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PERSPECTIVE

In preprints: allometry of cell types during animal growth and degrowth

Macey M. Wilson[1] and Rachel H. Roberts-Galbraith[2,*]

Ontogenetic allometry refers to the phenomenon in which features such as limbs or organs change size relative to the whole organism during growth and development (Huxley, 1932; Huxley and Teissier, 1936; Thompson, 1917). A familiar example of allometric scaling can be seen in the large head of a human infant relative to body length. Through postnatal development, the human head and brain grow more slowly than the body as a whole, which results in a strikingly different proportionality in the average adult body plan. In contrast, the human heart grows at a rate similar to whole-body growth; such change of organ size at a rate proportional to the whole is referred to as isometric growth (Moore, 1983; Thompson, 1917). Allometry has also been applied to describe scaling relationships between size and other biological measurements. In 1932, Max Kleiber first uncovered that many, if not all, animals follow a ¾ power scaling of metabolic rate relative to body mass (Kleiber, 1932). The concept of allometry has been more recently applied at the level of single cells to describe ratios of cell types to one another across time, and to express relationships between the size of organelles or other intracellular structures to the whole cell (e.g. Hara and Kimura, 2009; Rafelski et al., 2012).

One emerging model for the study of tissue scaling is the planarian, a type of aquatic flatworm well known for its regenerative prowess. Planarians display extraordinary plasticity in the adult form, growing and shrinking their body size by over tenfold in response to food availability. The unique features of planarians have allowed scientists to examine organ size and cell number in response to changing body size and regeneration. Baguñà and Romero first quantified cell types in the planarian body after dissociation, finding that most broad categories of cell types scale at near-constant ratios during growth, degrowth and regeneration, with the exception of stem cells, which become more abundant after feeding (Baguñà and Romero, 1981). When markers of cell types began to be identified, scientists showed that a specific subset of neurons scaled with body size in a near-linear fashion (Oviedo et al., 2003). Further, organs such as the brain also scale proportionally and regenerate to predictable sizes after injury (Hill and Petersen, 2015; Takeda et al., 2009). In contrast to a purely isometric scaling model, however, sexual planarians dynamically develop gonads during animal growth and sexual structures regress during degrowth (Ghirardelli, 1965; Wang et al., 2007).

In a recent preprint, Emili and colleagues comprehensively explored cell type-specific allometry in the planarian *Schmidtea mediterranea* (Emili et al., 2024 preprint). To characterize cellular ratios fully, the authors used single-cell transcriptomic methods to establish the number of each cell type within small, medium and large planarians. Their data allowed them to develop a model in which many planarian cell types have fixed ratios during growth and degrowth, therefore scaling isometrically (Emili et al., 2024 preprint). However, their research uncovered that small planarians had a relatively higher proportion of some head-enriched neurons and secretory cells and that large planarians have a higher proportion of select intestinal, muscle and parenchymal cells (Emili et al., 2024 preprint). They also found an over-representation of specialized neoblasts in the large planarian group, which could imply a higher cell turnover rate or an increased time to complete differentiation in larger animals. The author's findings largely support the conclusions from earlier work on planarian scaling, but also highlight new, important deviations from isometric scaling.

Emili and colleagues also provide cellular insight into size-dependent energy storage in planarians, which were previously shown to follow Kleiber's ¾ scaling law (Thommen et al., 2019). Thommen and colleagues argued that smaller planarians dedicate energy to cell proliferation and differentiation, whereas larger animals store excess energy as lipids and glycogen in the intestinal epithelium. Along with their data on cellular ratios, Emili and colleagues uncovered that basal cells of the intestine change their gene expression in response to animal size by dynamically upregulating lipid synthesis and assembly genes. They hypothesize that basal cells are most likely the specific cell type responsible for the lipid storage differences of small and large animals (Emili et al., 2024 preprint; Thommen et al., 2019). Basal cells were only recently characterized as a subset of intestinal cells that express transcripts consistent with lipid storage and synthesis (Fincher et al., 2018; Forsthoefel et al., 2020). Taken together, the data indicate that basal cells are highly responsive to animal size during growth and degrowth, potentially as a cause or effect of metabolic changes.

Although allometric observations abound in the animal and plant kingdoms and beyond, the mechanisms underlying the relative scaling of organs, physiological activity, and cell composition remain elusive. In this preprint, Emili and colleagues have laid a strong foundation and rationale for studying allometry in planarians. Their finding that distinct cell types scale isometrically and allometrically within the same organism indicates that different regulatory processes likely underlie cell number for each organ and/or cell type. Further, the findings of a disproportionate abundance of neurons in small animals and an abundance of basal cells in large animals indicate that tissue-specific regulatory processes can even act in contradictory ways across animal size. Diving into cellular and molecular mechanisms, researchers have already identified pathways that regulate brain size in planarians. During growth, degrowth and regeneration, brain scaling relies on cell birth and is regulated by a Wnt/Notum feedback system and a fibroblast growth factor receptor-like pseudoreceptor (Cebrià et al., 2002; Hill and Petersen, 2015). With a complete cellular atlas across animal scale, planarians are an ideal model organism with which to explore the regulation of tissue proportions and cellular ratios. Further, their

[1]Department of Genetics, University of Georgia, Athens, GA 30602, USA.
[2]Department of Cellular Biology, University of Georgia, Athens, GA 30602, USA.

*Author for correspondence (robertsgalbraith@uga.edu)

M.M.W., 0009-0005-0672-9673; R.H.R.-G., 0000-0002-2682-2366

strong regenerative ability will also allow researchers to understand the mechanisms underlying accurate rescaling of organ size and restoration of tissue composition after injury.

Competing interests
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