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Scaling of subcellular structures

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Abstract

As cells grow, the size and number of their internal organelles increase in order to keep up with increased metabolic requirements. Abnormal size of organelles is a hallmark of cancer and an important aspect of diagnosis in cytopathology. Most organelle vary in either size or number, or both, as a function of cell size, but the mechanisms that create the variation remain unclear. In some cases, organelle size appears to scale with cell size through processes of relative growth, but in others the size may be set by active measurement systems or by genetic programs that instruct organelle biosynthetic activities to create organelles of a size appropriate to a given cell type.

Keywords

Organelle size; Cell size; Mitochondria; Nucleus; Spindle

Introduction

Cells are not simply watery bags full of enzymes, but rather are highly complex structured systems composed of numerous sub-structures. This is most dramatically evident in eukaryotic cells, which are partitioned into membrane bound organelles that serve distinct biochemical functions. In any given species and cell type, it is observed that cells have a reproducible geometry, expressed in terms of the size, shape, and position of the organelles (Rafelski and Marshall 2008). But compared to our advanced knowledge of organelle composition and function, we still know far less about organelle size and shape. When viewed at a suitably abstract level, the cell faces the same challenges as a developing organism in terms of how to make each of its component parts, where to put them, and how big to make them. This last question gets us to the idea of scaling in biology. At the organismal level, it is commonplace knowledge that larger organisms have larger body parts, even within a single species. Adult humans have bigger organs than children do, and the same is true for taller adults compared to shorter adults of the same age. Starting with Huxley, it has been appreciated that the size of a body part or organ is often related to the size of the whole animal by a power law relation (Huxley 1932). This is to say that when the size of a part is plotted versus the size of the whole body, on a log-log plot, the result is a straight line. The slope of tis line is the scaling exponent. If the slope is one, then the sizes are proportional, and such a scaling relation is called isometric. If the scaling exponent is different from one, it means that as the whole organism grows, the part

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will become disproportionally large or small, and such scaling is called allometric. Scaling relations, defined by power laws, are seen throughout biology at the organismal scale, and it is naturally of interest to know how much this behavior will extend at the cellular and sub-cellular levels.

In the next section we will consider the experimental evidence that scaling exists for subcellular structures. We care about scaling within cells for three reasons. The first is that scaling of intracellular structures is a key factor that determines the geometry of cells. We can define cell geometry in terms of the size, shape, and positions of all intracellular structures. Scaling can affect all three of these geometrical aspects of the cell. As cells grow, scaling affects the relative sizes of the organelles. For membrane-bound organelles, shape is determined in large part by the surface to volume ratio, such that if the surface area and the volume of an organelle scale differently with cell size, the result is that organelle shape will change as the cell grows. Position of organelles can be affected by scaling when one organelle grows so large that it physically displaces other organelles within the volume of the cell. Thus, scaling is a major factor in cell geometry (Figure 1).

A second reason to care about scaling is that if biology has evolved mechanisms to ensure scaling of subcellular components, it suggests that this scaling may have a fitness benefit, that is, that larger cells may need larger organelles for some physiological reason. The mere fact that scaling takes place does not prove that it serves some useful purpose, but it does raise the possibility. If larger cells need larger organelles, this in turn suggests that organelle size is important for their physiological output, a common assumption but one that has seldom been tested experimentally. Knowing how organelle size contributes (if at all) to organelle function would provide a key missing element in the study of organelle size control.

A third reason to care about scaling within cells is that it provides a window into the pathways of organelle biogenesis and trafficking. Huxley interpreted power law scaling relations in terms of relative growth processes, which we will discuss below for cells, but in fact there are a number of possible mechanisms that could underlie scaling. By asking not just do organelles scale with cell size, but by what mechanism, we have a novel way to probe organelle biology. We note that the term “scaling” has a somewhat different meaning in physics, where it describes how one physical quantity varies as a function of another at a coarse-grained level. For example, we say that the end-to-end length of a polymer scales as the square root of the polymer length. A key point of scaling in such cases is that we can ignore the “pre-factor”, that is, we don't care about constants of proportionality, just about whether quantity A is proportional to B, or to the square root of B, or to some other power of B. The term Scaling in biology has the similarity that is also tends to focus on power law relations, but there is also, perhaps, a deeper relation. If we ask, why does some aspect of biological size scale with the size of the organism or cell, one possible answer is that a physical function of the part is related to some physical feature of the whole. For example, the fins of a fish may need to show a certain scaling relation to the surface area of the fish because bigger fish experience larger drag forces from the surrounding water. At the cellular level, one organelle may need to have a volume proportional to the cell surface area, while another may need to have a volume proportional to the cell volume. The nature

of the scaling relation may thus provide an important biophysical clue to organelle function in the context of the whole cell. One point that needs to be treated carefully is whether one should consider scaling relative to the size of the whole cell, or to the size of the cell minus the size of the organelle under consideration. For example, if a cell contains a huge vacuole, it may be the case that that vacuole constitutes a large fraction of the total cell volume, in which case plotting vacuole size versus cell size might give an impression of isometric growth simply because the growth of the vacuole dominates the growth of the whole cell. An alternative approach is to plot the vacuole versus the volume of cytoplasm outside the vacuole.

This review will start with a literature survey documenting examples scaling of subcellular organelles. This survey is not meant to be exhaustive, but is just intended to convince the reader that scaling is an issue for cells. Next, we will consider in more detail the idea described above that organelle size may contribute to organelle function. We will close by examining mechanisms by which the size of subcellular structures scales with cell size. As a starting point for this discussion, we will consider here some general types of scaling models.

The simplest scaling mechanism is “limiting precursor”, which can be summed up by the concept that larger cells make more of everything. For example, the number of ribosomes per cell is generally proportional to cell size, so bigger cells can make more protein per unit time. If larger cells produce more building blocks, due to more ribosomes, more surface area for nutrient uptake, etc., then they would be able to build larger subcellular structures. A second, and also very simple, model is known as “relative growth”. In this model for scaling, the cell as a whole grows at some rate that is independent of the size of the organelle, while the organelle grows at some rate that is independent of the size of the cell. The whole and the part each follow their own growth laws, whatever those are, and otherwise ignore each other. This is the type of scaling that Huxley proposed for scaling of body parts in animals. If both the whole and the part grow exponentially, such a relative growth model leads directly to the type of power law scaling relation that has been so extensively documented in animals. We say that relative growth is one of the simplest mechanisms for scaling, because it essentially ignores any interaction between the whole and the part. A third model is the “demand driven” model, in which organelle biogenesis is triggered by a lack of its output, such that organelles will grow until the cell has enough of whatever produce the organelle produces. The fourth model is in many ways the most interesting – size measurement. In this type of model, the size of one component, either the whole or the part, is measured, and then this measurement is used to regulate the size of the other. For example, an organelle biogenesis pathway may sense the size of the cell and adjust its rates accordingly. The last model we consider is a “programmed scaling” model, in which cells regulate biosynthetic processes so as to produce an organelle appropriate to the size that they cell will eventually attain. The analogy here would be an architectural plan for a building, which will then be used by construction engineers to place an order for the appropriate quantity of steel and concrete.

Among these five models, size measurement is perhaps the most interesting in the sense that it raises the most challenging mechanistic questions, but biology doesn’t exist to stimulate

our curiosity, just to survive. If it turns out that organelle scaling can be achieved by simpler mechanisms that don't require measurement of complex feedback signaling pathways, such an outcome should not be viewed as a disappointment. In fact, the simpler the system, the easier it would be to evolve.

Observations of Scaling within Cells

We will start with a few examples of organelles in which increased cell size appears to correlate with increased organelle size or number. In some of these cases the size has been carefully measured in a large number of cells and a scaling exponent calculated, but in other cases the observation is more qualitative in that we know that larger cells have larger organelles but we don't necessarily have careful data on scaling exponents.

Nuclei

By far the most well known example of scaling is the nearly universal correlation between nuclear size and cell size (Gregory 2001). Within any given type of organism, bigger cells have bigger nuclei, usually showing a linear scaling relation with nuclear volume proportional to cell volume (Jorgensen 2007; Neumann 2007). The relation between nuclear size and cell size is complicated by the need to also consider genome size. Large genomes require larger nuclei, and also are correlated with larger cell size (Gregory 2001). It is clear beyond any doubt that genomic content, itself, is a causal factor in determining cell size. Polyploidy, for example, always correlates with increased cell size (Fankhauser 1945; Baetcke 1967; Henery 1992). A recent summary of this correlation found that the relation between ploidy and cell size is well fit by a power law with scaling exponents in the range 0.7-0.9 (Gillooly 2015). This is provocatively close to ¾, which would be quite interesting and suggestive given the well known ¾ power law scaling of animal metabolism to body size (Glazier 2005). However, substantially more precise measurements with larger numbers and a larger range of ploidies would be needed before we can conclude that the scaling exponent is really ¾. It is also worth pointing out here the scaling as a function of ploidy is not just a quirk of amphibians – within the human body, and especially the central nervous system, many cells show increase levels of ploidy (Gillooly 2015). The tight scaling relation between genome size and cell size was exploited in an ingenious way to estimate the genome size of extinct dinosaurs based on cell size measurements of osteocytes from outlines visible in fossil remains (Organ 2007).

While it is clear that DNA content per se plays a causal role in nuclear size, the role of overall cell size is harder to demonstrate. There is clearly a correlation, but it could be that a single causative factor, genome size, affects both nuclear size and cell size, in which case cell size per se would not need to have a direct influence on the nucleus. The scaling of nuclear volume with cell volume during cleavage of amphibian embryos argues that changing cell size, without altering ploidy, is sufficient to change nuclear size. One biochemical factor that does seem to influence nuclear size is the nuclear import machinery (Levy 2010; Vukovic 2016). If larger cells have a greater capacity for nuclear import, this would lead to a direct influence of cell size on nuclear size. Because nuclei are generally spherical, nuclei with larger volume will also have larger surface areas. However,

expansion of the nuclear envelope does not lead to increases in nuclear volume (Walters 2019) suggesting that the increase in surface area as the nucleus grows may be a passive response to the increase in volume, rather than a determining causal factor that drives the volume increase.

Nuclear sub-compartments also show scaling, for example the nucleolus is larger in larger cells (Noel 1971; Wuehr 2008; Weber 2015)

Spindles

Mitotic and meiotic spindles are among the best-investigated examples of organelle size scaling. Spindle length and width both scale with respect to cell size (Wuehr 2008; Hara 2009) and with respect to ploidy (Hara 2013). Some of the scaling of spindle size appears to reflect scaling of microtubule dynamics as a function of cell size (Loughlin 2011; Lacroix 2018). It isn't just the microtubules of the spindle that scale with cell size, the size of the chromosomes and centrosomes are both larger in larger cells (Keiserman 2011; Ladouceur 2015; Decker 2011). Conversely, altering the number of centrosomes can cause a change in the length of the spindle (Greenan 2010; Keller 2010).

Microtubules

Microtubule asters have the tendency to grow until the microtubule tips hit the surface of the cell. In such a case, the scaling becomes trivial in that the average microtubule length within the aster would equal the diameter of the cell (Wuehr 2010; Mitchison 2012).

Mitochondria

In most cell types where it has been measured, the volume of mitochondria is proportional to the volume of the cell (Posakony 1977; Rafelski 2012). In budding yeast, the quantity of mitochondria is set during the budding process, such that each newborn bud is born with a well-defined ratio of mitochondrial to cell volume (Rafelski 2012). The mitochondria to bud volume ratio is robust and is maintained even in the face of reduced mitochondrial import or reduced mitochondrial biogenesis in the mother cell. An interesting aspect of mitochondrial scaling in budding yeast is that the mitochondria forms a network associated with the cell cortex (Agar 1957), which means that as the cell grows, the total size of the network increases as the cell radius cubed, but the network is constrained to a surface area proportional to the cell radius squared. This is expected to lead to a denser packing of the mitochondrial tubes on the surface of larger cells.

Vacuole/Lysosome

In budding yeast, the volume of the vacuole scales relative to the volume of the cell with a power-law scaling relation, such that vacuole surface area is proportional to cell volume while volume scales with a power law exponent of 1.4 relative to cell volume. (Chan 2014). Vacuoles grow constantly during the cell cycle (Uchida 2011; Chan 2016) at a rate that depends on membrane trafficking rates (Chan 2014). An important consequence of this scaling relation is that when cells become large, the vacuole takes up a disproportionally large portion of the total cell volume. This can lead to deceptive outcomes in screens for

vacuole size mutants, because any mutation causing cells to become larger on average, will potentially be interpreted as a vacuole size increase mutation.

Chloroplasts

Most plant cells contain numerous chloroplasts, and the number of chloroplasts per cell increases when cells become larger (Butterfass 1973; Possingham 1969; Pellegrini 1980). In unicellular algae, it is more common for a single large chloroplast to occupy most of the cell volume, and so in this case chloroplast volume is proportional to cell volume for the trivial reason that the chloroplast occupies most of the volume.

Endoplasmic Reticulum

Endoplasmic reticulum often ramifies throughout the cytoplasm, such that the total quantity would be expected to scale proportionally with the total cell volume. In some cases, though, when cell shape or size changes dramatically during differentiation, the ER may show substantial changes in its organization.

Plasma Membrane

The scaling relation between plasma membrane surface area and cell volume mainly depends on the shape of the cell. For very flat cells, the surface area can be roughly proportional to the volume. For spherical cells, volume scales as the radius cubed while surface scales as the radius squared, such that larger spherical cells will have less surface per volume compared to smaller spherical cells. In certain specialized cases, the membrane can invaginate into the cell in order to provide between access to extracellular ions or signals to deep cytoplasm. For example, when cardiomyocytes expand, the density of T-tubules per unit volume increases within the cell, presumably to allow better access to regions deep inside the cell (Hirakow and Gotoh 1980).

Cilia and flagella

The number of cilia or flagella present on the surface of a eukaryotic cell may, in some cases, scale with cell size. This is certainly true for ciliates (Bakowska 1980), and has more recently been shown to be true for multiciliated epithelial cells, with the number of cilia proportional to the apical surface area (Nanjundappa 2019). With respect to ciliary length, there is a tendency for larger Chlamydomonas cells to have longer flagella (WFM unpublished observations). Theoretical analyses show that the force that a cilium or flagellum can exert on the surrounding fluid depends on the ciliary length (Sleigh 1962).

Organelles that do not show size scaling

Ribosomes

At this point the reader may be starting to wonder whether there are any important cellular structures that don’t scale with cell size. Ribosomes are a perfect counter-example to the general scaling trend that we see. Each ribosome is composed of a fixed number of proteins and RNA molecules that self assemble. The size of a ribosome is thus set by self-assembly of the individual components, which only fit together one way, and hence ribosomes are

all the same size regardless of how big the cell is. This is going to be true for all strictly self-assembling protein machines, including for example RNA polymerase or the proteasome. But even in such cases, scaling is seen, in terms of the number of ribosomes per cell (Bakshi 2012).

Intracellular Trafficking Vesicles

As with ribosomes, the vesicles that mediate trafficking between cellular compartments are, for the most part, fixed in size, as dictated by the self assembly of protein scaffolds which set the curvature of the vesicle membrane (Zhang 1998; Bonafacino 2003; Miller 2015).

Centrioles

Centrioles typically have a constant length in a given cell type, that does not vary strongly with cell size. Unlike ribosomes or vesicles, centriole number also does not vary with cell size, at least in most cells. With the exception of multi-ciliated epithelial cells and ciliates (discussed above), cells typically have exactly two centrioles per cell. When this number is altered, for example by ablation or by mis-segregation of centrioles, a copy number of two per cell is re-established over the course of a few generations (Marshall 2007).

Functional Consequences of Subcellular Scaling

Scaling is an interesting phenomenon that lies at the heart of cell geometry, and while it poses a challenge to understand how scaling can be achieved, one also must ask whether it matters for the fitness of a cell. In this section we consider two avenues for exploring the biological relevance of scaling: biochemical output of organelles and organelle size alterations in cancer.

Organelle function

One reason that a cell might care about the size of its organelles is if organelle size relates to its function. One such relation has to do with biochemical output. We view organelles as containers in which chemical reactions take place. Just as with the reaction vessels inside a chemical factory, higher flux and capacity is expected to require large volumes and surface areas. Most of the evidence in this regard is correlative – cells that are specialized for certain biochemical activities generally show increased size for those organelles that encapsulate the relevant pathways. For example, peroxisomes increase in both size and number in cells undergoing fatty acid beta oxidation and other metabolic activities involving the peroxisome (Chang 1999; Smith 2000). A different type of scaling relation has recently been found in which mitochondria membrane potential and metabolic function seems to depend not only on mitochondrial size but also on the size of the cell as a whole (Miettinen 2016), suggesting that the relation between organelle size and function will be quite complex.

For organelles with mechanical functions, scaling with size can reflect the need for increased mechanical output (in terms of force, distance, etc.) in larger cells. For example, larger cells might require longer or more cilia to propel them through the water. In cells whose expansion is driven by an internal vacuole, it is self evident that increase in vacuole size will be related to increase in cell size. The correlation of spindle length with cell size is thought

to reflect the need to partition chromosomes over longer distances during division of larger cells.

The only problem with all of these examples is that they are correlations, and, strictly speaking, none of these examples actually proves that larger organelles can support larger metabolic flux. The only way to prove the thesis is to understand enough about the pathways that regulate organelle size that is would become possible to tune organelles to a specific size of our choosing, and then measure biochemical output. In the case of endoplasmic reticulum, one of its key biochemical functions, protein folding, does indeed appear to increase as a direct result of increased size (Schuck 2009), but to our knowledge this remains the only example for which this has been shown. As our understanding of organelle size control pathways develops (Chan 2012), we are rapidly reaching the point that such a test will become possible.

Cancer

Changes in organelle size are a hallmark of cancer, and frequently form the basis for diagnosis in cytopathology. Perhaps the best-known case is the Pap test for cervical cancer, in which increased nuclear size is one of the defining features of a positive test. As with the biochemical output question, the existing data from cancer cells is largely correlative – various organelle size and scaling changes correlate with different types of cancers. Quantitative measurements of nuclear size and shape, for example, can have high predictive value in classifying cancer cell types (Rosenblatt 1993). While we believe that the dramatic scaling alterations are likely to indicate different functional alterations in the affected organelles during neoplastic transformation, it is formally possible that the scaling changes are simply epiphenomena, and play no causal role in malignancy. The only way to demonstrate causation is to be able to alter organelle size in cancer size through direct effects on size control pathways, and then ask how this might affect cell functions such as invasivity or resistance to chemotherapy.

Mechanisms of Subcellular Scaling

Biological scaling is a description of a relation between the size of a part and the size of the whole. Often, scaling is depicted by plotting organelle size versus cell size on a log log plot, and then fitting a straight line to obtain a power law relation, and it is important to recognize that there is nothing magical about being able to fit a straight line to such data, especially on a log-log plot. Although it is true that Huxley’s relative growth concept can predict power law scaling, there mere observation of an apparent power law does not by any means prove that relative growth is the mechanism at work. For one thing, many different functional relationships will look like approximately like a straight line on a log-log plot, so even the conclusion of a power law relation is often on shaky ground. This is especially true because in most cases, cell size can only vary over about a two-fold range. Over such a restricted range of variation on one axis, almost any curve will be approximately a straight line on the plot. It is therefore important to consider possible mechanisms that could result in scaling, of which relative growth is just one, and not to be overly impressed by the power law relation, unless it is truly demonstrated with extensive data covering a larger range of

cell sizes. We will still use the term “scaling” to describe situations where larger cells make larger or more abundant organelles, even if the scaling may not truly follow a power law. With these disclaimers in mind, we consider several mechanisms, ranked roughly in order of how complicated that are to achieve, with the idea that simpler ideas should be explored first.

Limiting Precursor

An almost trivial explanation for scaling is the fact that larger cells will, in general, have a higher biosynthetic capacity (having more ribosomes and so forth; Figure 2) and hence be able to make more of everything (Bakshi 2012; Lin 2018), although it is not necessarily the case that individual protein quantities are linearly proportional to cell volume (Cookson 2010). It has recently been found that when cells become extremely large, the biosynthetic capacity is no longer able to scale with size, resulting in a cytoplasm that becomes progressively diluted (Neurohr 2019).

Specific cases in which increased quantity of precursor for an organelle lead to increased organelle size include microvilli (Stidwell and Burgess, 1986), whose growth is promoted by increased quantities of actin, peroxisomes which become larger in response to increased import of internal matrix proteins (Veenhuis 2003), and Woronin bodies, a specialized form of peroxisome in fungal cells whose volume is increased when its key internal protein, known as HEX, is provided in larger quantities, suggesting that increased import of HEX causes the peroxisomes to “inflate” as they differentiate (Liu 2011).

The idea that bigger cells make more of everything, which in turn leads to larger organelles, is most compelling when organelle size is set directly by the available pool of precursor molecules. Such a “limiting precursor” scheme was first proposed by Kuchka and Jarvik (1982) as a model for length determination in eukaryotic flagella, but is likely to apply, at least to some extent to other cellular structures (Goehring and Hyman 2012). The inspiration for this model was the observation that when cells are induced to regenerate flagella in the absence of new protein synthesis, they typically regenerate flagella of only half the normal length (Rosenbaum 1969). Under the assumption that flagellar length is set by the precursor pool, and with the further assumption that 100% of the precursor is consumed in the construction of the flagella, then a clear prediction is that in cells with variable numbers of flagella, the average length of the flagella should be proportional to 1/N where N is the number of flagella. Kuchka and Jarvik tested this prediction using mutants with variable flagellar number. Although they concluded that flagellar length was independent of flagellar number, more careful measurements showed that in fact flagellar length does decrease with increasing N, but it does so less steeply than 1/N, likely due to the dynamic nature of the flagellar length control system (Marshall 2005).

Centrosome size in *C. elegans* shows a very clear 1/N dependence of size on number, thus supporting the limiting precursor type of mechanism in this case (Decker 2011). Similarly, when spindles assemble in Xenopus extract encapsulated in droplets of varying size, larger droplets form larger spindles in a manner suggestive of a limiting precursor mechanism (Good 2013; Hazel 2013). It thus seems that when considering the size and scaling of any

subcellular structure, the limiting precursor mechanism should be considered as a simple mechanism for scaling and only rejected given additional experimental information.

Relative Growth

An appealing feature of the limiting precursor mechanism for scaling is that it does not require anything in the cell to "know" how big the cell is. Here we use the term "know" to mean that a pathway or process is regulated by a signaling pathway that responds to cell size. Another class of scaling mechanisms that avoid the need to measure size is the relative growth mechanism. Relative growth was proposed by Huxley as a way to explain the power law relations between the size of organs and whole animals. In the relative growth model, the part grows according to some exponential growth process, while the whole grows according to another exponential growth process, and in general the two processes will have different growth constants. As a result of these two growth processes, the size of the part ends up being related to the size of the whole through a power law (Huxley 1932). Because, in general, the growth constants for the part and for the whole are different, this is referred to as allometric growth. In the case of subcellular scaling, the "part" would be the organelle, and the "whole" would be the cell.

How do we know if relative growth explains a particular example of scaling? It is not sufficient to simply measure growth and show that the organelle grows at a constant rate, because this could simply indicate a regulated growth process that is responding to growth of the cell as a whole. The key is to perturb the size of either the organelle or the cell, and ask whether this has any effect on growth rates. This is easiest to do in systems capable of regeneration (Tang 2017). For example, red deer shed their antlers each year and have to re-grow them, and each year they re-grow to a size appropriate to the size of the animal, requiring faster growth from year to year as the animal grows (Huxley 1932). Such a phenomenon clearly rules out simple relative growth as the explanation fro scaling. An almost identical case is seen in the flagella of Chlamydomonas. These flagella can be induced to shed via pH shock, after which they grow back to a length appropriate to the size of the cell (Rosenbaum 1969). This regrowth takes place even in cells that are arrested in their own growth (gametes), showing that it is not a relative growth process. A more dramatic example was provided by Morgan using the giant ciliate Stentor. This single celled organism can be up to a millimeter in length and is able to regenerate after being cut into pieces. Morgan showed that when a Stentor cell is cut in half, each half re-forms a normal looking cell in which all visible structures have re-scaled to half their normal size (Morgan 1901).

For situations in which a cell or organelle does not regenerate, other means are required for transiently changing the size ratios. In budding yeast, mutations affecting organelle inheritance were used to produce mother or daughter cells with increased or decreased vacuole size, and it was found that such perturbations had no effect on vacuole growth rates, suggesting in this case that indeed a process of relative growth provides the basis for size scaling (Chan 2016).

Demand driven size regulation

Given that organelle size and function are related, one can imagine a scheme in which the function of an organelle is assessed, and if the level of function is not high enough, this would serve as a stimulus to trigger increased organelle biogenesis. Such demand-driven size regulation would then lead to subcellular size scaling since larger cells would presumably require more functional output from the organelle. One simple example of evidence supporting demand-driven scaling is the fact that inhibition of protein synthesis lead to reduced size and number of the Golgi apparatus (Flickinger 1971). A clear case of such demand-driven synthesis is seen for endoplasmic reticulum. Secretory specialist cells always have a high ER content compared to other cell types. For example, When B cells differentiate into antibody-secreting plasma cells, they show a large increase in ER content, presumably as a result of increased demands on the secretory system (Wiest et al. 1990).

A key biochemical function of the ER is to fold proteins, and when protein folding capacity is insufficient, this leads to transcriptional up-regulation of genes involved in ER biogenesis (Cox 1997). Larger cells, with their increased quantity of ribosomes, presumably synthesize proteins at a faster rate, and therefore require a larger quantity of ER to fold them. We can predict, therefore, that abrogation of the UPR may alter the scaling relation of ER to cell volume, but this idea has not to our knowledge been tested. It is, however, known that artificial triggering of the UPR will cause cells to accumulate increased quantities of ER (Bernales 2006).

Measurement-based scaling

One of the reasons that biological scaling is so interesting, in any context, is that it suggests the possibility of a system capable of measuring its own size. If a cell can measure its size and adjust organelle size accordingly, an explanation would be called for regarding how a cell is able to measure its own size in the first place. Here, scaling is viewed as a hallmark of measurement. However, in order to avoid anthropomorphism, we should be careful about what we mean by “measurement”. We do not mean to imply a conscious mind that reads some measuring instrument. In the context of subcellular scaling, measurement can be defined as a mechanism by which the rate or extent of some cellular process depends on the size of the cell.

Direct evidence that organelle biosynthetic pathways are regulated by measurements of cell size are few and far between. Perhaps the most clear-cut instance has been found in the nuclear import pathway. Importin alpha, a protein that regulates both nuclear transport as well as aspects of spindle assembly, can be localized as a peripheral membrane protein on the inner surface of the plasma membrane (Brownlee 2019). Because smaller cells have a higher surface to volume ratio, a larger proportion of the importin alpha protein will be stuck on the cell surface in smaller cells. This provides a natural feedback control by which larger cells experience a higher concentration of free importin alpha, and are thus able to assemble larger nuclei and spindles.

A second aspect of measurement-based control is the possibility that scaling may involve measurement of not only cell size but also organelle size. Flagellar assembly

in Chlamydomonas (Wemmer 2007) shows evidence of being regulated as a function of flagellar length. When flagella regenerate after being shed, the do so with decelerating kinetics, with a growth rate roughly proportional to 1/L (Marshall 2005). The growth rate is a function of length, rather than time after the start of regeneration, as evidenced by experiments in which growth was arrested part way through regeneration and then restarted, in which case the growth rate was exactly that expected given the length (Marshall 2005). This length dependence of growth rate is due to the fact that entry of cargo proteins, carried by a motor based transport system, into the growing flagellum, is itself length-dependent (Engel 2009; Ludington 2013; Wren 2013; Craft 2015; Wemmer 2020). How the entry of the transporters is regulated as a function of length remains an open question. Several theoretical models for length sensing mechanisms have been proposed and analyzed mathematically and experimentally (Ludington 2015; Ishikawa 2017; Hendel 2018), but the precise mechanism by which length is sensed in this case remains to be determined. Part of the challenge with any measurement model is understanding not only how the size is measured, but how this measurement is transduced into assembly rates. In the case of flagella, possible points of regulation include actin-mediated entry of transport cargo (Avasthi 2014), assembly of motor proteins with cargo complexes (Hendel 2018), and loading of cargo proteins onto transporters (Wren 2013; Craft 2015; Wemmer 2020).

Programmed Scaling

Discussions of scaling can be complicated by the fact that there are at least two sources of cell size variation. One type of variation is cell-to-cell variation within a given cell type. For example, among a genetically homogenous population of yeast cells, some are larger than others due to differences in cell cycle state, replicative age (mothers are larger than buds, and older mothers are larger than younger mothers), environmental conditions (nutrients, temperature, etc.), and even just random biological noise. Scaling in response to such variation among genetically identical cells requires a way to link organelle size to cell size on a per-cell basis. All of the mechanisms discussed above fall into this category – something about the size of a particular cell influences the machinery that determines organelle size.

There is, however, a second source of cell size variability, and that is genetically programmed variation between cell types or species. Within a given multicellular organism, some cell types are larger than others. For example, in humans, the Mueller cells of the retina dwarf the neurons that they support. During cell differentiation, distinct cell types turn on different patterns of gene expression which encode biochemical and functional differences. It is highly likely that these same programs of gene expression may include differences in pathways that determine cell and organelle size. For example, a cell destined to be a secretory cell “knows” that it is a secretory cell, in the sense that it turns on genes required for secretion. It would be logical, therefore, to include in this program of gene expression high levels of expression of genes required for secretory organelle biogenesis. One can say that since a cell “knows” it will have to secrete protein, it can “predict” the need to build a large ER. Note that this idea is quite distinct from the demand-driven scaling discussed above, in which the key transcriptional even is turning on secretion, and then this is sufficient to trigger ER expansion indirectly via pathways that sense secretory output.

These two models can be distinguished by, for example, inhibiting protein secretion in secretory specialist cells during differentiation, and asking if they still show ER expansion.

Programmed differences in cell size also exist between species. For example, different species of Xenopus differ in terms of cell size in the early embryo. Both the size of the nuclei and the length of spindles scales with the size of the cells in these different species. This species-specific scaling appears to be, at least in part, specified by differences in biochemical activity of enzymes involved in microtubule turnover (Loughlin 2011) and nuclear import (Levy 2010). The enzymatic activity of katanin, a microtubule severing enzyme, is slower in species that have large cells, allowing them to make longer spindles. These species also have a higher concentration of key proteins in the nuclear import machinery, allowing them make larger nuclei. These activity differences are programmed into the proteins and expression levels themselves, and therefore represent an example of programmed scaling. The level of key nuclear import proteins also varies during development as cells become smaller and smaller, thus allowing the nucleus to become smaller ad smaller (Chen 2019), possibly representing another instance of programmed changes in gene expression giving rise to observable changes in organelle size that happen to track changes in cell size. This ability of nuclear size to be regulated by alterations in nuclear import carries over to mammalian cells (Jevtic 2019) although it is not clear whether such alterations are involved in scaling relative to cell size.

Prospects and Questions

Throughout this article, we have treated organelles one at a time, but in reality, no organelle is an island. A rapidly growing number of biochemically defined organelle contact interactions have been recognized. Quantitative measurements of multiple cellular structures show a high level of correlation between the sizes of different structures (Chang 2019). Understanding the scaling of any one organelle will, ultimately, require us to understand the scaling of all the organelles, and indeed it might prove more effective to treat cell geometry as a holistic question involving the complete set of organelles. New types of questions arise when we consider organelles together rather than individually. For example, the organelles must be packed together in a confined volume. Does the expansion of one organelle lead to compression of others? This currently remains very much an open question, and one that will need to be answered if we are to understand how a cell is built.

A second open question is how fluctuations in organelle size are related to cell size variation. It is known that organelles can show substantial cell-to-cell variation in both size and number (Hennis and Birky 1984; Mukherji 2014; Chang review 2017). Some of this variation is likely to reflect biological noise within organelle biogenesis pathways, but fluctuation in overall cell size is another source of variation that will need to be taken into account. Understanding how cells reduce fluctuations can provide new clues into regulatory mechanisms. For example, some cells have mechanisms in place to equalize the size of their organelles, as demonstrated dramatically for Chlamydomonas flagella. In this case, a cell typically has two flagella, and if one is cut off, as it growth back, the other flagellum will shorten until both flagella have achieved the same length, a behavior that is predicted from the fact that individual flagellar growth rates are adjusted based on their individual

lengths (Ludington 2012). Analysis of organelle size and number fluctuations thus provides a new window into the regulatory mechanisms controlling scaling and cell geometry, but the challenge is to develop approaches for quantifying multiple organelles in large populations of cells, in such a way that small variations in both organelle and cell size can be reliably measured. New methods for measuring cell volume (Bryan 2010; Park 2010; Sung 2013; Son 2015; Zlotek-Zlotkiewicz 2015; Cadart 2017; Martinez-Martin 2017) will be essential for this research program.

By delving into the correlations and fluctuations in cell geometry, it will be possible to bring our understanding of the cell to a quantitatively predictive level. As discussed above, such understanding will be the key to testing the relation between scaling, size, and biochemical function of organelles. Knowing how the geometry of organelles are determined within the context of the whole cell will also be an essential component in efforts to engineer cells for new purposes. Most current work on metabolic engineering or immune cell engineering has focused on providing new or altered biochemical functions, but being able to custom-design cellular sub-structure could open up entirely new engineering possibilities. Scaling, a concept that dates back to the golden age of natural history, will have a key role to play in such modern efforts.

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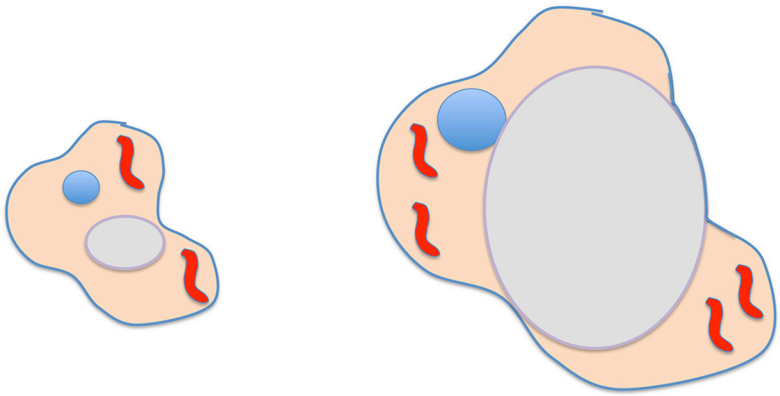

Figure 1.

Effect of subcellular scaling on cell geometry. Left panel shows a hypothetical cell containing three types of organelles, a nucleus in blue, mitochondria in red, and a vacuole in grey. The right panel shows the cell after doubling in size, under a scaling regime in which the nuclear volume shows isometric scaling with cell size, mitochondrial number shows isometric scaling with cell size, and the vacuole shows allometric scaling with cell size, with a scaling exponent greater than one. Because of allometric scaling, the vacuole takes up a disproportionate amount of the cell volume, to the extent that it begins to crowd other organelles and force them into different positions inside the cell.

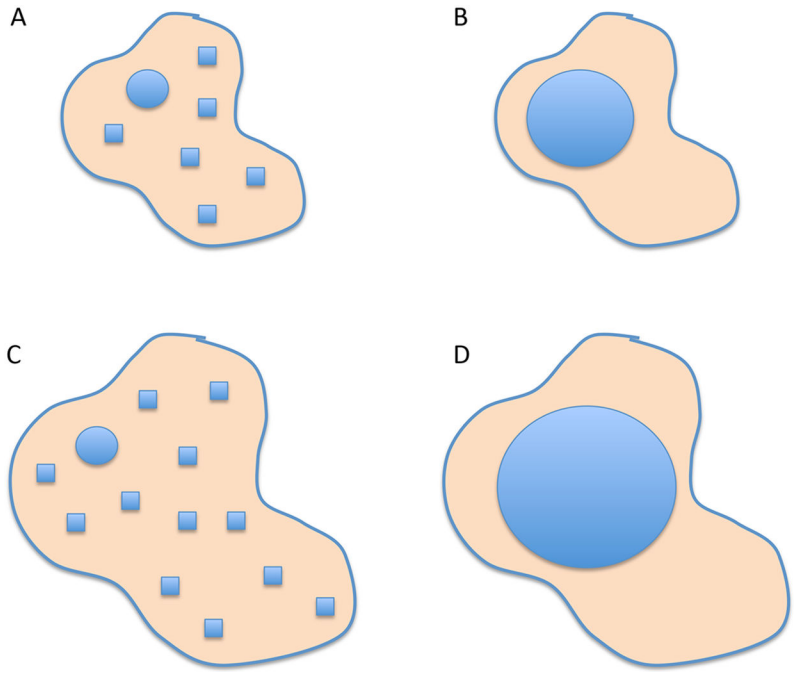

Figure 2.

Limiting Precursor model for scaling. Diagrams illustrate a growing organelle (blue sphere) whose growth requires a supply of precursor molecules (blue squares) produced in the cytoplasm. In small cells (A), the supply of precursor is small, so the growth of the organelle is restricted (B). In larger cells (C), the supply of precursor is larger simply because the cell has more biosynthetic capacity (ribosomes, etc.), hence the final size of the organelle is proportionally larger (D).