single body, show differences in the sizes of individual traits depending on whether the trait has female or male genetic identity [80]. The fact that these female and male traits grew in the same body indicates that their size differences arise at the level of individual traits, and suggest the involvement of patterning genes in the generation of these differences in size.

There is some evidence that this is the case (Fig. 3C). One study on development of the wing imaginal discs has demonstrated that overexpression of Sxl (which is only expressed in females) enhances signaling through the Hedgehog (Hh) signaling pathway, a highly conserved pathway involved in patterning morphological traits in both insects and vertebrates. Hh is a diffusible morphogen that regulates cell fate and proliferation during development, but in the wing imaginal disc is only active immediately anterior to the disc's anterior-posterior boundary. Patterning of the rest of the disc is achieved by the Hh-activation of the Decapentaplagic (Dpp), another diffusible morphogen that also stimulates growth [81,82]. Consequently, the sex-specific difference in wing size appears, in part, to be due to the Sxl up-regulation of Hh-signaling in females relative to males [83]. Sxl also

regulates Notch signaling, which is also involved in regulating cell proliferation and patterning in the wing imaginal disc [84], as well as other tissues around the body. Sxl has been shown to down regulate Notch signaling, and while this does not appear to affect size dimorphism it does regulate the sexual dimorphism of bristle number on the abdominal sternites (females normally have more bristles) [16]. Interestingly, aspects of the effects of Sxl on wing size and bristle number appear to be independent of Tra. Wing-specific expression of *tra* does not increase wing size [70,83]. Similarly, expression of the female isoform of *tra* in males, while giving males female-like abdominal pigmentation, does not affect bristle number [16]. However, knock down of *tra* expression in the posterior compartment of the wing does reduce compartment size, through a reduction in cell size [70]. There may, therefore, be multiple mechanisms by which different components of the sex-determination pathway affect the cell- and trait-autonomous regulation of SSD in individual morphological traits. More generally, the differences in size between traits in females and males often reflects subtle (or not so subtle) differences in shape [85,86], which suggests that we might expect other examples of sex-determination genes directly impacting the expression and activity of patterning genes. As we discuss below, this appears to be the case for the horns of *Onthophagus* beetle, where males and females have dramatic differences in the size of their horns.

5. Sex-specific growth in *Onthophagus*

Onthophagu beetle comprise over 2000 described species and are characterized by single or paired horns projecting from the head and/or thorax of males, which are used to attract and compete for females. As discussed above, these horns develop during the late larval and pupal phase, and either do not grow in females, or are resorbed before emergence as an adult. Importantly, while horns are characteristic of males, their expression is tightly linked to the male's nutritional status: small malnourished males typically have small horns that resemble those of females, while large well-fed males have disproportionally large horns (Fig. 4 A).

Early studies on horn development indicated that the transcription factor Doublesex (Dsx) is involved in the specification of horns [87] (Fig. 4B). Intriguingly, Dsx appears to not only be involved in regulating the horn dimorphism between males and females, but also in regulating the nutritional-sensitivity of the horn. In *O.* tuarus, the expression of *dsx* is tissue specific and the level of expression in the head correlates with horn size: Expression is higher in large males – which typically have exaggerated horns – than in small males or females [88]. Correspondingly, knockdown of *dsx* expression in large males has much more of a dramatic effect on horn size in large males than small males. Conversely, knockdown of the female-specific isoform of *dsx* in females has the opposite effect, and induces horn growth in a nutrient-dependent manner, so that large females, which typically have small horns, now have disproportionally large horns [88]. Collectively, these data suggest that it is the tissue-specific expression of the sex-specific isoforms of Dsx that either promote or inhibit differential horn growth among males of different sizes and between males and females. Subsequent analysis indicates that Dsx mediates these effects at a molecular level using two mechanisms: The sex-specific isoforms either direct transcription of genes that are expressed in only one sex, or they direct transcription of genes that are expressed in both sexes but in opposing directions (up-regulated in males and down-regulated in females or vice versa) [89].

While the upstream regulation of Dsx isoform expression has been well described in a number of insect species [6,90], the downstream targets of Dsx, which confer sex-specific identity on individual tissues, are much less well elucidated. Nevertheless, we might expect that key targets would include patterning genes, and this appears to be the case for *O. taurus* horns. Indeed, as in the *Drosophila* wing, growth of the horns in appears to be regulated by Hh signaling, albeit in the opposite direction (Fig. 4B). Knockdown of Hh signaling promotes horn growth in small males that would otherwise have small horns, while activation of Hh signaling inhibits horn growth in all males [91]. Consequently, while Hh-signaling appears to drive sex-specific growth in the *Drosophila* wing, making female wings larger than male wings, Hh-signaling appears to inhibit sex-specific growth of the *O. taurus* horn in small males, making male horn length comparable to that of females. Interestingly, knockdown of the *forkhead transcription factor* (*FOXO*), a key component of the IIS pathway, also increases in horn size in small but not large males (Fig. 4B). FOXO activity is negatively regulated by IIS and up-regulates the transcription of growth inhibitors when IIS is low [92–94] Knockdown of *FOXO*, however, also reduces the expression of *smoothened* (*smo*) [95], which in turn reduces Hh-signaling, implicating IIS in the regulation of sexual-dimorphism of horn size in *Onthophagous*.

Other patterning genes have also been implicated in the development of *Onthophagus* horns, including Dpp [96], Distal-less [97], homothorax [97], and Notch [98]. Indeed, sex-specific horn development, not just in *Onthophagus* but also in the rhinoceros beetle *Trypoxylus dichotomus*, appears to involve the co-option of genes previously known to be involved in patterning the head and appendages of *Drosophila* [99].

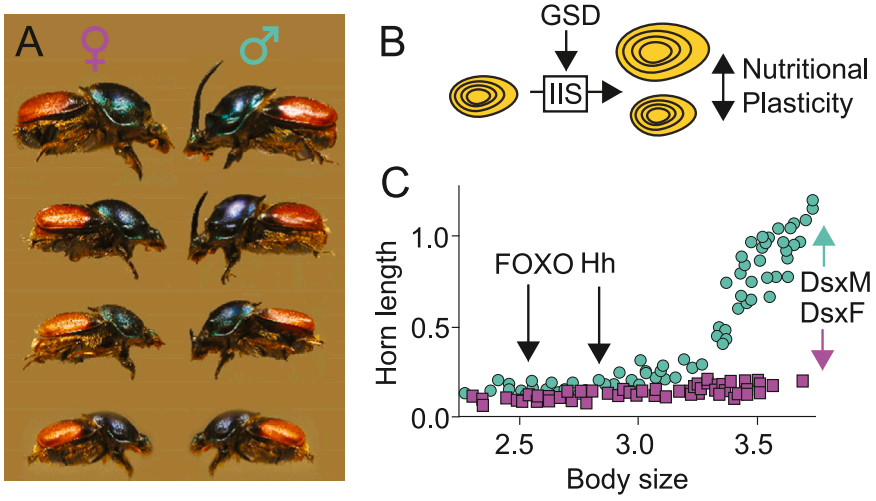

Fig. 4. Developmental regulation of sexual dimorphism in *Onthophagus.* (A) Horn growth is sexually dimorphic in *O. taurus*. (B) Suppression of horn growth in small males is through FOXO (part of the IIS) and Hh, while increase in horn growth in large males is regulated by DsxMIn large females, in contrast, DsxF. (C) Genetic sex determination (GSD) mechanisms appear to act on horn growth via the insulin/IGF-signaling (IIS) pathway to enhance the insulin-sensitivity of the horn imaginal discs in males alone and increase their nutritional plasticity.
(B,C) Adapted from [54].

6. Sex-specific growth and sex-specific plasticity

Theory suggests that sexual selection acting on male traits will generate sexual dimorphism if males with larger traits achieve higher mating success (Darwin 1874). Further, if an increase in relative trait size is of greater benefit, or lower cost, to large males relative to small males, then that trait should evolve heightened condition-dependence relative to other traits in the body, and to the same trait in the other sex, called the *condition dependence hypothesis* [100,101]. The result is that for many (but not all) exaggerated male secondary sexual characteristics, as body size increases with an increase in condition, trait size increases even more, such that the trait becomes disproportionally larger in larger males, and example of positive allometry, or hyperallometry [102]. One important aspect of this heightened condition-dependence is that, as body size varies with environmental factors, particularly developmental nutrition, the sexually dimorphic trait should also show heightened phenotypic plasticity: That is, there should be sex-specific plasticity (SSP), where the trait is more plastic in one sex than the other. Several studies support this hypothesis. For example, the strength of condition dependence increases with the degree of sexual dimorphism among different traits in *Prochyliza xanthostoma* and *Telostylinus angusticollis* flies [103,104]: Traits that are more dimorphic show greater differential plasticity between sexes. The same pattern is observed for sexually-dimorphic traits among species [105]. The condition-dependence hypothesis can also be applied to body size, when there is stronger directional selection on body size in one sex relative to the other, generating SSD [44,106]. Again, theory suggests that as SSD increases so does condition dependence of body size in the larger relative to the smaller sex. This hypothesis is supported by data showing a positive correlation between SSD and SSP among species [105]. Further, this correlation holds among isogenic lineages of *Drosophila*, indicating a genetic correlation between SSD and SSP [107].

Collectively, these studies suggest that the developmental mechanisms that regulate the differential growth of sexually-dimorphic traits, including body size, overlap with the mechanisms that regulate their sex-specific plasticity. This is certainly supported by the research reviewed in this paper, which implicates IIS – canonically a regulator of growth in response to nutrition and other environmental factors – in the generation of sex-specific growth of the body in *Drosophila* and horns in *Onthophagus*. Perhaps most telling is that experimental manipulations of the genes and pathways that affect SSD and sexual-dimorphism also affect the plasticity of the traits in question [74,88,95]. This has important implications for our view of how SSD and sexual-dimorphism evolves. Rather than selection favoring differences in body and trait size between females and males per se, selection may be favoring difference in body- and trait-size plasticity between females and males, the result of which is sexual dimorphism but only under certain conditions. Further studies elucidating the developmental mechanisms that regulate sexual-dimorphism of trait and body size in different animals are clearly needed to test this hypothesis. Indeed, because the developmental-genetic mechanisms that regulate plasticity are evolutionarily conserved, if this hypothesis were correct, identifying the mechanisms that regulate SSD in other animals may be relatively straightforward.

7. Sex-specific metabolism: an overview

Sex-specific differences in the developmental response of males and females to nutrition reflect, in part, the fact that males and females have different metabolic requirements as adults. Adult females require a metabolism that supports the production of eggs, while adult males require one that supports the production of sperm. This in turn leads to sex-specific differences in life-history characteristics that also impact metabolism. There is increasing awareness of sex-specific differences in human metabolism, including energy balance and glucose and lipid metabolism, that impact the progression and treatment of myriad diseases, and there is an extensive literature describing these differences (Seee [160–162] for a review). Because mammalian sex-differences are canonically a response to gonadal hormones, much of this research has focused on the influence of sex steroids on different aspects of metabolism [108,109]. However, evidence from the Four Core Genotype mice – XX and XY mice, both with either ovaries or testis – indicates that sex-specific metabolism is also impacted by the cell-autonomous effects of sex chromosomes [110,111]. The fruit fly serves as an excellent potential model for understanding these cell-autonomous effects of genetic sex on metabolism.

Despite the obvious differences in sex-specific physiology in vertebrates versus invertebrates there are some common metabolic themes associated with oogenesis versus spermatogenesis across all animals. In particular, females of many species either slow or delay egg production when malnourished ([163]), and conversely adjust their feeding in anticipation of mating [112]. The provisioning of the cytosol of the egg with nutrients, particularly lipids, sufficient to support embryonic development leads to the general trend of differences in lipid metabolism between males and females. This differences is even more acute in mammals, where females continue to provision the embryo and young after fertilization. Sex-specific differences in metabolism may in turn help explain observed sex-specific differences in mortality and aging. In humans, females show greater longevity than men, and this trend may be true for animals in general, although there are many exceptions [113–116]. While sex differences in longevity likely reflect differences in sexual-selection acting on males versus females [115], the general increased longevity of females may also be due to sex-specific differences in mitochondrial function and turnover that result from maternal inheritance of mitochondria. This in turn allows optimization of nuclear–mitochondrial genetic interactions for metabolic function in females but not in males [117].

8. Sex-specific metabolism in *Drosophila*

While adult male and female *Drosophila* show distinct differences in their metabolism (ref), the evidence that they differ in their metabolic rate is equivocal, and reflects a highly variable and contradictory literature that employs multiple methods to measure metabolic rate [118]. Mass-specific routine oxygen consumption (VO_2) has been reported as higher in male than in females, but decreases with density (10–50 flies), and more steeply in male. This suggests that sex-specific metabolic rates measured in groups of flies may reflect behavioral differences in social interactions in males versus females. When metabolic rate is measured in individual flies, in the absence of social interaction, then mass-specific metabolic rates (VO_2 and/or VCO_2) is recorded as either higher in females than in males [119,120] or the same [121]. Nevertheless, even in individual flies, these differences in metabolic rate may reflect sex-specific differences in activity, which vary between males and females during the day [121]. Thus assays of metabolic rate are likely to be highly contextual, which probably accounts for the variability in sex-specific metabolic rates observed among different studies.

Regardless of the rate at which metabolism runs in females and males, the products of metabolism show clear sex-specific differences in *Drosophila*. As noted above, a general trend in all animals is for females to show higher levels of lipid metabolism than males. Triglycerides are the main form of lipid storage in *Drosophila*, and females have higher levels of triglycerides than males [122]. Females also have higher levels of polyunsaturated fatty acids while males have higher levels of saturated fatty acids [123]. These differences in lipid profile and storage are evident even when the gonads have been removed and so do not solely reflect the presence or absence of the ovaries [123,124]. Sex-specific differences in triglyceride storage are not, however, evident in newly eclosed adult flies, but rather emerge over the first five days of adult life due to a reduction in triglyceride storage in males but not in females [120]. There are multiple genes that regulate the synthesis and storage of lipids in *Drosophila* [125,126], but the observation that differences in

triglycerides between females and males arises due to the sex-specific reduction in males points to genes involved in the breakdown of triglycerides as central to generating sex differences in triglyceride levels [120].

A number of mechanisms have been identified that regulate the sex-specific breakdown of triglycerides in *Drosophila* (Fig. 5). First, the triglyceride lipase *brummer* (*bmm*) is more highly expressed in males than females, and loss of *bmm* substantially reduces the sexual dimorphism in triglyceride levels [120]. Intriguingly, the sex-specific effects of *bmm* on triglyceride levels appears to be mediated by its expression not in the fat body, but in the gonads and neurons [120]. Second, the adipokinetic hormone (Akh), which is the fly homolog of glucagon and plays a central role in fat storage and breakdown [127], is also more highly expressed in males than in females [128]. Ablation of the Akh-producing cells (APCs) in the corpora cardiaca increases fat storage in males but not females, while augmenting Akh release decreases fat storage in females [128]. This sex-specific activation of Akh signaling appears to be due to the action of Transformer (Tra), which is only spliced into its functional form in females. Driving expression of the functional *tra* in male APCs increases fat storage in males, while females that lack functional Tra protein show both elevated levels of *Akh* expression and reduced triglyceride storage. Epistatic analysis of the effects of *bmm* and *Akh* knockdown suggest that these two mechanisms act in parallel to regulate sex differences in fat storage.

These are unlikely to be the only mechanisms that regulate sex-specific differences in lipid metabolism in *Drosophila*. In particular, both ecdysone and juvenile hormone (JH) may be involved. JH, which is released by the corpora allata, is best known as a regulator of molt identity during development, while ecdysone controls the timing and coordination of developmental transitions. In particular, ecdysone regulates remodeling of the late-larval fat body to support development during the non-feeding stages and very early adult life. Loss of ecdysone signaling in the larval fat body increases lipid accumulation [129], in part by suppressing IIS signaling in the fat body via the effects of *microRNA-8* on PI3K [130,131]. Females show greater mass loss during the non-feeding larval stages [41], and this may reflect differences in the timing or level of ecdysone synthesis in males versus females. Indeed expression of dILP6, which may be involved in sex-specific mass loss during later larval instar, is regulated by ecdysone [79]. In the adult female, JH is critical for the maturation of eggs, particularly vitellogenesis [132]. However, the eggs comprise 30–40% lipids so it would be surprising if JH were also not involved in fat metabolism in females. JH is also a positive regulator of IIS, further implicating its involvement in sex-specific metabolism.

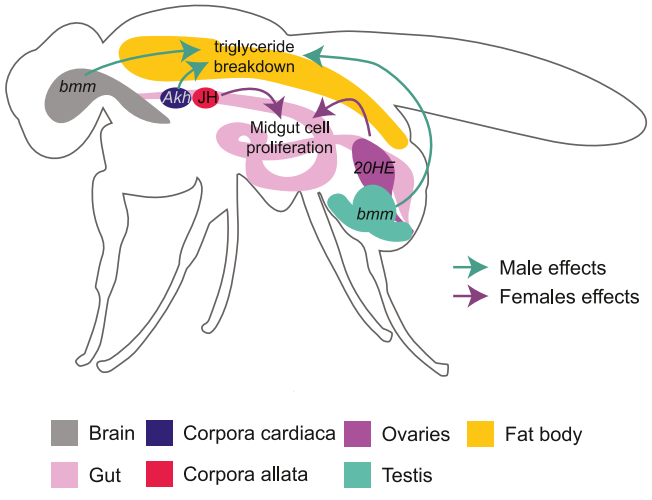

Fig. 5. Sex-specific metabolic regulation in *Drosophila*. In males (green arrows), the action of *bmm* in the nervous system [120] and testis and the action of Akh secreted by the corpora cardiaca [128] leads to triglyceride breakdown and a reduction in lipid content in males relative to females. In mated females (purple arrows), the action of JH from the corpora allata [134] and ecdysteroids (20HE) from ovaries [137,138] stimulates the proliferation and differentiation of the midgut cells to increase the size and absorptive capacity of the midgut. JH also activates the expression of genes involved in lipid synthesis in the midgut. Note that the illustration is of a fly with both male and female body parts. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

Supporting sex-specific differences in metabolism necessary to generate eggs versus sperm are corresponding physiological differences in the organs involved in nutrient acquisition and processing, particularly the gut (Fig. 5). In *Drosophila,* the midgut is the major site of digestion and absorption, and comprises three cell type: (1) intestinal stem cells (ISCs) that continuously divide to generate (2) absorptive enterocytes and (3) hormone-producing enteroendocrine cell [133]. In female flies, mating stimulates an increase in the number of dividing and differentiating midgut cells, as well as an overall increase in midgut size [134]. This response is due to JH signaling from the corpora allata, which also acts on the absorptive enterocytes to activate the transcription of genes involved in lipid synthesis [134]. Intriguingly, mating also stimulates the ovaries (and possibly other tissues) to synthesize ecdysteroids [135,136], which act on the proliferating midgut cells and drives them towards differentiating into absorptive enterocytes, thereby further increasing the absorptive epithelium to support the metabolic requirements of egg production [137,138]. These characteristics of the female gut do not appear to be mediated solely by hormones, however. Female ISCs show a heightened proliferative response to damage to the intestinal epithelium compared to males, and this is due to the presence of Sxl/Tra in the cells of the female midgut [139,140]. Whether Sxl/Tra also mediates the effects of ecdysteroids and JH on female gut physiology, or regulates cell proliferation through an independent pathway is an open question. One final intriguing observation is that feminizing the male gut both reduces lifespan but also increases the effect of dietary restriction on extending lifespan, which is greater in females than in males [140]. This suggests that gut sex plays an important role in aging and in the physiological response of males and females to diet.

9. The metabolic regulation of sex-specific growth and development

Differences in growth between females and males inevitably affect differences in their metabolic requirements during development, and these differences continue into adulthood as the two sexes pursue different strategies to ensure reproductive success. As outlined above, the developmental mechanisms that regulate sexual size dimorphism of body and trait size in invertebrates include mechanisms that canonically regulate metabolism, in particular the IIS pathway. A compelling hypothesis, therefore, is that the sex-specific differences in IIS that generate differences in male and female development also impact metabolism. More generally, we should observe sex-specific differences in metabolism that match differences in the growth and developmental dynamics of females and males.

Problematically, this hypothesis is not yet supported by data. The fact that the genes involved in regulating metabolism are highly conserved across all animals, the tractability of *Drosophila* for the functional manipulate these genes, and the rise in metabolomics, have all made the fruit fly a particularly powerful model for studying metabolism in general and the metabolism of development in particular [141,142]. Nevertheless, almost all of the studies of the metabolism of growth and development in *Drosophila* do not analyze females and males separately, possibly because of the challenges of sexing embryos and larvae. There have been some studies on sex-specific differences in dietary intake in other insects. For example, in the gypsy moth *Lymuntriu dispar,* male and female larvae show sex-specific shifts in their preference for protein versus lipid during ontogeny [143]. In *Drosophila*, however, despite differences in male and female growth rate [41], there are no

differences in feeding rate [70]. Further, while molecular and genetic evidence supports a role for IIS in generating SSD, circulating levels of dILP2 are not different between female and male larvae, at least using current methodologies to measure hormone levels [74].

There are more data on sex-specific metabolism during development of vertebrates, particularly humans, where juvenile sex is easily determined. Nevertheless, the data are equivocal. For example, SSD changes during human puberty, reflecting differences in the timing of growth between males and females [144] and in both sexes this growth spurt is marked by an increase in absolute metabolic rate [145]. Much less clear is whether this increase in metabolic rate is sex-specific and matches differences in growth between males and females. Two studies suggest that metabolic rate plateaus earlier in females than in males, relative to the beginning of puberty (which is approximately one year earlier in females) [146,147]. This does not appear to be reflected in differences in male and female growth curves, however, when controlling for differences in the timing of puberty [148]. In humans, growth is regulated by the hypothalamic-pituitary-somatotropic (HPS) axis, which includes growth hormone and insulin growth factor 1 (IGF-1). IGF-1 also has major metabolic effects, in particular as a regulator of protein synthesis [149]. IGF-1 levels are elevated prior to the pubertal growth spurt, which occurs earlier in females than males [150]. While the timing of IGF-1 elevation is different in males and females, however, the absolute levels of IGF-1 are not, and so do not appear to explain sex-specific growth and metabolism [150].

Collectively, therefore, there are a paucity of data indicating metabolic differences between females and male during development, despite established sex-specific differences in growth and development in myriad species. This is in contrast to an extensive literature describing differences in metabolism between male and female adults, only briefly covered in this review. It is well established that adult metabolism is profoundly influenced by developmental metabolic factors, particularly in response to environmental stress [151–153]. Our lack of data describing sex-specific developmental-differences in metabolism is therefore unlikely to be because such differences do not exist. Rather, the scarcity of data may be due to the challenges of integrating development and metabolism in general, and especially in a sex-specific manner. Growth and development are intrinsically dynamics processes, and while developmental geneticists have been hugely successful at describing the genetics of development by perturbing gene function at one point in development and looking at the effect on the adult phenotype, such an approach may have limited utility in studying developmental metabolism. Instead, researchers will need to assay metabolism at multiple time-points throughout development – a much more challenging prospect. Further, the frequency of assays may need to be increased if we are to detect possibly subtle differences in the developmental metabolism of males and females. Nevertheless, new genetic tools that allow the application of functional genetics to non-model organisms [154,155], an increasingly good understanding of the genetic basis of metabolic regulation, and recently developed technologies in metabolite sensors and analytics [156,157], mean that our lack of understanding of the sex-specific regulation of metabolism during development is only a temporary state.

10. Conclusions

This review has focused on the developmental and growth processes that generate differences in male and female body and trait size, and on the metabolic mechanisms that support this sex-specific development and growth and the final adult phenotype. While there is almost certainly a diversity of mechanisms that generate and maintain female and male phenotypes, work in *Drosophila* and horned beetle suggests some general themes as to how development, growth and metabolism are affected by sex.

First, biologists are increasingly recognizing that while individual traits have autonomous aspects to their development, each trait is part of a network of traits that comprise the whole. For example, developmental perturbations of one trait can have profound implications for development across the rest of the body [158]. Consequently, we should not expect that sex-specific developmental mechanisms either act wholly at the level of individual traits, nor wholly through systemic mechanisms, but rather a combination of both.

Second, sex-specific growth, both of individual traits and the body as a whole, appears to involve mechanisms that also regulate growth plasticity, particularly in response to nutrition via the IIS pathway. The observation that selection for SSD has targeted these mechanisms suggests that selection is not simply acting to increase trait or body size of one sex relative to the other per se, but rather it is acting to increase size under favorable conditions in one sex more than the other.

Third, even though sex-specific development and growth likely involves metabolic differences between males and females, and involves key regulators of metabolic rate, there are a paucity of data supporting this hypothesis. Future studies on the metabolism of development and growth should include sex as an explanatory factor.

Differences in adult female and male phenotypes, in particular morphology and physiology, have important implications for sex differences in metabolism, environmental stress responses, aging and disease progression. If we are to better understand these differences in adults, we need to understand how these differences arise during development. The exploration of sex-specific development, while in its infancy, is clearly an important area of future research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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