

# Genome streamlining and the elemental costs of growth

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**Pervasive relationships between growth rate, genome size and RNA content exist. One interesting potential consequence of these interrelationships is that selection for high growth rate should be associated with small genomes and high RNA content. Here, we use phosphorus (P) and nitrogen (N) demands of growth along with nucleic acid production as the currency to explore the interrelationships between growth rate and genome size in eukaryotes. We argue that reallocation of P (and eventually N) from DNA to RNA under sustained selection for rapid growth in nutritionally limited environments can lead to genome streamlining in eukaryotes, and that this mechanism might contribute to the evolution of reduced genome size.**

## Growth and genome size: correlations and causalities

Growth rate (see [Glossary](#)) is a key life-history trait that is correlated to other important traits, including metabolic rate, fecundity, and life span, and is an important predictor of fitness [1]. Although growth rate is generally defined as increase in size (biomass) per unit of time, and would thus *a priori* include all forms of mass accumulation (e.g. of adipose tissue), we focus here on growth in terms of protein synthesis.

Most species exhibit plasticity in growth rates; however, there are also patterns of interspecific variation that are tightly linked to life-cycle strategies. Such patterns have been explained by invoking both proximate and ultimate mechanisms. For example, eco-evolutionary studies have viewed growth rate variation from the perspective of environmentally driven life-history tradeoffs and corresponding fitness gain [2,3]. Concurrently, molecular biologists have primarily implicated variation in molecular-level mechanisms, such as the genetic regulators of protein synthesis, as explanations for variation in growth phenotypes [4]. Although both approaches are important to understanding differences in growth rate within and among species, there has been little integration between these ultimate and proximate lines of enquiry. In consequence we still are far from understanding how and why growth rate varies, and how it plays into the evolution of key genomic and physiological characters.

We begin by reviewing the extensive but poorly understood variation that characterizes growth rate and genome size. We then move on to explain how there might be a causal link between the two. We focus on the material costs of rapid growth in terms of P demands for ribosomes (the site of protein synthesis), but there are also N demands for the proteins themselves. We hypothesize that maintaining high growth rate under nutrient limitation can promote an evolutionary pressure for reduced genome size because there will be a tradeoff between material costs in terms of P allocated to either RNA or DNA. This implies that close causal links might exist between growth rate, cell- (or biomass-) specific RNA, genome size and cell size in some taxa ([Box 1](#)) and, hence, that reduced genome size could be a consequence of a selective pressure for high growth rate. This is a novel but also speculative hypothesis, and we do not claim that this is the universal ultimate cause of genome streamlining, which probably has several non-mutually exclusive explanations. In particular, we suggest that a causal connection between growth rate and genome size is a plausible mechanism for genome streamlining in both plants and invertebrates.

## Glossary

**Allometry or allometric growth:** the study of change in the proportional relationships of either different body parts or other characteristics (e.g. metabolic rate) in relation to body size.

**Ecological stoichiometry:** the study of the balance of multiple chemical substances and their ecological interactions and processes (*sensu* Ref. [28]).

**Elemental ratios:** the molar ratio of two or more chemical elements as constituents of a given substance.

**Genome size:** the haploid nuclear DNA content cell<sup>-1</sup> measured in either picograms (pg) cell<sup>-1</sup> (C-value) or number of base-pairs (bp).

**Genome streamlining:** the overall reduction in genome size via a number of mechanisms (e.g. differential loss of non-functioning 'junk' DNA by means of selection and/or genetic drift).

**Growth rate:** increase in size (biomass) per unit of time; maximal growth rate is represented by  $\mu_{max} = \ln(M_t/M_0)/t$ , where M = mass (g) and t = time (days).

**Nutrient limitation:** the condition whereby an organism has either insufficient access to nutrients (e.g. nitrogen or phosphorus) or nutrient reserves to support basic growth, maintenance and reproductive functions.

**Ploidy level:** the number of complete chromosome sets in the normal somatic cells of a (eukaryotic) organism.

**Polyplody:** having three (or more) complete sets of chromosomes in normal somatic cells.

**RNA:DNA ratio:** a nucleic acid index used extensively as a measure of physiological and nutritional state; often used as a surrogate for growth rate.

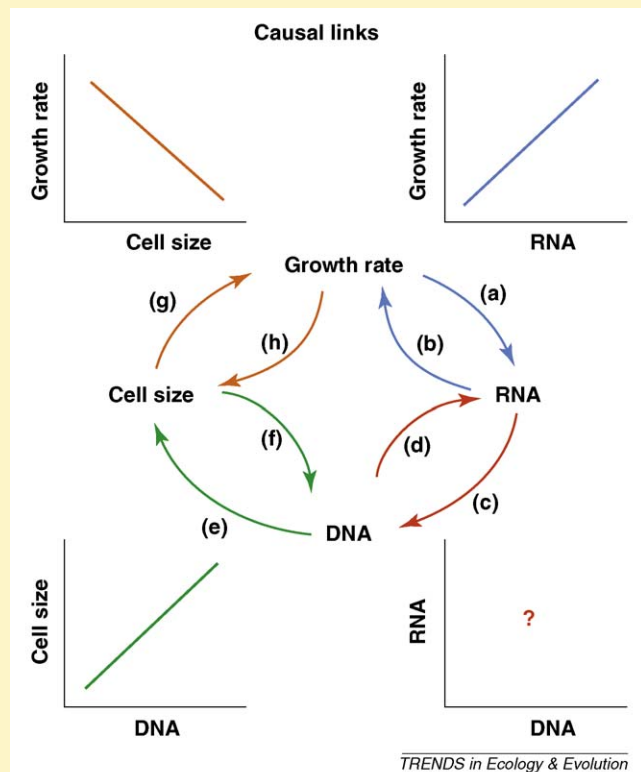
**Transposons:** 'mobile' DNA sequences that can move to different positions throughout the genome of a cell (a type of mobile genetic element).

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### Box 1. Relations between growth, genome size and cellular properties

There are many strong positive and negative correlations that tie growth rate, RNA concentration, genome size and cell size together (Figure 1). Although these patterns are central to fundamental aspects of metabolism, growth and life-history strategies, the mechanistic basis and causal directions are still unclear.

- There are strong positive correlations between cellular concentrations of RNA and maximum growth rate within and across organisms (Figure 1 a,b) [5,7,18]. The causality can work in both directions.
- There are subtler relationships between RNA and DNA content (Figure 1 c,d). The main hypothesis addressed here is that, under scenarios of P limitation, there should be a negative relationship between DNA and RNA concentrations.
- A close coupling between genome size and cell size is universal for both plants and animals (Figure 1 e,f) [9,11,12], although the cause and effect relationship is not yet clear.
- There is a strong empirical inverse relationship between genome size and cell division rate for both plants and animals (Figure 1 g,h) [9,11], although the mechanisms remain unclear.



**Figure 1.** Conceptual diagram of common relationships between growth rate, RNA, DNA (genome size) and cell size. Arrows (a–h) denote potential causality. Question mark represent the relationship under scrutiny. See text above for further explanation.

We conclude by discussing some implications of this hypothesis and suggest an empirical framework for evaluating the extent to which this hypothesis has explanatory power. Our hope is that this article will stimulate and initiate research that could increase understanding of variation in these organismal traits of fundamental importance.

### The elemental costs of growth

We start by considering the growth rate hypothesis (GRH) [5] because this logically links the elemental costs of

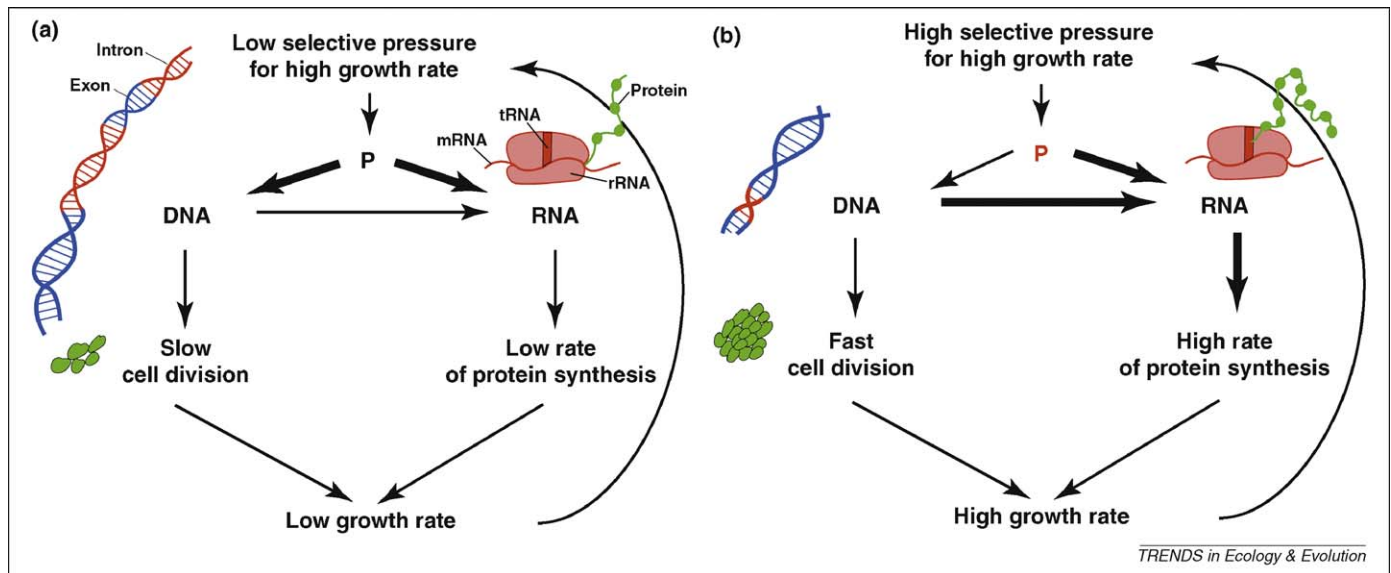
growth to the biosynthetic apparatus for protein synthesis, namely the ribosomes. The GRH is based on the observation that rapidly growing invertebrate taxa have a comparatively high percentage of P (i.e. %P by dry weight), and that a major portion of this P is found in ribosomal RNA (rRNA). We now know that there is a strong correlation between growth in terms of protein synthesis and RNA content across taxa from prokaryotes to invertebrates [5]. Given the central role of rRNA in protein synthesis and, thus, organismal growth [6], these patterns indicate that rapid growth is a P-intensive endeavor [6,7]. Scarcity of P results in major growth retardation in disparate organisms. Importantly, there is considerable genetic variation in the degree of such growth penalties, implying that P availability can be a strong selective force shaping the evolutionary trajectories of genotypic and phenotypic traits [6,8].

Evaluating this possibility requires an understanding of whether and how nutrient scarcity and high demands for P allocation to RNA covary with genome size. There is a well-established correlation between genome size and life-history traits (Box 1) that are generally under intense selection. In particular, small genomes are associated with small cell size and high growth rate across plant and animal taxa [9–11]. Given that genome size and cell size are also tightly coupled [10,12], both cell and genome size should also show a strong negative correlation with growth rate or minimum developmental rate.

Whereas rapid growth might translate into competitive advantages both within and across species, it does not come for free. Organisms have mechanisms to regulate growth rate and, thus, material investment in P. Examples of regulatory mechanisms include: (i) increasing the rate of ribosome biosynthesis [13]; (ii) altering the efficiency of ribosomal (r)RNA synthesis [14]; (iii) increasing ploidy level within somatic cells [15]; (iv) increasing the rDNA copy number [16]; and (v) regulating rDNA intergenic spacer (IGS) length variation [6,17]. Mechanisms (i) and (ii) have general validity across a wide range of taxa, where a tight correlation between body RNA concentration and maximum growth rates ( $\mu_{max}$ ) have been reported [5,18], to the extent that the specific concentrations of RNA (or the RNA:DNA ratio) are frequently used as a proxy of growth rate within species [19,20]. This apparent link between RNA concentration and growth rate implies a need for allocation of material resources to RNA when growth rate is high. Mechanisms (iv) and (v) have been shown to be potential targets of both artificial and natural selection [6], the outcome of which has major effects on the evolutionary trajectories of a range of organisms, from microbes to metazoans. Polyploidy (iii) could enhance growth [21] under certain conditions (e.g. low temperatures), but can also be associated with increased material costs for DNA, increased cell size and slower growth [22,23].

### The elemental costs related to genome size

A high growth rate confers costs, not the least of which involves high demands of P for ribosomes and N for proteins. A variety of costs have also been attributed to large genomes, especially increased mutational load [24,25] and longer replication times [9,11]. Our focus here



**Figure 1.** Two scenarios illustrating the effects of different evolutionary allocations of P to DNA or RNA. (a) Under low selective pressure for high growth rate, a significant share of P is allocated to DNA (and implicit large genome size) potentially causing slow growth rate and low rate of protein synthesis. (b) Under strong selection for high growth rate, there will be selective pressure for reallocating P from non-coding DNA to RNA that promotes high growth rate. Selection favoring ‘r-selected’ life-history traits under nutrient scarcity might generate evolutionary pressure for this sequence of events. Thickness of arrows indicates relative importance of P allocation or causality. Scenario (a) indicates large genome, high intron:exon ratio, slow rate of protein synthesis and slow cell division as opposed to scenario (b).

is on whether there are energy and material costs that could select against large genomes. We argue that the tight coupling of rapid growth and cellular rRNA copy numbers means that high growth rate under nutrient scarcity could represent an evolutionary pressure favoring reallocation of P (and N) from DNA to RNA.

One perspective is that the material costs of producing and maintaining DNA are marginal and, thus, unlikely to pose any significant selective force towards streamlined genomes [26,27]. This could be the case if simply considering dry weight, where the mass of DNA rarely exceeds 3% of total mass. However, material costs of DNA content might not be trivial for other key cell constituents such as P (and N), where a substantial portion of the total P pool might be bound in DNA. The N content (by mass) of nitrogenous bases varies from 21.5% for thymine to 51.8% for adenine [28]. Assuming 1:1-proportions between purines and pyrimidines, we can set the average N-content to 39%. For P, the average fraction of nucleotide mass is 8.7%, yielding a typical ratio of carbon:nitrogen:phosphorus of 9.5:3.7:1 [28]. This means that, in relative terms, it is costly in amounts of N and especially P to build DNA and RNA. The C:N:P stoichiometry of a typical animal tissue is ~50:7:1 [28], meaning that nucleic acids are P-demanding relative to other bodily constituents. Taken together, this reasoning implies that the number of N and P atoms used to build nucleic acids can be viewed as direct material costs associated with supporting a large genome.

RNA often constitutes the primary cellular sink of P owing to its high specific P content and bodily concentration relative to other P-rich molecules, such as ATP, AMP, ADP, free nucleotides and phospholipids [29,30]. Typically, the fraction of P bound in RNA scales inversely with body size, and is relatively small in large endotherms compared with smaller ectotherms [31]. In rapidly grow-

ing, ‘r-selected’ invertebrates, a major fraction (50–80%) of cellular P is allocated to RNA, perhaps because of a high demand for ribosomes to drive protein synthesis [7,31]. rRNA makes up some 85% of the bulk RNA and is, thus, a major player in the cellular mass-balance of P.

Although RNA generally dominates the pool of nucleic acids, DNA might not be a trivial fraction of that pool. RNA:DNA ratios in organisms typically range from unity to >10, but are often ~2–3 [20,32]. Under low growth rates, this ratio can be <1 [20]. This means that for P-limited organisms, the fraction of cellular P allocated to DNA might comprise a large proportion of bodily P content. Substantive P savings could come from an evolutionary reallocation of P from genomic DNA to growth-promoting machinery, in that it could both reduce the time needed for replication and cell division and provide additional machinery for protein synthesis. In line with this, one can envision one scenario with a large genome size (high allocation of P to DNA), a restricted allocation of P to RNA, and low growth rate (Figure 1a), and another with reallocation of P from DNA to RNA and high growth rate (Figure 1b). The shift from Figure 1a to Figure 1b might follow selective pressure for high growth rates.

### Empirical support for reallocation of P

To what extent does this prediction hold? Probable candidates for selective pressure towards streamlined genomes are taxa suffering a chronic or temporary shortage of P, especially in cases where rapid growth and high metabolic rates translate into increased fitness. There are some empirical data consistent with such an evolutionary reallocation of P from non-coding DNA to RNA. Autotrophs are often P limited [33] and often face challenges associated with allocating enough P to ribosomes to achieve optimal rates of growth [29]. The prevalence of haploidy versus diploidy in some unicellular autotrophs could be linked

with a P- (or N-) sparing strategy [22,23] and, perhaps, a reallocation of nutrients from DNA to RNA. For higher plants, it has been hypothesized that polyploidy is counter-selected under strong P limitation [34,35]. This hypothesis finds indirect support from studies indicating that increases in plant ploidy level are often associated with evolutionary reductions in genome size that could counter-balance the material costs of chromosome duplication [34,36,37]. The intriguing recent finding that unicellular algae under chronic P limitation can replace P-rich membrane lipids with sulphur- or N-containing lipids [38] also demonstrates the capacity to restructure biochemical make-up as a P-sparing mechanism.

For plants, both rapidly growing annual species and 'weedy' species tend to have small genomes [39]. Data on algal C values are relatively scarce, but the mean C values of the 240 species of unicellular algae in the Plant C value database (<http://data.kew.org/cvalues/>) appear to be smaller (0.86) than other plant taxa (6.46). In turn, the average  $\mu_{\max}$  of algae (1.08) is greater than the mean calculated from other plant taxa (0.11) [40]. Although a fair test of whether elemental reallocation from DNA to RNA is responsible for these differences between algae and higher plants requires control for phylogeny, there is indirect evidence consistent with a scenario where these tradeoffs exist. For example, the close correlation between cell volume and genome size [12] indicates that larger cells can have higher P demands and, therefore, should be inferior competitors under P-limiting conditions. Such patterns are common among diatom assemblages [41], where larger diatoms dominate areas with higher nutrient concentrations.

Whereas autotrophs are generally believed to face some degree of nutrient limitation, there is a growing body of evidence that the growth rate of animals can also be constrained by access to P [7,28,29]. There are several studies demonstrating that herbivorous invertebrates experience constrained growth owing to low concentrations of P or N in their diet (Ref. [28] and references therein). There is also direct evidence for increased RNA content and growth rate in invertebrates as a direct short-term response to adding P-enriched food to their diet [42,43]. One possibility is that the miniaturized genomes of several animal taxa known to have high growth rates and commonly facing dietary P-limitation (such as aphids, cladocerans and some dipterans) might also be linked to an evolutionary reallocation of P from DNA to RNA [44].

Similar to what have been found for plants, there seems to be compelling evidence for a link between growth rate and genome size for a range of invertebrates (Ref. [11] and references therein). For example, developmental rate is negatively associated with genome size in invertebrates from copepods [45,46] to Drosophilidae [47] to polychaetes [48]. Parasites are also often characterized by miniaturized genomes [11]. Although this trait has often been attributed to their homogenous environment, it could also be linked to their characteristically high growth rates [49–51].

The case for a role for P in genome downsizing in vertebrates is less clear-cut. Although there is some evidence for a negative correlation between growth rate, developmental time and genome size in fish and amphi-

bians [11], few data directly addressing a link between growth rate and genome size are available for vertebrates. One major potential roadblock in assessing the extent to which P limitation could help explain genome downsizing in vertebrates is the fact that vertebrate bones are one of the most P-rich biological materials [52]. This translates into a sharp decrease in the fraction of bodily P associated with RNA with increasing size of animals [31]. The phosphorus stores in bones can even be mobilized to meet metabolic demands under chronic P starvation [53]. This leads us to predict that the high P content of bones could ultimately obscure underlying relationships, if any, between C values and growth rates in vertebrates.

There are also other life-history attributes besides growth rate that might be affected by genome size and would thus obscure the correlation between growth and genome size. For example, for insects, developmental complexity appears to be closely related to genome size [11,12]. Other non-mutually exclusive explanations for reduced genome size include a means of counterselecting the proliferation of transposons.

Whereas several molecular explanations have been proposed for mechanisms determining genome size [11,26,39]; we believe that the reallocation of key atoms between molecules (RNA to DNA) might also impinge on genome size evolution. Such notions are yet to be tested in the context of genome size evolution, but recent studies have identified striking signatures of elemental supply and reallocation at the genome and proteome level [54–56]. Moreover, even small changes in the elemental composition of amino acids can be subject to strong selection [57].

Finally, genome size also correlates negatively with mass-specific metabolic rate [11,58], which is itself positively (but not invariably) linked to growth rate. Metabolic rate is also positively associated with RNA content [31], and cell division rate is in addition tightly coupled to metabolic rate and nutrient availability [59,60]. Interestingly, in poikilotherms, body temperature and rate of biosynthesis correlate negatively with genome size [61]. These interrelationships highlight the close coupling between body size, metabolism and demands for allocating resources to RNA, but their full exploration is beyond the scope of this paper.

### Conclusions and future directions

The evolution of reduced genome sizes is probably due to multiple interdependent mechanisms. We argue that an evolutionary reallocation of material resources from non-coding DNA to RNA could be one such mechanism, at least for plants and invertebrates where P limitation exerts a toll on oversized genomes. This poses a mechanistic explanation for the observed negative correlation between genome size and growth rate and the positive correlation between RNA and growth rate. In addition, we make the case that smaller genome size per se could also promote high growth rate by reducing the time needed for mitosis and meiosis. The well-established relationships between genome size and cell size, and the likelihood that cell size is a determinant of traits likely to be important in competitive interactions (e.g. photosynthetic rate or storage), are also important considerations in evaluation of a role for

material costs in genome size evolution. We have highlighted numerous patterns that point to the potential for material tradeoffs between DNA and RNA that influence key traits, such as growth rate and genome size. We see several routes for testing our hypothesis.

First, meta-analyses of relationships between genome size (eventually cell size) and growth rate should be conducted for various taxa. One expectation is that plant species growing under chronically P-deficient conditions will have smaller genomes than those growing under naturally nutrient rich (or fertilized) conditions. The kind of meta-analysis performed by Grime and Mowforth [62], where geographical patterns in plant genome size can be attributed to climatic regions and growth rates, could also be followed up.

Second, experiments using rapidly growing taxa should be run for several generations under P-limited medium (autotrophs) or diets (heterotrophs) relative to P-rich conditions to test for evolved differences in RNA:DNA ratio, genome size, cell size and body size under different diets. Individuals with fast versus slow development could be selected during the course of the experiments. For plants, one could also select species growing on low and high P (or N) soils to check for evolved differences in growth rate, genome size and RNA:DNA ratios.

Furthermore, whereas the ultimate driver for genome downsizing by the proposed mechanism would be P sparing, a proximate consequence of this could be reduction of 'junk' DNA. To test for this, one could screen for the occurrence of repetitive elements and transposons in different species of model organisms for which extensive genomic data are available. Localization of species-specific transposons for each species could be performed on chromosome sequences.

In conclusion, our main aim here was to highlight the 'growth rate–genome size–nutrient limitation' hypothesis as a plausible mechanism that could explain some consistent empirical observations, hoping to stimulate further empirical research directed at enhancing our understanding of the mechanisms underlying the staggering variation in C values among eukaryotes. We hope this will enable a fair evaluation of whether or not selection imposed by nutrient limitation has a role in the evolution of genome size.

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