



SYMPOSIUM

Evolution of, and via, Developmental Plasticity: Insights through the Study of Scaling Relationships

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Synopsis Scaling relationships emerge from differential growth of body parts relative to each other. As such, scaling relationships are at least in part the product of developmental plasticity. While some of the developmental genetic mechanisms underlying scaling relationships are starting to be elucidated, how these mechanisms evolve and give rise to the enormous diversity of allometric scaling observed in nature is less understood. Furthermore, developmental plasticity has itself been proposed as a mechanism that facilitates adaptation and diversification, yet its role in the developmental evolution of scaling relationships remains largely unknown. In this review, we first explore how the mechanisms of scaling relationships have evolved. We primarily focus on insect development and review how pathway components and pathway interactions have evolved across taxa to regulate scaling relationships across diverse traits. We then discuss the potential role of developmental plasticity in the evolution of scaling relationships. Specifically, we address the potential role of allometric plasticity and cryptic genetic variation in allometry in facilitating divergence via genetic accommodation. Collectively, in this article, we aim to bring together two aspects of developmental plasticity: the mechanistic underpinnings of scaling relationships and their evolution, and the potential role that plasticity plays in the evolutionary diversification of scaling relationships.

Introduction

Scaling relationships, or allometries, emerge from differential growth of body parts relative to one another. As such, our understanding of the diversity of morphological shape across taxa can be informed by the study of specific scaling relationships. For example, the diversity of wings across insect orders is produced in part by the change of wing size relative to body size (Mirth et al. 2016). Even within species and populations, organ growth differs both among organ types and in relation to body size (static scaling relationships), with some body parts growing proportionally with body size whereas others exhibit disproportionate growth (Shingleton et al. 2007). Variation in body size across individuals, as is true for most traits, is shaped through genotype-by-environment interactions. One of the best-known environmental factors determining body size is nutrition, and most organisms exhibit some degree of developmental plasticity in response to varying

nutritional conditions (Moczek 1998; Karino et al. 2004; Moore et al. 2004; Shingleton et al. 2009). Developmental plasticity, the ability of a single genotype to develop into a range of phenotypes, is ubiquitous and plays a critical role in determining final body size in most organisms (reviewed in Beldade et al. 2011). Plastic changes in body size are therefore accompanied by plastic adjustments of trait size, thereby ensuring functionally well integrated organisms despite overall variation in size. While the developmental-genetic mechanisms of scaling relationships are starting to be elucidated (reviewed in Koyama et al. 2013) ecological evolutionary developmental biology (Eco-evo-devo) has also begun to highlight the role that developmental plasticity itself may play in evolutionary diversification, for example through the genetic accommodation of initially environmentally induced phenotypes. Yet, whether and how developmental plasticity impacts the evolution of scaling relationships has

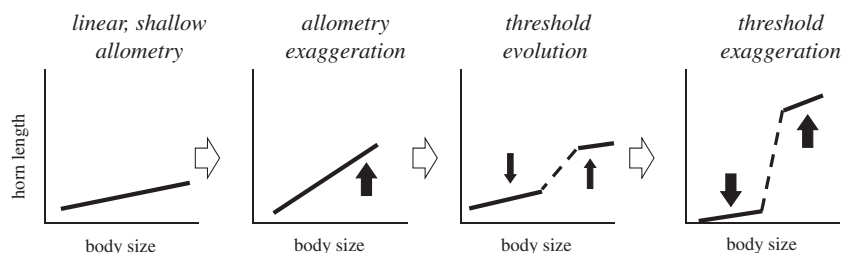


Fig. 1 Evolution of sigmoidal allometries. Sigmoidal allometries are thought to have evolved from linear, relatively shallow allometries (left), whose slopes became exaggerated, followed by the evolution of body size thresholds and the subsequent elaboration of threshold parameters.

remained largely unexplored. In this article, we thus try to bring together two aspects of developmental plasticity: we first review how the mechanisms underlying scaling themselves evolve, and then discuss the potential role that plasticity in scaling relationships may play in evolutionary divergence. Throughout the article, we predominantly focus on the horned beetle *Onthophagus taurus*, a powerful model system to study the mechanisms and consequences of scaling.

Beetles in the genus *Onthophagus* offer promising opportunities to investigate both the developmental mechanisms of scaling relationships and the role of developmental plasticity in evolution. *Onthophagus* are dung beetles that dig tunnels underneath dung pads within which mothers build “brood balls” made of dung (Fincher and Woodruff 1975; Halffter and Edmonds 1982). A single egg is laid per brood ball, which constitutes the sole amount of food available to developing larvae. Offspring respond to variation in nutritional conditions due to variation in maternal provisioning (quantity and quality of provisioned dung) by increasing body size (Moczek and Emlen 1999). Intriguingly, different organs may display strikingly different growth patterns. For instance, at one extreme male horn development exhibits non-linear growth relative to body size, where small individuals develop as hornless males that sneak to get access to females and large individuals develop as horned males that use horns as weapons to guard tunnels and fight to secure mating opportunities (Moczek and Emlen 2000). At the other extreme, male genitalia are almost entirely insensitive to nutritional conditions, resulting in very shallow, hypoallometric body size-genitalia size scaling (Parzer et al. 2018). Whereas genitalia size maintains its insensitivity to nutritional conditions across most species, the nutrition-responsiveness of horn allometries has undergone an enormous amount of diversifying evolution across the *Onthophagus* phylogeny (Emlen et al. 2005). In fact, the genus

Onthophagus is famous in part for the diversity of horn polyphenisms present in most species, which are thought to have evolved from a simple, linear, ancestral scaling relationship that first became exaggerated, followed by the evolution of a distinct body size threshold, and finally the subsequent diversification of various allometric parameters (Fig. 1), such as amplitude or precise threshold location. Intriguingly, this genus is also one of the most speciose genera in the animal kingdom, with over 2,000 described species (Balthasar 1963), many of which display striking diversity in the relative sizes of horns and the nutritional plasticity underlying their allometries (Casasa et al. 2017).

Developmental mechanisms of scaling and their evolution

Our understanding of the mechanisms underlying scaling relationships largely derives from studies on *Drosophila*. While this system has offered unprecedented mechanistic insights, it is limited by the scaling relationship present within *Drosophila*, which excludes for instance exaggerated sexually selected traits otherwise common among animals (e.g., antlers in deer, horns in rhinoceros beetles, and eye stalks in stalk eyed flies; Iguchi 1998; Hingle et al. 2001; Malo et al. 2005), necessitating the need for additional study systems. Furthermore, how scaling relationships diversify not just among organs but also species, or to assess the degree to which similar scaling relationship may evolve through disparate developmental means, by definition requires a comparative approach across diverse non-model systems. Lastly, mechanistic studies of the regulation of static scaling relationships in insects have typically focused on relatively few candidate pathways underlying growth responses to nutritional conditions. Pathways such as insulin/insulin-like growth factor signaling (IIS) and target of rapamycin (TOR) signaling and major insect hormones, such as ecdysone and juvenile hormone (JH), are well known to be

involved in the regulation of nutrition-responsive growth across different organs (Colombani et al. 2003; Colombani et al. 2005; Sheng et al. 2011; Herboso et al. 2015). How growth may be regulated through the interactions among some of these pathways has been reviewed in detail elsewhere (Jindra et al. 2013; Koyama et al. 2013). However, what is much less well understood is how these pathways and their interactions have diversified across taxa, thereby facilitating the enormous diversity of scaling relationships observed both across traits and species. The section that follows will therefore begin by focusing on this issue, and in particular how the study of emerging model systems has contributed recent novel insights.

The IIS pathway and its evolution in the regulation of nutrition-sensitivity

The IIS pathway is a highly conserved pathway (from insects to mammals; Brogiolo et al. 2001; Barbieri et al. 2003) known to mediate nutrition-dependent growth. In insects, the IIS pathway is activated at high nutrition conditions, when high levels of insulin-like peptides (ILP) are released from the brain to the hemolymph. These ILP bind to the insulin receptor (*InR*), which induces a signal transduction cascade that promotes growth (Brogiolo et al. 2001). An important component of the IIS is the forkhead box subgroup O (*Foxo*) transcription factor, a downstream component that acts as a growth inhibitor under low nutrition conditions (Burgering 2008). While this pathway's role in mediating nutrition-responsive growth is highly conserved across taxa, the precise components utilized to mediate growth have diverged. For example, the scarab beetle subfamilies Dynastinae and Scarabinae have independently evolved nutrition-responsive horn exaggeration. While they both regulate horn growth via the IIS, recent studies have shown that they utilize different IIS components to achieve this purpose. In the rhinoceros beetle (*Trypoxylus dichotomus*; Dynastinae), which exhibits a linear body size-horn size allometry for thoracic horns, *InR* is responsible for nutrition-dependent horn exaggeration. Knockdown of this component results in a decrease in horn size (Emlen et al. 2012). In contrast, in the bull-headed dung beetle (*O. taurus*; Scarabaeinae), which exhibits a sigmoidal body-size horn size allometry for head horns, *InR* knockdown has no effect. Instead, *Foxo* is involved in regulating horn growth. Specifically, *Foxo* knockdown transforms the normally highly sigmoidal scaling

relationship between horn length and body size toward a more linear allometry (Casasa and Moczek 2018).

A partially similar scenario occurs in hemipteran wing polyphenism. In the brown planthopper *Nilaparvata lugens*, two *InR* paralogs with opposing roles mediate winged versus wingless morph development, and knockdown of *Foxo* results in largely long-winged morph development (Xu et al. 2015). In contrast, in the soapberry bug *Jadera haematoloma*, *Foxo* seems to have the opposite effect, that is, *Foxo* knockdown results in predominantly short-winged morph development (Fawcett et al. 2018). Similar to the beetle example above, the two hemipteran species belong to different higher order taxonomic groups, in this case families (*N. lugens*: Delphacidae; *J. haematoloma*: Rhopalidae), and the components of IIS recruited into the regulation of wing polyphenism are clearly divergent across the two species studied so far. Interestingly, for both *O. taurus* and *J. haematoloma* *Foxo* could have been key in the evolution of their polyphenisms. In *O. taurus*, a linearization of the sigmoidal allometry in response to *Foxo* knockdown suggests it could have played a critical role in the transition from an ancestral linear to a derived sigmoidal allometry (Casasa and Moczek 2018). Similarly, *Foxo* knockdown in *J. haematoloma* phenocopies a derived change in the wing polyphenism in response to novel host plant adaptation (Fawcett et al. 2018). Altogether, these studies suggest that the insulin signaling pathway constitutes a key pathway that has been repeatedly recruited in the evolution of highly derived scaling relationships, yet the precise IIS component employed to regulate complex allometries and their specific roles in that process may be highly divergent (Fig. 2).

In contrast to exaggerated traits such as horns, genitalia of male insects are largely nutrition-insensitive. Absolute size of male genitalia remains constant across a range of body sizes, a response originally thought to be shaped by selection favoring a fit to a wide range of female genitalia (i.e., “the lock and key” hypothesis; Shapiro and Porter 1989; but see Eberhard 2009 for more recent arguments on the “stimulatory fit” and “mechanical fit” hypotheses). While the evolutionary aspects of this topic remain the subject of much debate, low variability in genitalia size across a range of body sizes is a ubiquitous feature among arthropods (Eberhard 2009; Eberhard 2010; Eberhard et al. 2018). Interestingly, this response is also regulated by components of the insulin signaling pathway. In *Drosophila*, low nutrition-sensitivity of male genitalia is achieved by

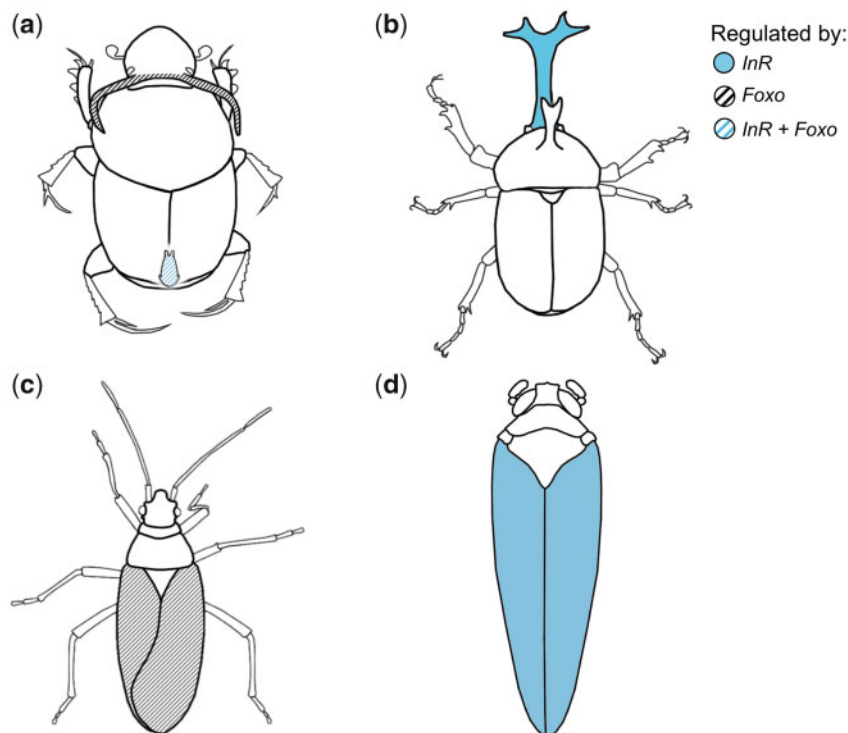


Fig. 2 Regulation of insulin signaling across taxa. Different components of the insulin signaling pathway contribute to the regulation of diverse body parts across taxa. (a) Horn growth in the bull headed dung beetle *O. taurus* is regulated via *Foxo*, which promotes threshold formation, whereas genitalia growth is regulated by both *Foxo* and *InR*, whereas (b) horn growth in the rhinoceros beetle *T. dichotomus* is regulated via *InR*. (c) Wing polyphenism in the soapberry bug *J. haematoloma* is regulated through *Foxo*, whereas a corresponding polyphenism in (d) the planthopper *N. lugens* is regulated through *InR*.

maintaining low *Foxo* expression levels even under low nutrition conditions, which would otherwise result in an activation of *Foxo* and growth inhibition (Tang et al. 2011). Experimental upregulation of *Foxo* results in an increased nutrition-sensitivity whereas decreased expression does not alter the already shallow genitalia-body size allometry (Tang et al. 2011). In contrast, knockdown of *Foxo* in *O. taurus* results in a further decrease of the shallow male genitalia-body size slope (Casasa and Moczek 2018). However, knockdown of *InR* results in a decrease of genitalia growth across all nutrition conditions, an effect not observed in *Drosophila*. While both *O. taurus* and *Drosophila* exhibit similar allometric slopes when plotted on a log–log scale (Tang et al. 2011; Casasa and Moczek 2018), these results may reflect a developmental constraint in the evolution of *Foxo* expression levels in *O. taurus*. Results to date (see above) suggest that high *Foxo* expression in head horns confers high horn nutrition-sensitivity (Ledón-Rettig et al. 2017; Casasa and Moczek 2018), enabling large males to develop exaggerated horns, allowing them to secure mating opportunities through contest competition. Yet, doing so may be accompanied by higher than ideal *Foxo* expression levels in other traits, such as genitalia. If so,

additional mechanisms buffering genitalia growth in variable nutrition environments may be operating. For example, the TOR effector 4E-binding protein (4E-BP) could function as a potential buffering mechanism, as expression levels in genitalia are much higher than for other traits (Ledón-Rettig et al. 2017) and preliminary data suggest that knockdown of 4E-BP may be increasing genitalia nutrition-sensitivity (Casasa S et al. unpublished). While more studies are necessary to fully understand how buffering mechanisms have evolved across traits and taxa, it is clear that the insulin signaling pathway acts mostly in a tissue-specific manner to regulate nutrition-sensitivity.

Pathway interaction in the evolution of nutrition-responsive growth

In addition to nutrient sensing pathways, recent studies have implicated additional pathways in the regulation of nutrition-responsive growth, most notably Hedgehog signaling and doublesex (*Dsx*) pathways. The Hedgehog signaling pathway is best known for its patterning role in anterior/posterior polarity (Nusslein-Volhard and Wieschaus, 1980; Mohler 1998). However, functional analyses in *O. taurus*, the only horned beetle species studied thus

far, also identified this pathway as a critical regulator of nutrition-sensitive horn growth. Knockdown of one of its components, *smoothened*, resulted in a dramatic increase in horn development in low nutrition, normally hornless individuals, whereas high nutrition and normally horned individuals were unaffected (Kijimoto and Moczek 2016).

In contrast, the transcription factor *Dsx*, a cardinal member of the sex determination pathway, has already been shown to be involved in the regulation of nutrition-sensitive trait development in several beetle species (bull headed horned beetle *O. taurus*: Kijimoto et al. 2012; rhinoceros beetle *T. dichotomus*: Ito et al. 2013; stag beetle *Cyclommatus metallifer*: Gotoh et al. 2014). In *O. taurus*, *Dsx* is known to promote male horn growth under high nutrition conditions, while at the same time inhibiting it in females, which normally remain hornless (Kijimoto et al. 2012). Furthermore, a separate study carried out a genome wide analysis of *Dsx* binding sites across *O. taurus* tissues by knocking down *dsx* followed up by RNA sequencing in knockdown and control individuals (Ledón-Rettig et al. 2017). This study identified repertoires of genes putatively targeted by *Dsx*, which were found to be largely tissue and sex-specific. Subsequent assessments of specific candidate pathway interactions then provided evidence that *InR* and *Foxo* regulate expression of *dsx* and *smo*, respectively (Casasa and Moczek 2018). While the precise interactions between IIS, Hh, and *Dsx* pathways clearly remain to be fully elucidated, these results suggested that complex interactions across the three pathways underlie the regulation of growth in response to nutritional variation.

In addition, the *Dsx* signaling pathway has also been found to interact with insect hormones in the regulation of nutrition sensitivity. Insect hormones, such as ecdysone or JH, have been previously implicated in the regulation of nutrition-responsive growth, in part by their interactions with IIS and TOR signaling (Jindra et al. 2013; Koyama et al. 2013; Herboso et al. 2015). However, in the stag beetle *C. metallifer*, *Dsx* interacts with JH to regulate sex specific nutrition sensitivity. *dsx* knockdown combined with JH treatment increases mandible length and nutrition sensitivity in normally short mandibled, nutrition insensitive females (Gotoh et al. 2014). In males, however, JH treatment itself increases mandible growth, but *dsx* knockdown severely reduces mandible growth that cannot be rescued by JH treatment. These results suggest that *dsx* mediates JH sensitivity in a sex-specific manner to regulate male- and female-specific nutrition-responsive growth (Gotoh et al. 2014). Altogether, results

from diverse beetle species suggest that the exaggeration of nutrition sensitivity employs traditional nutrition sensing pathways alongside pathways and pathway interactions typically not associated with nutrition-responsive growth.

Genetic accommodation and scaling relationships

Developmental plasticity, the ability of a genotype to adjust its phenotype in response to environmental conditions, is receiving significant attention given its potential role in facilitating evolutionary diversification through the process of genetic accommodation (Pfennig et al. 2010; Moczek et al. 2011). Genetic accommodation is defined as gene frequency change due to selection on the regulation of an environmentally induced response (West-Eberhard 2003). Plastic responses can be adaptive, non-adaptive, or neutral, but in cases where they provide greater fitness, selection on such responses may be able to refine initially environmentally induced phenotypes such that they can become genetically canalized. One of the best laboratory examples of genetic accommodation comes from the tobacco hornworm *Manduca sexta* (Suzuki and Nijhout 2006). Larval coloration in this moth is typically green; however, a mutation in the JH pathway results in increased melanization. Heat shock of this black mutant is able to expose a range of larval color phenotypes, from black to almost wild type green. Interestingly, selection for green coloration following heat shock resulted in the evolution of a temperature sensitive polyphenic line, whereas selection for black coloration resulted in the evolution of a temperature insensitive monophenic line (Suzuki and Nijhout 2006). This study provided a clear example of a novel environment (heat shock treatment) that revealed a range of larval coloration phenotypes that can be selected on to either increase or decrease environmental sensitivity. Genetic accommodation is an evolutionary process enabled by developmental plasticity, yet whether and how this process may contribute to the evolution of scaling relationships remains largely unexplored. In the previous section, we explored how the developmental-genetic mechanisms of scaling relationships have evolved to give rise to the wide diversity of scaling relationships across traits and taxa. Below, we explore potential scenarios whereby genetic accommodation can facilitate the evolution of scaling relationships, particularly though allometric plasticity and cryptic genetic variation in allometries.

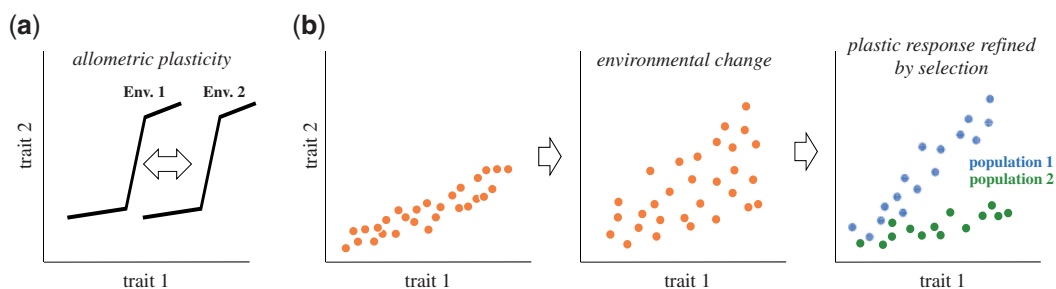


Fig. 3 Model for allometric plasticity and the evolution of allometries through genetic accommodation. (a) Scaling relationships can themselves exhibit plasticity in response to environmental factors. (b) In response to a novel environmental change, a shallow allometry (left) can release cryptic genetic variation (middle), which can be selected upon, resulting in population divergence (right).

Scaling relationships, like any other trait, are the product of environmental and genetic factors. On one hand, different genotypes may generate different scaling relationships, resulting in different trait size values for the same nutritional condition (Dreyer et al. 2016). This variation can then be selected on and enables scaling relationships to diversify. On the other hand, scaling relationships themselves may exhibit some degree of plasticity (Fig. 3a). For example, the *O. taurus* body size-horn size allometry responds to diet in a plastic manner. Field populations utilizing cow dung exhibit a lower body size threshold that separates alternate male morphs than those utilizing horse dung, and experimental rearing of laboratory populations on both diets was able to generate similarly divergent scaling relationships (Moczek 2002). A similar situation occurs in *O. acuminatus*, a dung beetle native to Barro Colorado Island, Panama, that feeds on howler monkey (*Alouatta palliata*) dung and exhibits seasonal variation in the body size-horn size allometry. This change partly coincides with the change in the average population body size, thus, when the average population body size is smaller there is a shift in the threshold that allows smaller individuals to develop horns (Emlen 1997). This seasonal allometric plasticity has been proposed to reflect an adaptive shift in threshold sizes due to howler monkey diet variation across seasons (Nagy and Milton 1979; Emlen 1997), although alternative non-adaptive explanations have also been put forth (Moczek 2002).

The above example showcases instances where scaling relationships themselves exhibit plasticity. Should such responses prove adaptive, coincide with the release of heritable selectable variation, and the inducing environment persists, such a response could become genetically canalized over time. The evolution of a threshold such as this can in fact be seen across exotic *O. taurus* populations. This species was introduced around 50 years ago from its native range, the Mediterranean (Balthasar

1963), to the Eastern United States and Western Australia (Tyndale-Biscoe 1996; Fincher and Woodruff 1975). The latter was part of an effort to control cow dung and dung breeding flies in the region, whereas the former was an accidental introduction. Since establishment, exotic populations have diverged heritably in diverse traits, including brood ball burial depth, brood ball weight, brood ball number produced per mother, average body size, offspring survival, and the threshold separating alternative morphologies (Moczek et al. 2002; Moczek and Nijhout 2003; Beckers et al. 2015; Macagno et al. 2016). These rapid trait divergences (~50 years/~100 generations) are thought to have evolved in response to extremely disparate population densities across the two populations (Moczek 2003) and a recent study sought to test the hypotheses that ancestral plasticity related to population densities present in the Mediterranean source population may have facilitated and biased these divergences. Indeed, a short exposure of Mediterranean adults to either low or high densities induced plastic responses in several traits, including offspring body size, matching the direction of canalized divergences across populations (Casasa and Moczek 2018b). These results provided at least partial support for the hypothesis that genetic accommodation could have contributed to the early stages of population divergence in this species. While this population density treatment was not enough to induce a plastic response in the horn size threshold separating alternative morphologies, it does not necessarily exclude the possibility that longer exposures to high population densities or interactions with additional environmental factors may be sufficient to induce plastic shifts in the allometry. In natural populations, multiple environmental conditions are likely to act in synergy over longer time periods to induce plastic responses.

Genetic accommodation of scaling relationships may be facilitated by cryptic genetic variation.

Plastic responses induced by novel environmental conditions have the potential to make visible genetic variation that has no phenotypic effect under normal conditions but contributes to heritable phenotypic variation in novel circumstances (Waddington 1953; Bateman 1959; True and Lindquist 2000; Ledón-Rettig et al. 2014; Paaby and Rockman 2014). Such cryptic genetic variation has been proposed to accumulate through diverse buffering mechanisms, such as duplicate genes, redundant pathways, or the role of Hsp90 in suppressing the effects of misfolded proteins (Rutherford and Lindquist 1998; Queitsch et al. 2002; Paaby and Rockman 2014). While static scaling relationships are highly regulated, growth responses such as beetle horns are often underlain by diverse interacting pathways (Kijimoto et al. 2012; Kijimoto et al. 2014; Kijimoto and Moczek 2016; Casasa and Moczek 2018) possibly predisposing them to the accumulation of cryptic genetic variation. The release of cryptic genetic variation can be apparent as an increase in phenotypic variation, and this can apply to any trait, including scaling relationships themselves (Rohner et al. 2013; Paaby and Rockman, 2014). If the variation released is adaptive in the novel environment, it can provide a substrate for selection to act on and result in a shift in the trait mean or in the allometry (Fig. 3b).

Although the extent and consequences of cryptic genetic variation associated with scaling relationships has yet to be assessed, previous studies exploring the role of cryptic genetic variation in diverse morphological traits have started to provide some critical information. For example, in threespine stickleback genetic variation for body size increases when oceanic populations are exposed to a novel environment (low salinity). Furthermore, this release of cryptic genetic variation is thought to have contributed to the repeated colonization of freshwater habitats (McGuigan et al. 2011). Similarly, spadefoot toad tadpoles reveal genetic variation for gut length when exposed to a shrimp diet, a novel environmental factor not normally encountered by the population. This change could have facilitated the evolution from omnivory to facultative carnivory observed in closely related taxa (Ledón-Rettig et al. 2010). Finally, eye-size variation in surface populations of the cavefish *Astyanax mexicanus* can be increased in response to Hsp90 inhibition, which suggests that cryptic genetic variation may have played a key role in the evolution of eye loss in cavefish (Rohner et al. 2013). Combined, these studies suggest that cryptic genetic variation has the potential to play a critical role in the evolution of morphological

traits. Moreover, at least some of the previous examples (Ledón-Rettig et al. 2010; Rohner et al. 2013) assessed trait variation by correcting values for body size, which provides at least indirect evidence that cryptic genetic variation may also contribute to the evolution of traits values *relative to each other*.

The interplay between genetic accommodation, developmental plasticity, and cryptic genetic variation is beginning to be understood for at least some morphological and life history traits (Waddington 1953; Dworkin 2005; Suzuki and Nijhout 2006; Ledón-Rettig et al. 2008; Badyaev 2009). However, studies explicitly addressing the role of allometric plasticity and cryptic genetic variation in allometries in evolutionary divergence remain scarce. As discussed earlier, scaling relationships can be extraordinarily diverse, diverge rapidly, and exhibit allometric plasticity and likely cryptic genetic variation. Thus, all the components to study the potential role of genetic accommodation in the evolution of scaling relationships are in place. Yet, studying genetic accommodation is challenging (for more detail see Levis and Pfennig 2016), and doing so in the context of scaling relationships adds the complications associated with assessing effects on multiple traits relative to each other. Below we discuss some potential avenues to overcome these challenges.

Conclusions and future directions

The study of scaling relationships is now at a point where we are beginning to understand the developmental genetic mechanisms of scaling across diverse species, and are therefore able to assess how these mechanisms have evolved. In the first part of this review, we sought to highlight examples of what can be learned from such an effort. It is now critical to design future empirical studies that facilitate meaningful comparisons across taxa so we can start to formulate a comprehensive evolutionary framework for the mechanisms of scaling relationship evolution. To that end, the availability of next generation sequencing is opening doors to investigate the genome wide underpinnings of scaling relationships and their evolution. Particularly, genome-wide comparative studies across closely related species with diverse allometries will be essential to better understand how the mechanisms of scaling relationships evolve. Similarly, it is now becoming clear that growth responses are the product of diverse, interacting pathways; therefore, it will be critical to place our study of scaling relationship evolution in the

explicit context of gene networks and gene network evolution.

An interest in scaling relationships and their evolution have been the motivation of numerous studies (Lande 1979; Moczek and Nijhout 2002; Eberhard 2009; Macagno et al. 2011) but scaling relationships have rarely been considered traits in their own right. As the role of developmental plasticity in trait evolution keeps gaining attention, it will also be critical to study the role of developmental plasticity in the evolution of scaling relationships. This will not only allow us to better understand how scaling relationships evolve but also elucidate key aspects of the process of genetic accommodation. For example, is genetic accommodation more common in exaggerated traits compared with traits that scale proportional to body size (i.e., legs or wings)? Moreover, in this article, we reviewed two aspects of developmental plasticity, yet the gap between the two, that is, understanding the developmental genetic mechanisms that in turn underlie genetic accommodation of scaling relationships, remains far from being fully understood. Genome wide comparative studies may provide critical information in this area and could shed some light on the significance of plasticity in evolutionary divergence. For instance, by contrasting gene expression patterns derived from individuals sampled from across diverse population- or species-specific allometries, we can begin to assess if and how genetic accommodation may contribute to and shape the evolution of scaling relationships.

Authors' contributions

S.C. and A.P.M. contributed to the writing of this manuscript.

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Conflict of interest statement

None declared.

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