

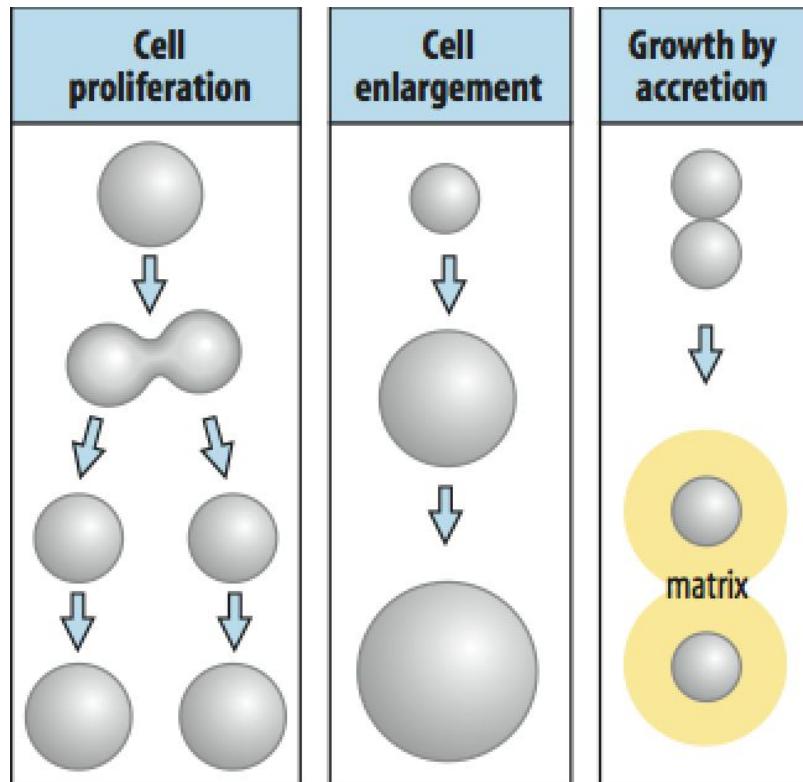
Model organisms and developmental biology

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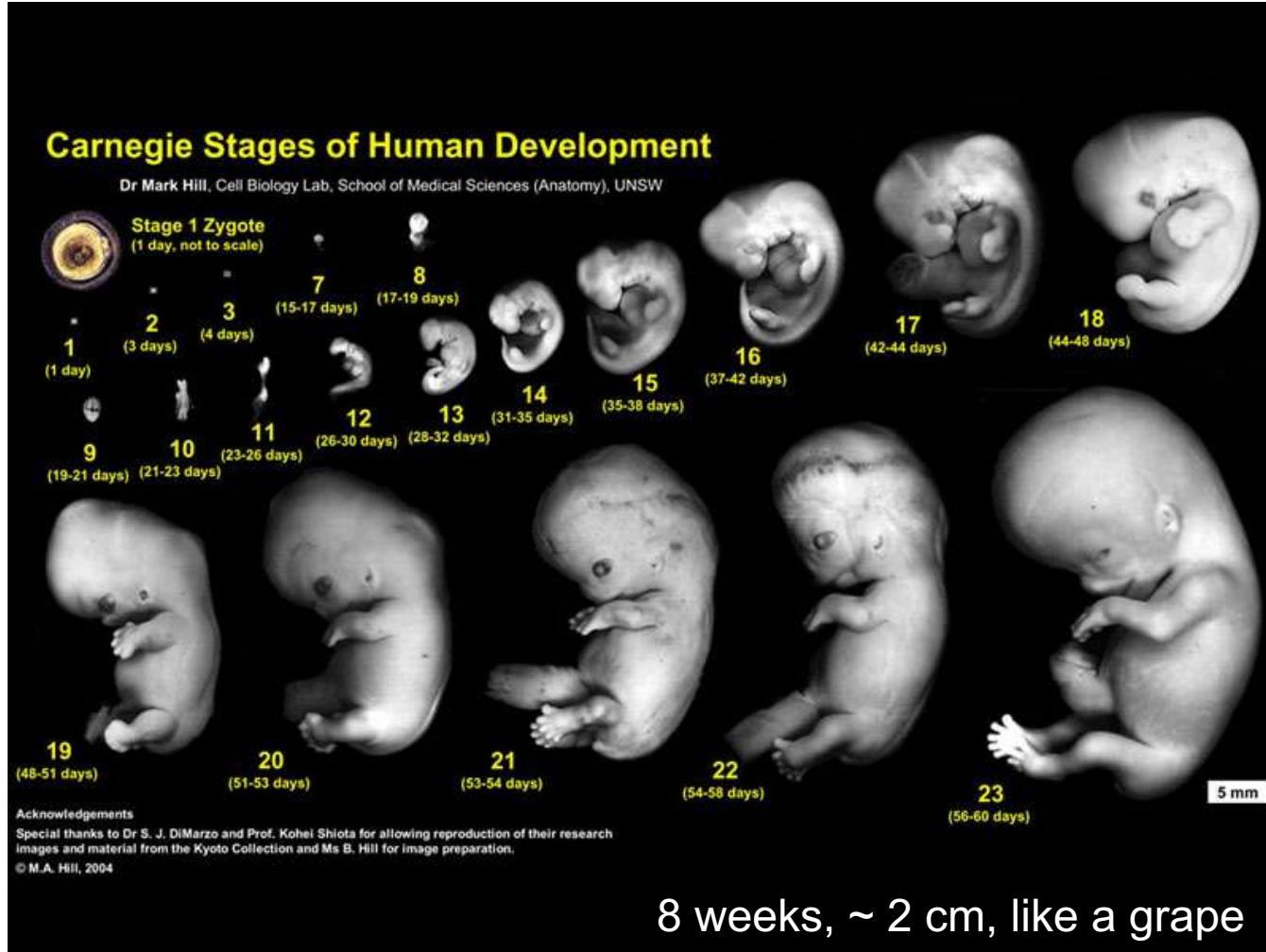
zhong.hb@sustc.edu.cn

The three main strategies for growth in vertebrates



- Cell proliferation, main strategy.
- Cell enlargement, *Drosophila* larval growth, skeletal and heart muscle cells, neuron.
- Accretion, cartilage and bone.

Growth, the increase in the mass of a tissue or organ

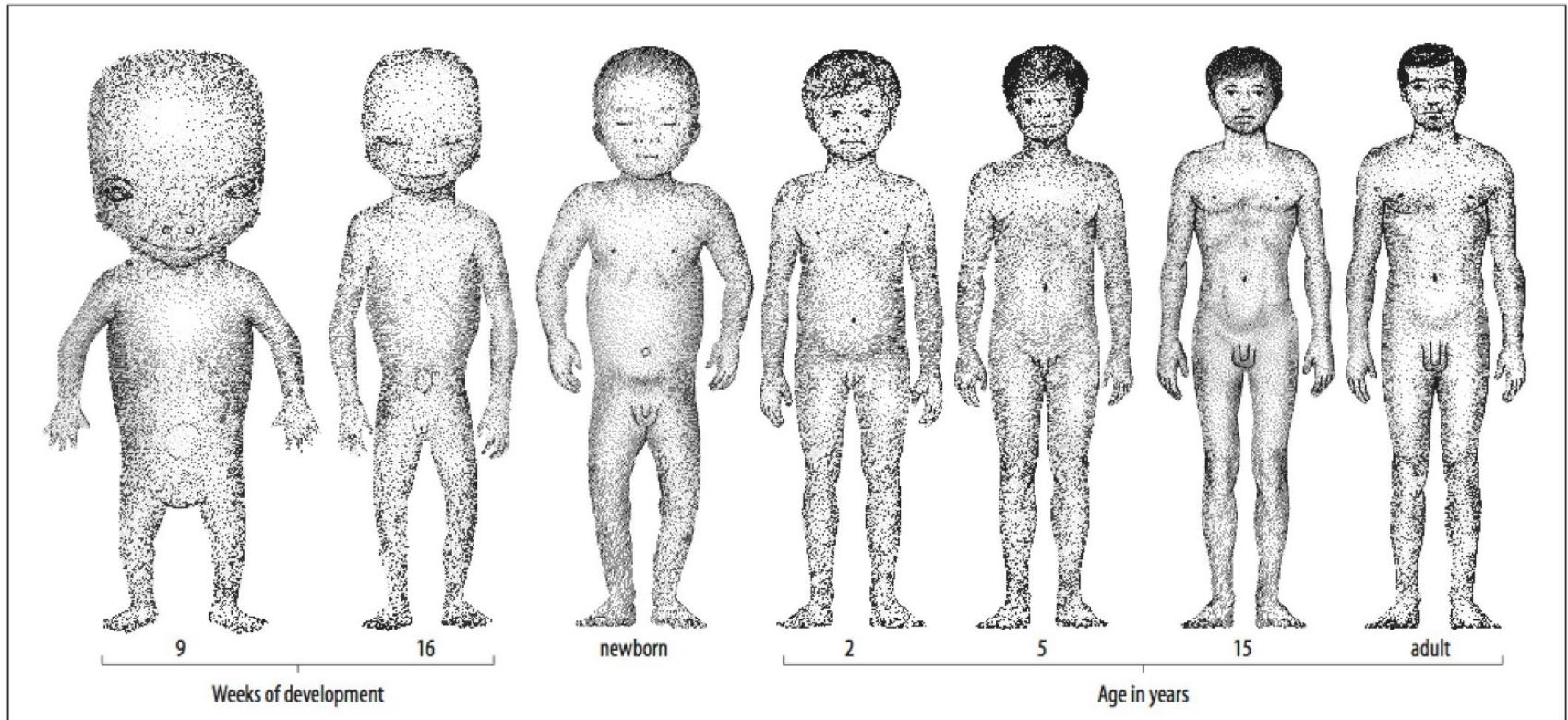


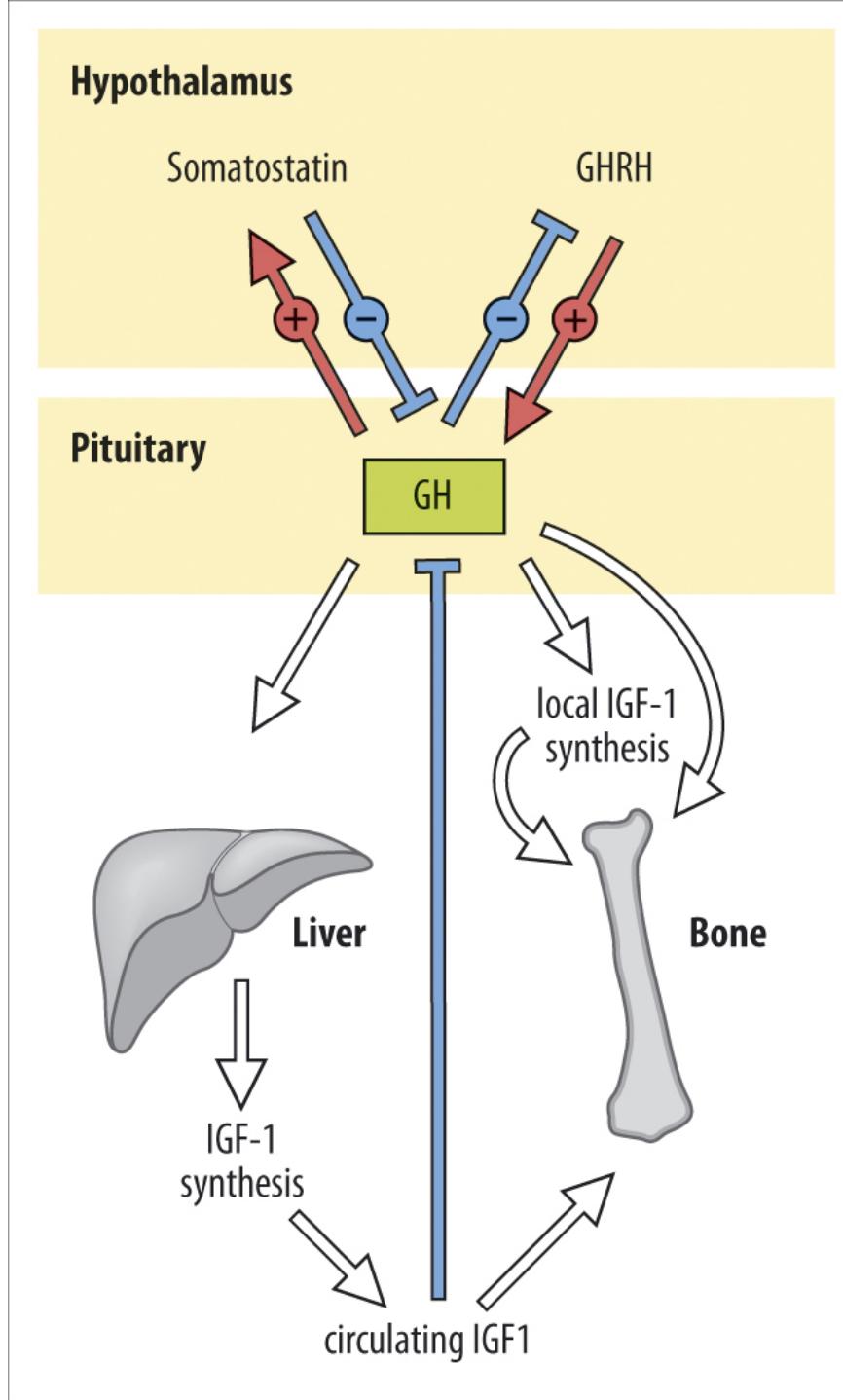
Growth, the increase in the mass of a tissue or organ

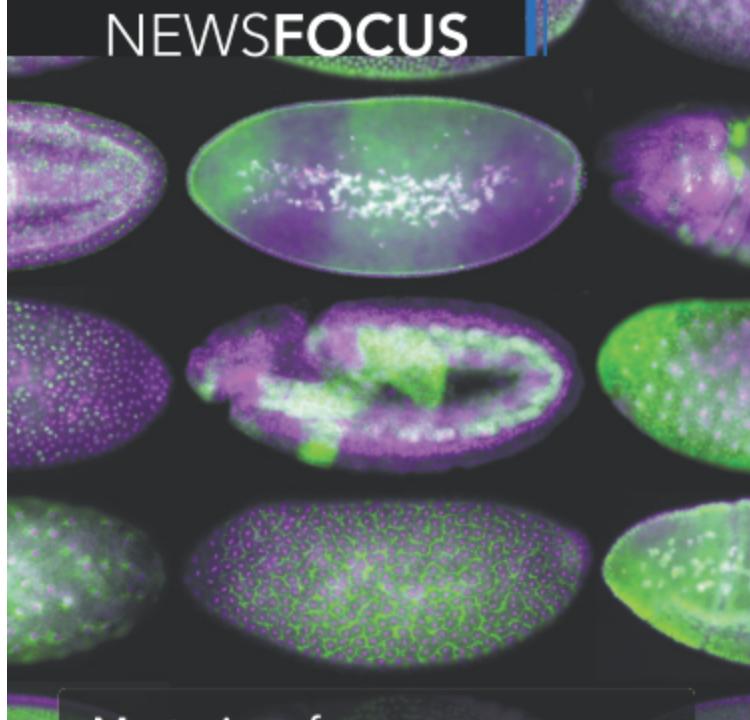
Fetal Growth From 8 to 40 Weeks



Different organs grow at different rates







Mysteries of Development

DEVELOPMENT IS, LITERALLY, THE JOURNEY OF A LIFE time, and it is a trip still as mysterious as it is remarkable. Despite new methods to probe how an animal or plant forms from a single cell, biologists have much to learn about the unimaginably complex process. To identify some of the field's persistent riddles, Senior Editors Beverly Purnell and Stella Hurtley and the news staff of *Science* have consulted with developmental biologists on our Board of Reviewing Editors and elsewhere. The mysteries offered here are a humbling reminder that our knowledge of development remains to a great extent embryonic.

—JOHN TRAVIS

Fly balls. Images of fruit fly embryos, revealing locations of different mRNA molecules.

How Do Organs Know When They Have Reached the Right Size?

In the 1920s, biologists began exploring a new way of studying development: surgically removing rudimentary tissues that would form organs and limbs from embryos of one species and transplanting them into those of a related species. In one visually striking example, Yale University zoologists Victor C. Twitty and Joseph L. Schwind removed embryonic tissue that would become a leg in the large salamander species, *Ambystoma tigrinum*, and transplanted it into the embryo of a smaller species, *Ambystoma punctatum*. Despite the early stage of the transplant—before limb buds even appear in the subsequent larvae—the legs grew to the size that they would have on their original body; small salamanders ended up with a longer-than-normal leg, and large salamanders with a short leg. The result, published in 1931 and considered a classic experiment today, suggested that something intrinsic in the leg, rather than signals from the rest of the body, determines a limb's final size.

Since then, developmental biologists have found dozens of proteins and genes that play a role in the growth of plants and animals. But how growing organs and organisms can sense their size and know when to stop is still a mystery.

Developmental biologists continue to explore that mystery today, although most of their experiments now use fruit flies instead of salamanders. The current objects of their attention are imaginal discs, flattened sacs of cells that grow during the fly's larval stages. During the pupal stages and morphogenesis, specific discs differentiate to form the adult wings, legs, eyes, antennae, or other structures. Although they seem undifferentiated in the larval stages, the cells of the different discs are already destined to become a particular body part. Scientists can transplant a wing imaginal disc from a larva into the abdomen of an adult fly, leaving it there for months, and if it is transplanted back into a larva, it will still form wing tissue during pupation and morphogenesis.

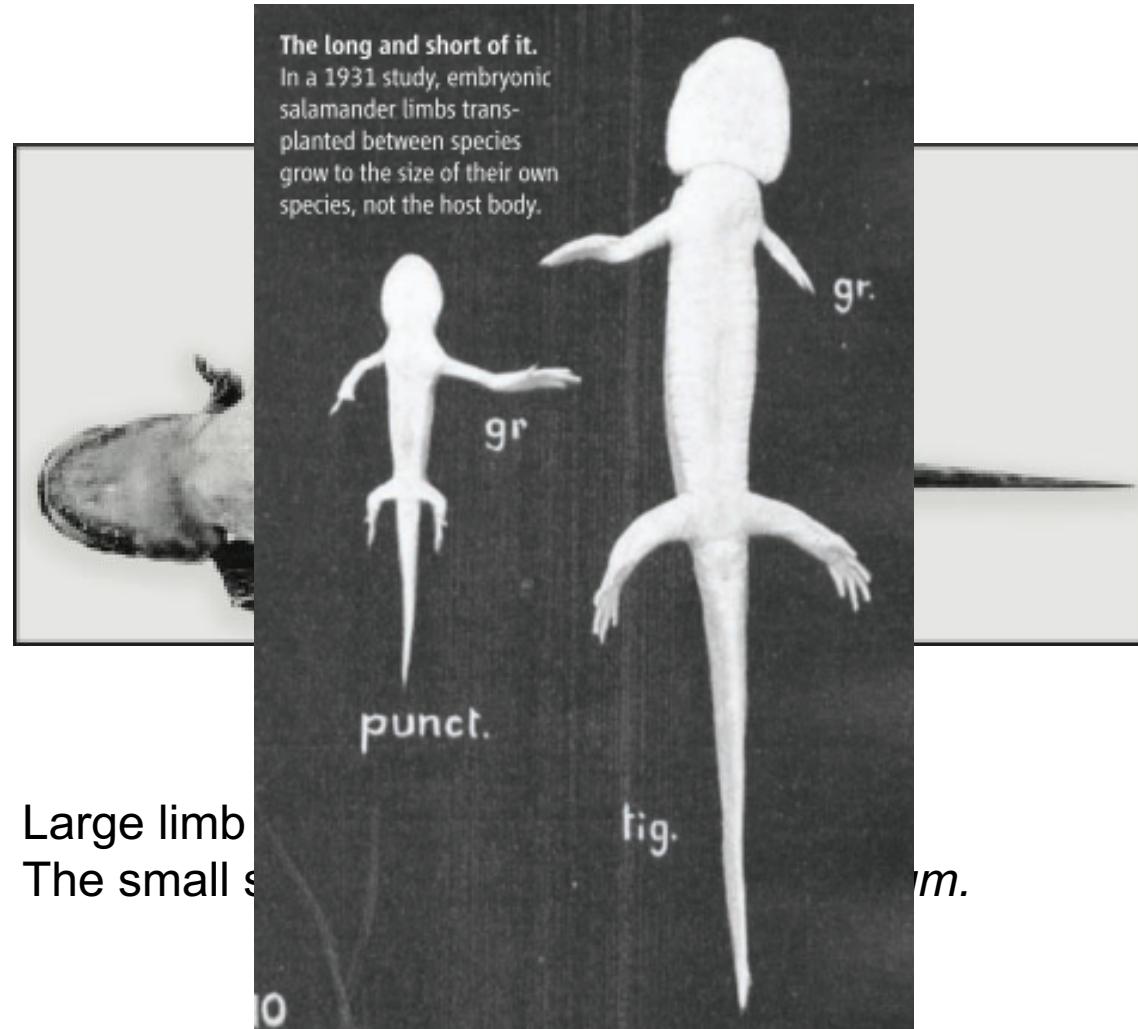
A variety of experiments have shown that both the size of imaginal discs and the organs they form are very tightly controlled. When researchers transplant the wing imaginal disc from an early fly larva to a later one or vice versa, the wing still reaches normal size despite having different growing times. If researchers kill a portion of the imaginal disc cells with radiation or other techniques, the insect can have cell division and still form a normal-size adult. If a fly carries

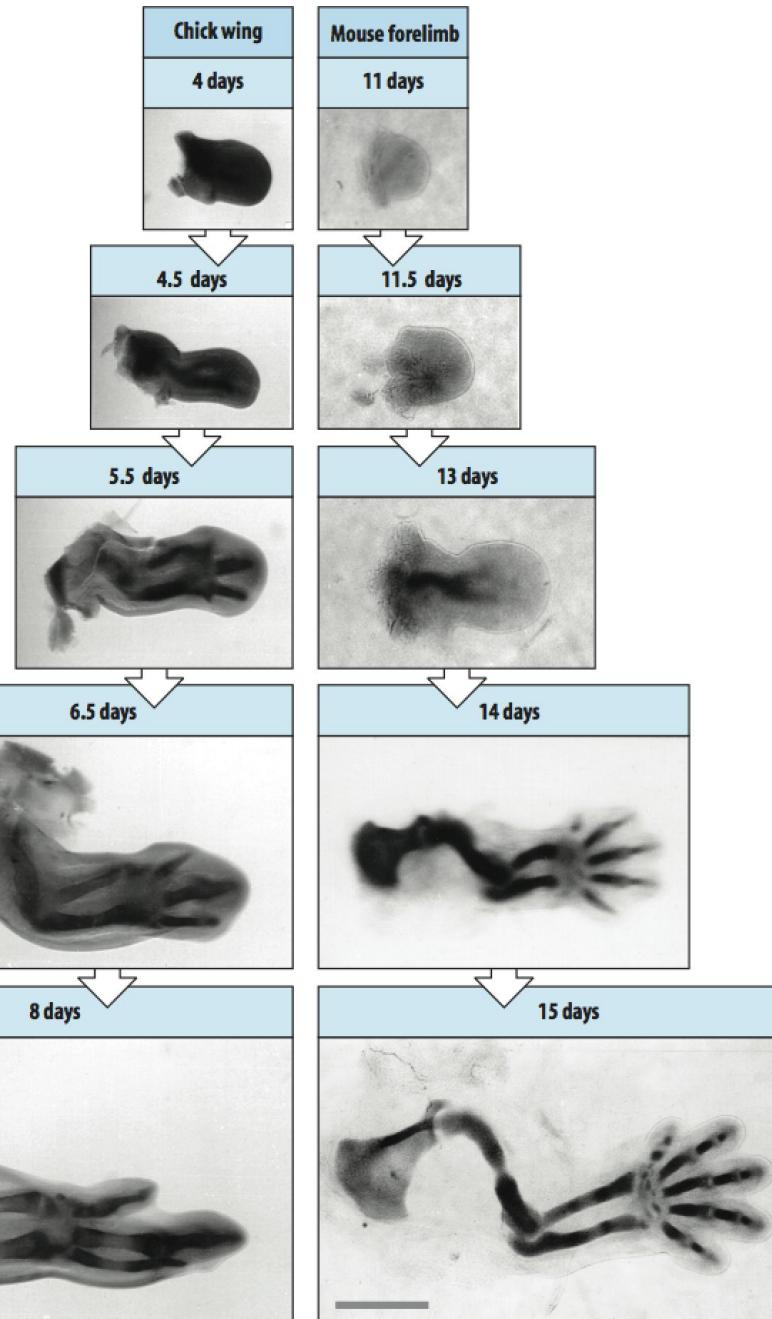
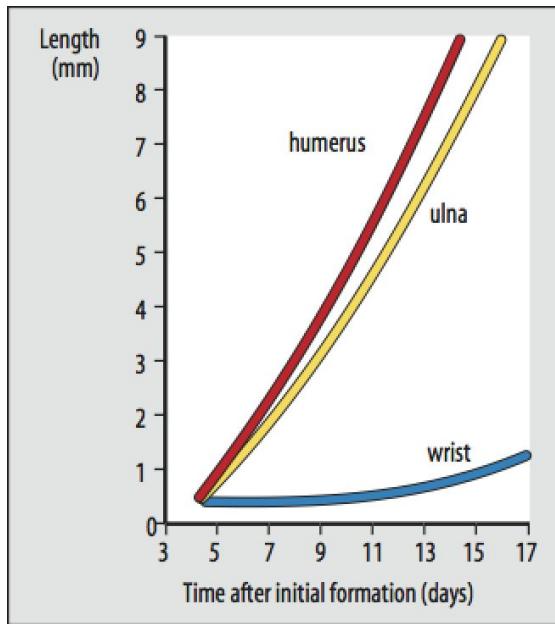
The size of limbs is genetically programmed in salamanders – a classic illustration



Large limb is from *Ambystoma tigrinum*.
The small species is *Ambystoma punctatum*.

The size of limbs is genetically programmed in salamanders – a classic illustration





Humerus 肱骨
 Ulna 尺骨
 Wrist 腕骨

Organ size can be controlled by both intrinsic growth programs and extracellular signals

- Thymus gland. If multiple thymus glands are transplanted into a mouse embryo, each one grows to full size.
- Spleen. If the same experiment is done, each spleen grows much smaller than normal, so that the final total mass of the spleens is equivalent to one normal spleen.
- Removal of one kidney leads to an increase in size of the remaining kidney, mainly the result of cell enlargement.

Transplantation of wing imaginal disc

- Scientists can transplant a wing imaginal disc from a larva into the abdomen of an adult fly, leaving it there for months, and if it is transplanted back into a larva, it will still form wing tissue during pupation and morphogenesis.
- A variety of experiments have shown that both the size of imaginal discs and the organs they form are very tightly controlled.
- The organ isn't counting cell divisions. It's measuring something about dimension.
- There is also evidence that a cell's sense of which direction is up—called planar cell polarity—helps control growth.

Transplantation of wing imaginal disc

- When researchers transplant the wing imaginal disc from an early fly larva to a later one or vice versa, the wing still reaches normal size despite having different growing times.
- If researchers kill a portion of the imaginal disc cells with radiation or other techniques, the insect can boost cell division and still form a normal-size adult.
- If a fly receives just a fragment of a disc as a transplant, the animal won't move to the next stage of development until the disc has reached the correct size — pausing overall development to allow the disc to catch up.
- Scientists can also change the rate at which imaginal disc cells divide, prompting either too many or not enough cells to form, but the cell size adjusts so that organ size remains the same.

Determination of organ size involves coordination of cell growth, cell division, and cell death

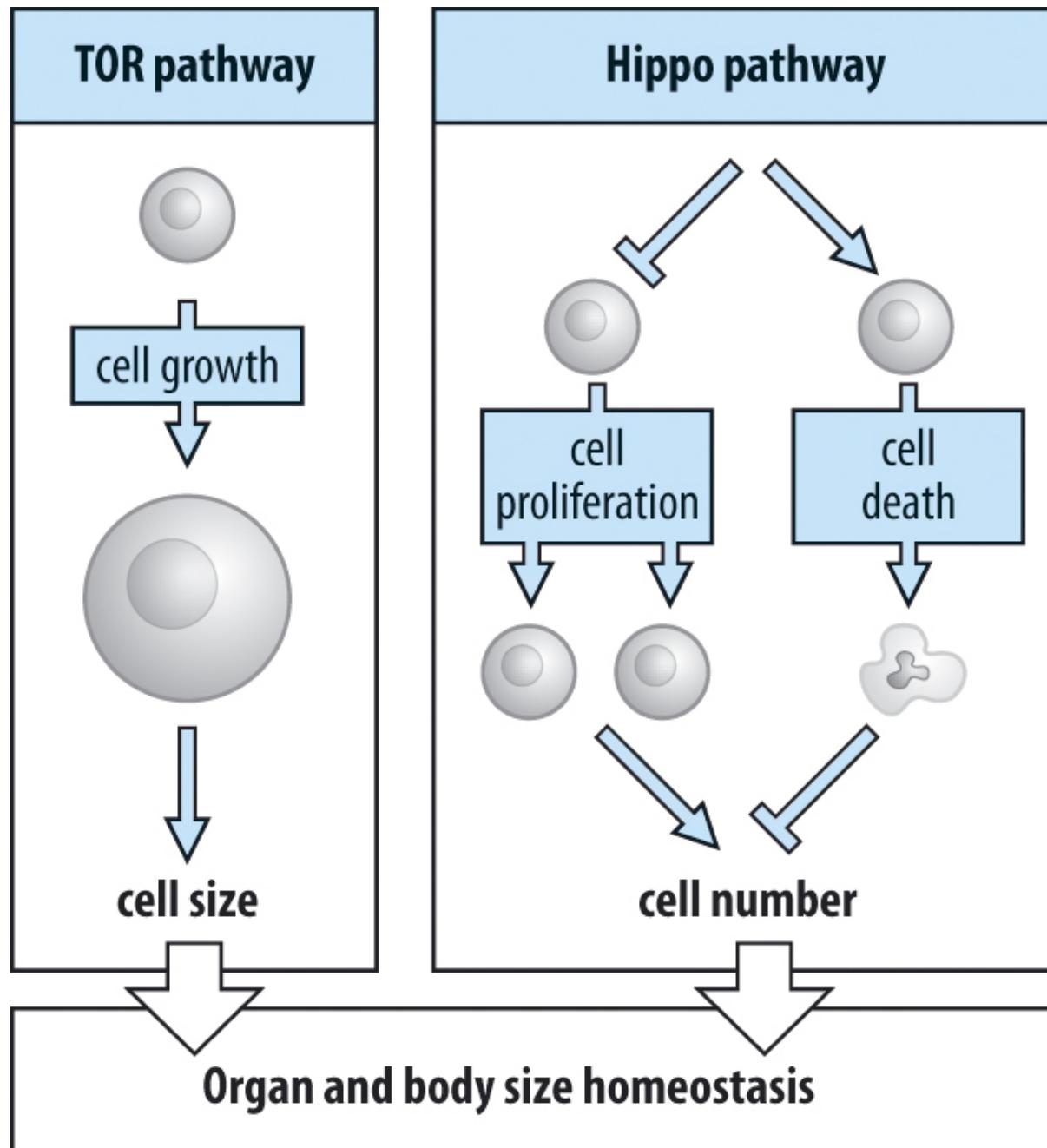
- Monitoring overall dimensions rather than the absolute number of cells or cell divisions.
- For a given cell type, cell size is usually proportional to ploidy.

Some tetraploid salamander grow to the same size of their diploid relatives but have only half the number of cells.

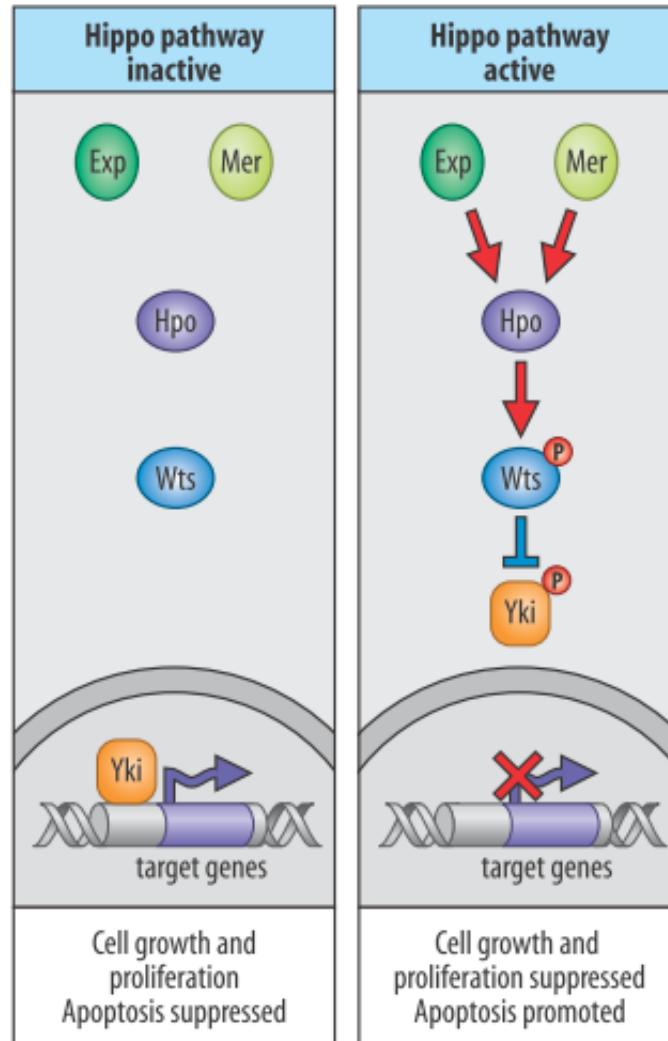
Artificially produced tetraploid mouse embryos also compensate for having larger cells by having fewer numbers, but usually die before birth.

In *Drosophila*, the final size of animals that are a mosaic of haploid and diploid cells is normal, with the haploid regions containing smaller but more cells.

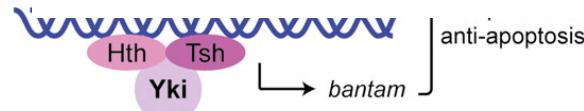
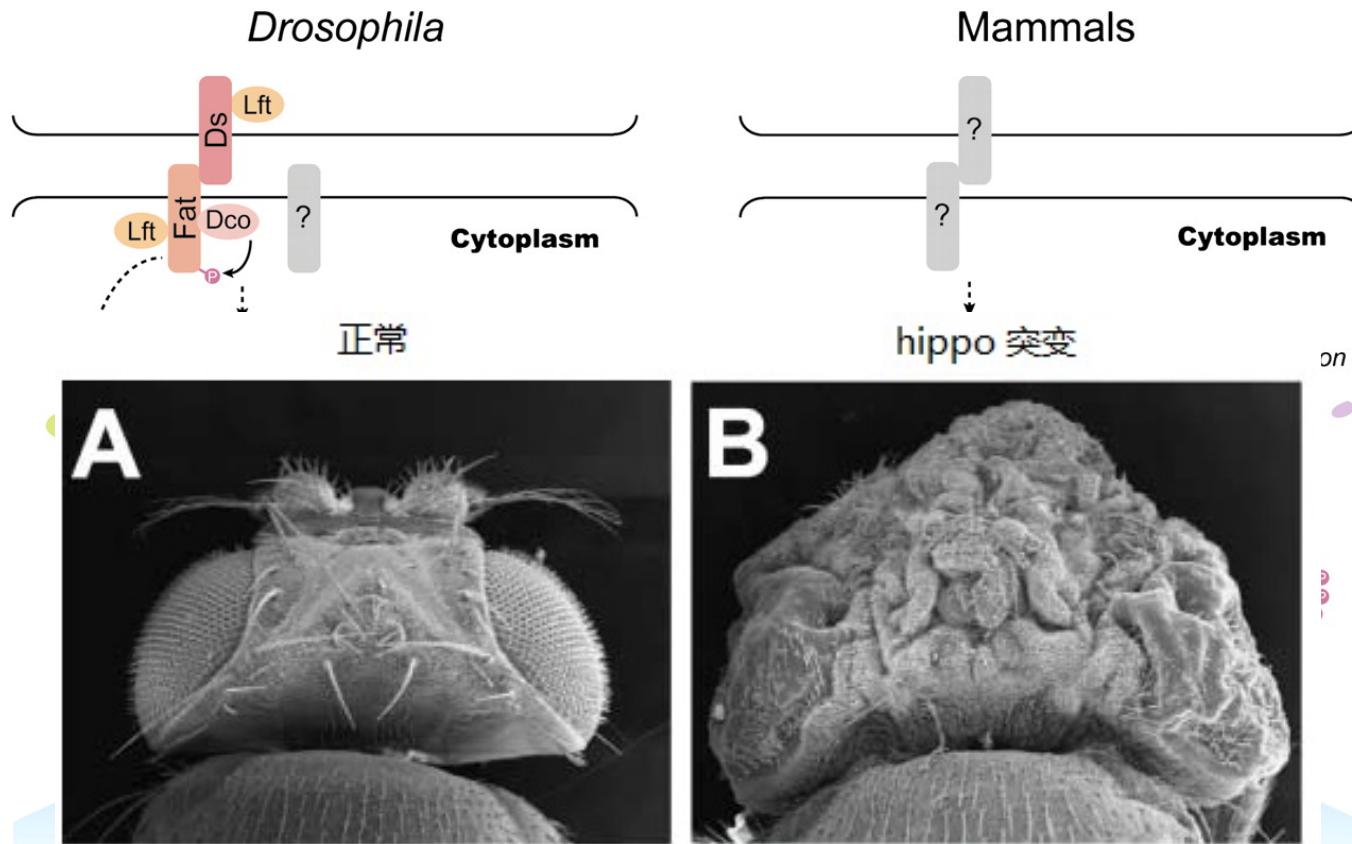
Polyplloid species of plants are generally larger than their diploid relatives.



The Hippo signaling pathway



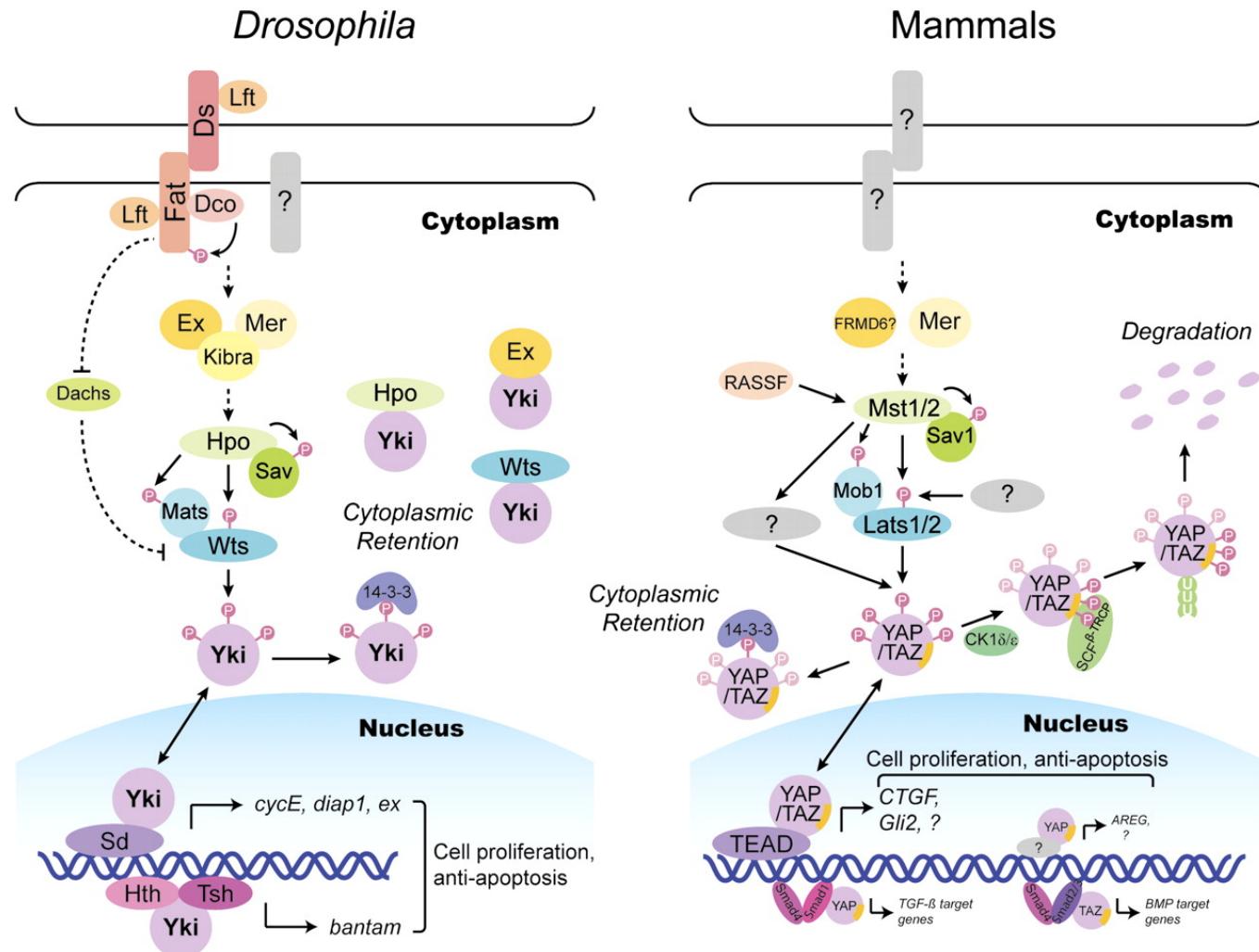
Models of the Hippo pathway in Drosophila and mammals.



Zhao B et al. Genes Dev. 2010;24:862-874

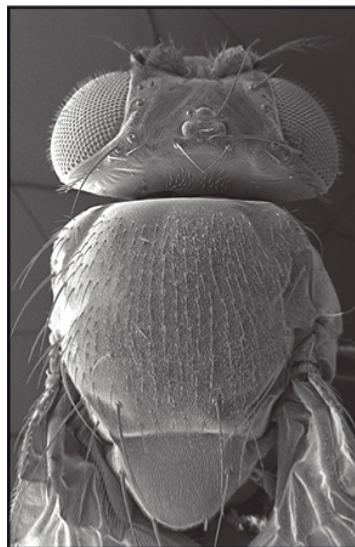


Models of the Hippo pathway in Drosophila and mammals.



Zhao B et al. Genes Dev. 2010;24:862-874





Adipose cells and overweight

- Human fatty tissue comprises about 40 billion adipose cells, most of them stashed under the skin.
- Overweight represents both greater numbers of adipose cells and excessive deposition of fat in these cells, which increases cell size, compared with lean people.
- Humans are born with a certain number of adipose cells. The number increases throughout late childhood and early puberty, and after this remains fairly constant. They seldom die. Each month about 1% of adipose cells in the human body die and are replaced.
- Adipose cells can be induced to iPS.

Striated (skeletal) muscle

- The number of striated muscle cell (fibers) in vertebrates is determined during embryogenesis.
- Post-embryonic growth of muscle tissue results from an increase in individual fiber size, both in length and girth, during which the number of myofibrils within the enlarged muscle fiber can increase more than 10-fold.
- Additional nuclei are provided by the fusion of satellite cells with the fiber.



Arnold Schwarzenegger

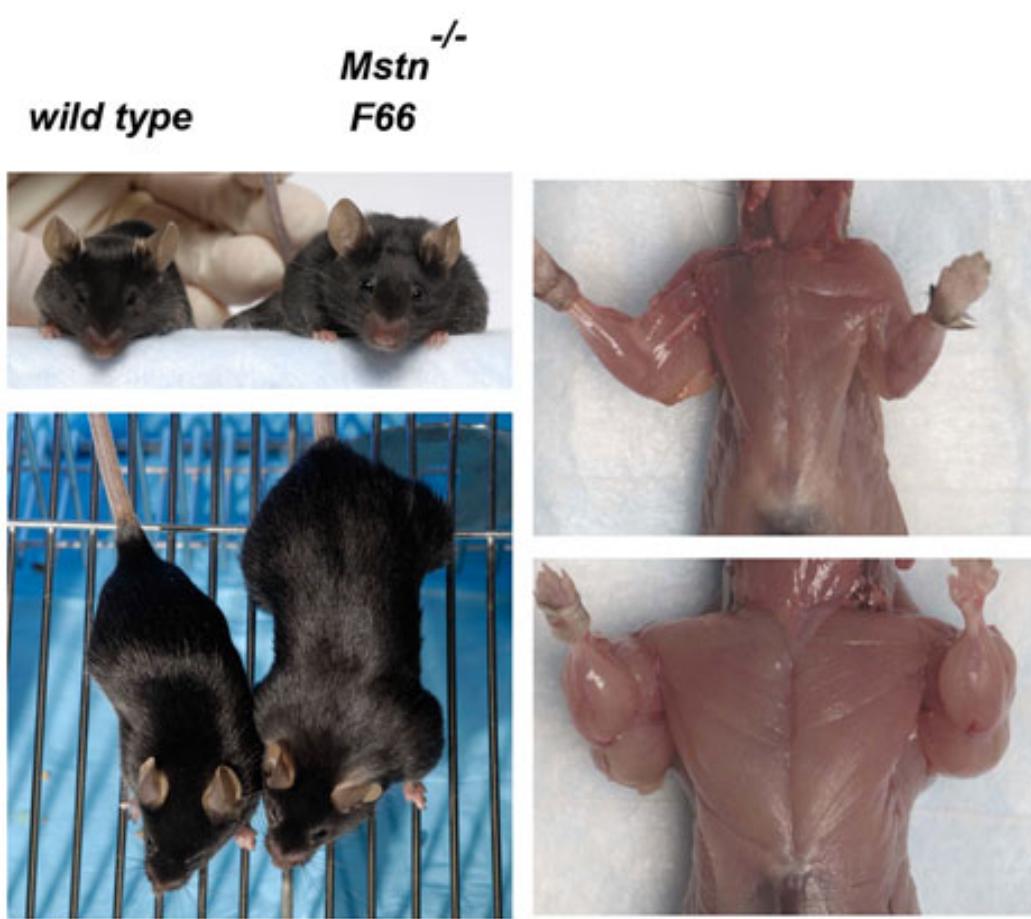
Belgian blue cattle, first documented in 1807



Wendy the Whippet



Myostatin (*Mstn*, also known as Growth differentiation factor 8, GDF-8) mutation leads to overgrowth of muscle



SUPER BABIES REVEAL THE KEY TO STRENGTH GENE



Super strong Liam Hoekstra just after turning 3. Those are 5 lb weights, and he only weighed around 30 lbs at the time.



Neonate

7 Months

One of the few photos showing the physique of the German Super Baby.

Letter to the Editor

Generation of gene-target dogs using CRISPR/Cas9 system

Dear Editor,

Dogs (*Canis familiaris*) serve as human companions and are raised to herd livestock, aid hunters, guard homes, perform police and rescue work, and guide the blind. Dogs exhibit close similarities to humans in terms of metabolic, physiologic, and anatomical characteristics, and thus are ideal genetic and clinical models to study human diseases (Tsai et al., 2007). Gene target technology is a powerful tool to create new strains of animals with favorable traits. However, thus far, gene-target dogs have not been developed due to their unique species-specific reproductive characteristics, which limits the applications of dogs especially in the field of biomedical research. Recently, clustered regularly interspaced short palindromic repeats (CRISPRs)/CRISPR-associated (Cas) 9 system was applied to edit specific genes with a high efficiency (Cong et al., 2013; Mali et al., 2013). Here we attempt to explore the feasibility of producing gene knockout (KO) dogs by using this technology. Beagle dog, the most widely used breed in biomedical research, was used as our animal model. *Mystatin*

PCR products were used for T7 endonuclease I (T7E1) cleavage assay. Cleavage bands were found in seven colonies (Figure 1B). Further sequencing showed that 13 colonies (59.1%) were mutated at the cleaved site with various mutation sizes (from –13 to +1; Figure 1C). Among them, five colonies (22.7%) showed monoallelic mutation. There are eight colonies (36.4%) showing biallelic mutation, in which six colonies had the same mutation in both alleles (homozygous mutation) and two colonies displayed different mutation in each allele (Supplementary Figure S1). There are short repeats (GT, ATGT) around the sgRNA target locus, which probably cause microhomology-mediated end joining contributing to the high homogenous mutation rate (Morton et al., 2006; Qi et al., 2013). The other nine colonies (40.9%) were detected without mutations. These data demonstrated that our sgRNA functioned effectively in canine cells.

We next sought to generate MSTN KO dogs by manipulating dog zygotes. In initial trials, allo-transplantation of embryos was performed. A total of 30 presumptive zygotes were collected. Twenty-five embryos with

oocytes in the metaphase II stage, dogs release immature oocytes in the germinal vesicle stage, and these oocytes require another 48–72 h in the oviduct to reach maturation (Holst and Phemister, 1971). Therefore, the failure of pregnancy by allo-transplantation approach was probably ascribed to the asynchronous reproduction stage in donor zygotes and recipient female dogs. To address these concerns, we designed an auto-transplantation strategy. Briefly, we flushed one side of the canine oviduct corresponding with the ovary with more corpus luteum to collect zygotes. After injected with the mixture of Cas9 mRNA and MSTN sgRNA, these zygotes were immediately transferred back into the other side (not flushed) of the oviduct of the same female dog. A total of 35 injected zygotes were transferred into 10 donor-recipient females. Among them, 8 females were pregnant to term (80.0%) and gave birth to 27 puppies (Figure 1D).

Ear punch tissues were collected from all the puppies for detection of any mutation in MSTN locus. PCR products amplified from the genome of all the 27 puppies were sequenced. Two puppies from different

Muscle-gene edit creates buff beagles

Test of CRISPR gene-editing tool in dogs shows mixed results

BY TINA HESMAN SAEY 1:01PM, OCTOBER 23, 2015

2 months old



4 months old



14 months old



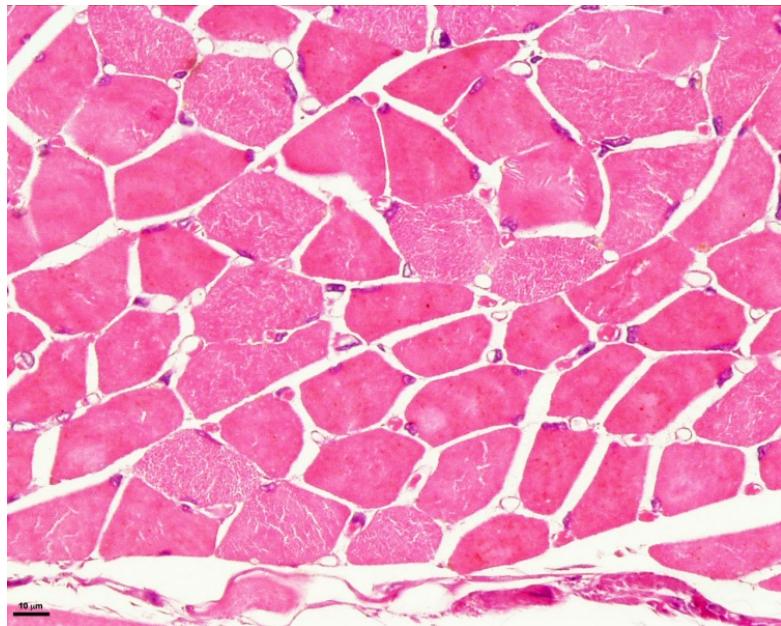
BULKING UP Two beagles named Hercules (left) and Tiangou (right) are the first dogs to have a gene edited with a tool known as

Muscular dystrophy (肌肉萎缩症)

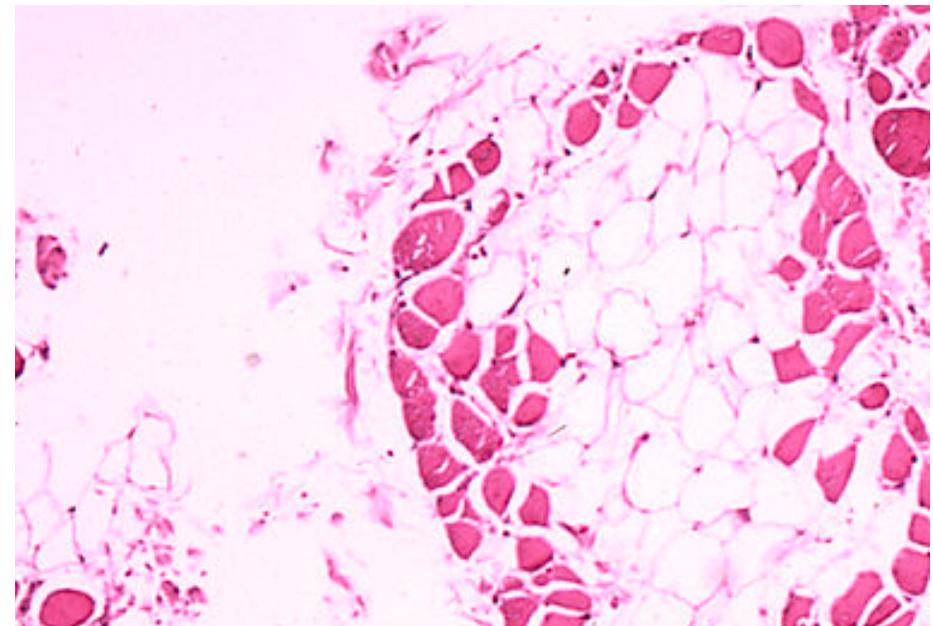


Muscular dystrophy (肌肉萎缩症)

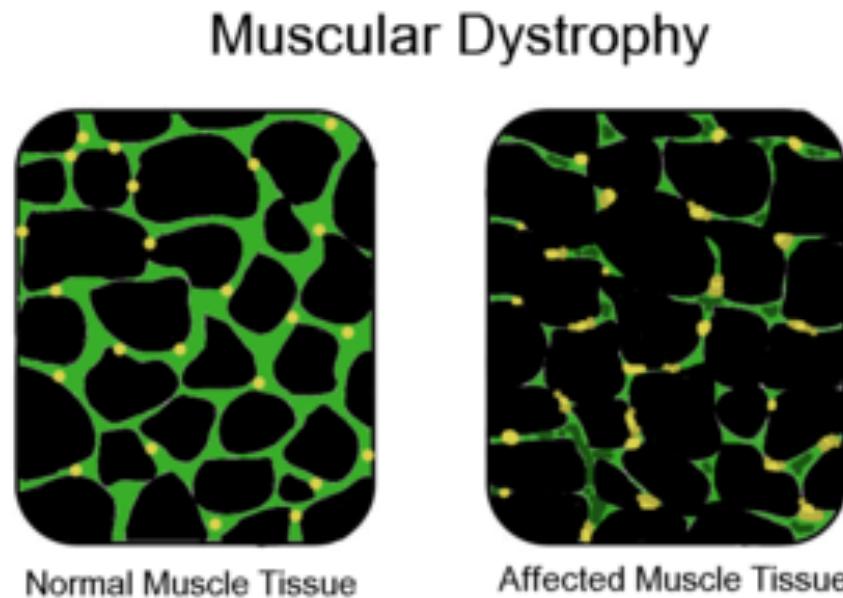
Control



Patient



Muscular dystrophy (肌肉萎缩症)



In affected muscle the tissue becomes disorganized and the concentration of dystrophin (green) is greatly reduced.

Pygmy peoples (俾格米人)



~ 140 cm

LOOKING DOWN ON THE REST OF THE WORLD

(Average male height in m)



Holland

182,9 cm



Sverige

181,6 cm



Danmark

180,6 cm



Norge

179,6 cm



Estland

179,1 cm



Finland

178,3 cm



Tyskland

178,1 cm



Filippinerne

161,9 cm



Bolivia

160 cm



Indonesien

158 cm

PROCEEDINGS B

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Research



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Does natural selection favour taller stature among the tallest people on earth?

Gert Stulp^{1,2}, Louise Barrett^{3,4}, Felix C. Tropf² and Melinda Mills⁵

¹Department of Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

²Department of Sociology, University of Groningen, Grote Rozenstraat 31, Groningen 9712 TG, The Netherlands

³Department of Psychology, University of Lethbridge, 4401 University Drive West, Lethbridge, Alberta, Canada T1 K 3M4

⁴Applied Behavioural Ecology and Ecosystems Research Unit, University of South Africa, Private Bag X6 Florida 1710, Johannesburg, South Africa

⁵Nuffield College/Department of Sociology, Manor Road, Oxford OX1 3UQ, UK

GS, 0000-0003-0173-5554; MM, 0000-0003-1704-0001

The Dutch are the tallest people on earth. Over the last 200 years, they have grown 20 cm in height: a rapid rate of increase that points to environmental causes. This secular trend in height is echoed across all Western populations, but came to an end, or at least levelled off, much earlier than in The Netherlands. One possibility, then, is that natural selection acted congruently with these environmentally induced changes to further promote tall stature among the people of the lowlands. Using data from the LifeLines study, which follows a large sample of the population of the north of The Netherlands ($n = 94\,516$), we examined how height was related to measures of reproductive success (as a proxy for fitness). Across three decades (1935–1967), height was consistently related to reproductive output (number of children born and number of surviving children), favouring taller men and average height women. This was despite a later age at first birth for taller individuals. Furthermore, even in this low-mortality population, taller women experienced higher child survival, which contributed positively to their increased reproductive success. Thus, natural selection in addition to good environmental conditions may help explain why the Dutch are so tall.

Larger Mammalian Body Size Leads to Lower Retroviral Activity



Aris Katzourakis^{1*}, Gkikas Magiorkinis^{1,2*}, Aaron G. Lim³, Sunetra Gupta¹, Robert Belshaw⁴, Robert Gifford⁵

1 Department of Zoology, University of Oxford, Oxford, United Kingdom, **2** Virus Reference Department, Public Health England, London, United Kingdom, **3** Wolfson Centre for Mathematical Biology, Mathematical Institute, University of Oxford, Oxford, United Kingdom, **4** School of Biomedical and Healthcare Sciences, Plymouth University, Plymouth, United Kingdom, **5** MRC-University of Glasgow Centre for Virus Research, Glasgow, United Kingdom

Abstract

Retroviruses have been infecting mammals for at least 100 million years, leaving descendants in host genomes known as endogenous retroviruses (ERVs). The abundance of ERVs is partly determined by their mode of replication, but it has also been suggested that host life history traits could enhance or suppress their activity. We show that larger bodied species have lower levels of ERV activity by reconstructing the rate of ERV integration across 38 mammalian species. Body size explains 37% of the variance in ERV integration rate over the last 10 million years, controlling for the effect of confounding due to other life history traits. Furthermore, 68% of the variance in the mean age of ERVs per genome can also be explained by body size. These results indicate that body size limits the number of recently replicating ERVs due to their detrimental effects on their host. To comprehend the possible mechanistic links between body size and ERV integration we built a mathematical model, which shows that ERV abundance is favored by lower body size and higher horizontal transmission rates. We argue that because retroviral integration is tumorigenic, the negative correlation between body size and ERV numbers results from the necessity to reduce the risk of cancer, under the assumption that this risk scales positively with body size. Our model also fits the empirical observation that the lifetime risk of cancer is relatively invariant among mammals regardless of their body size, known as Peto's paradox, and indicates that larger bodied mammals may have evolved mechanisms to limit ERV activity.

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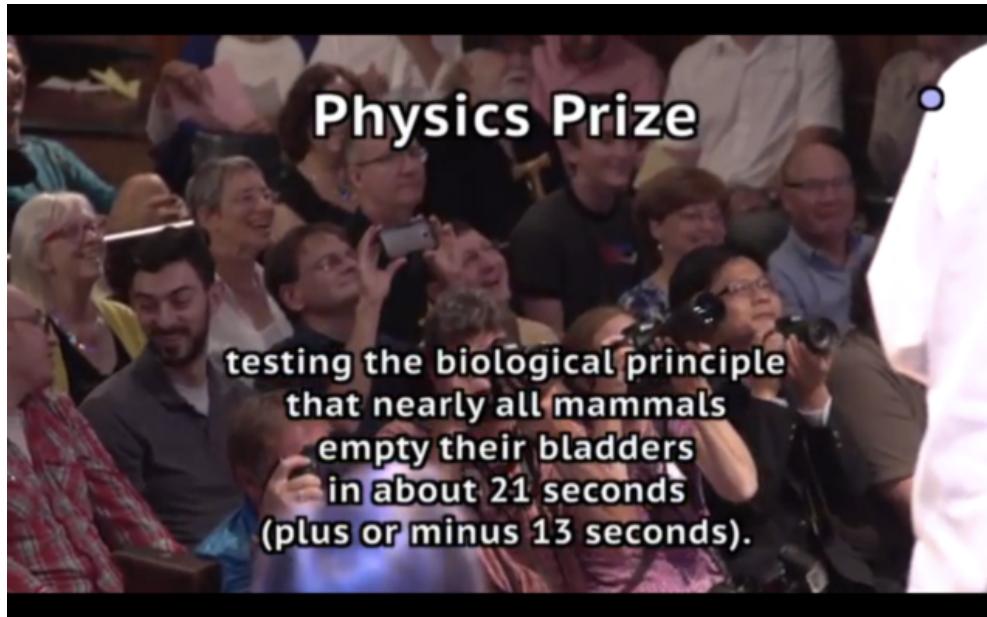
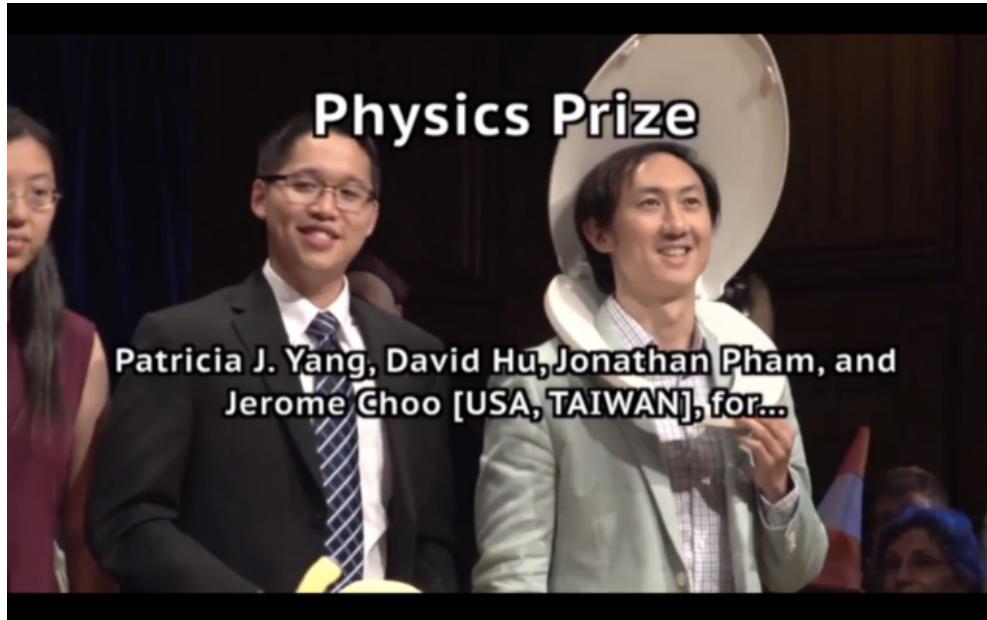
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* Email: aris.katzourakis@zoo.ox.ac.uk (AK); gkikas.magiorkinis@zoo.ox.ac.uk (GM)



Duration of urination does not change with body size

Patricia J. Yang^a, Jonathan Pham^a, Jerome Choo^a, and David L. Hu^{a,b,1}

Schools of ^aMechanical Engineering and ^bBiology, Georgia Institute of Technology, Atlanta, GA 30332

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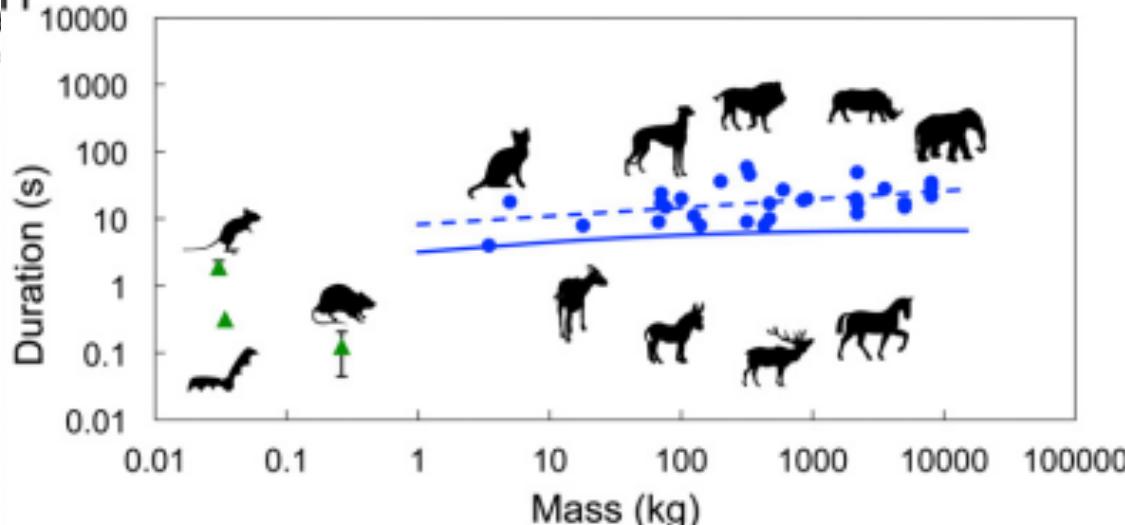
Many urological studies rely on models of animals, such as rats and pigs, but their relation to the human urinary system is poorly understood. Here, we elucidate the hydrodynamics of urination across five orders of magnitude in body mass. Using high-speed videography and flow-rate measurement obtained at Zoo Atlanta, we discover that all mammals above 3 kg in weight empty their bladders over nearly constant duration of 21 ± 13 s. This feat is possible, because larger animals have longer urethras and thus, higher gravitational force and higher flow speed. Smaller mammals are challenged during urination by high viscous and capillary forces that limit their urine to single drops. Our findings reveal that the urethra is a flow-enhancing device, enabling the urinary system to be scaled up by a factor of 3,600 in volume without compromising its function. This study may help to diagnose urinary problems in animals as well as inspire the design of hydrodynamic systems based on those in nature.

urology | allometry | scaling | Bernoulli's principle

generate jets. Instead, they urinate using a series of drops, which is shown by the 0.03-kg lesser dog-faced fruit bat and the 0.3-kg rat in Fig. 2 A–C, respectively.

Fig. 1H shows the urination time for 32 animals across six orders of magnitude of body mass from 0.03 to 8,000 kg. Despite this wide range in mass, urination time remains constant, $T = 21 \pm 13$ s ($n = 32$), for all animals heavier than 3 kg. This invariance is noteworthy, considering that an elephant's bladder, at 18 L, is nearly 3,600 times larger in volume than a cat's bladder at 5 mL. Using the method of least squares, we fit the data to a clear scaling law shown by the dashed line: $T \sim M^{0.13}$ (Fig. 1H).

For small animals, urination is a high-speed event of 0.01- to 2-s duration and therefore, quite different from the behavior of



Thanks!

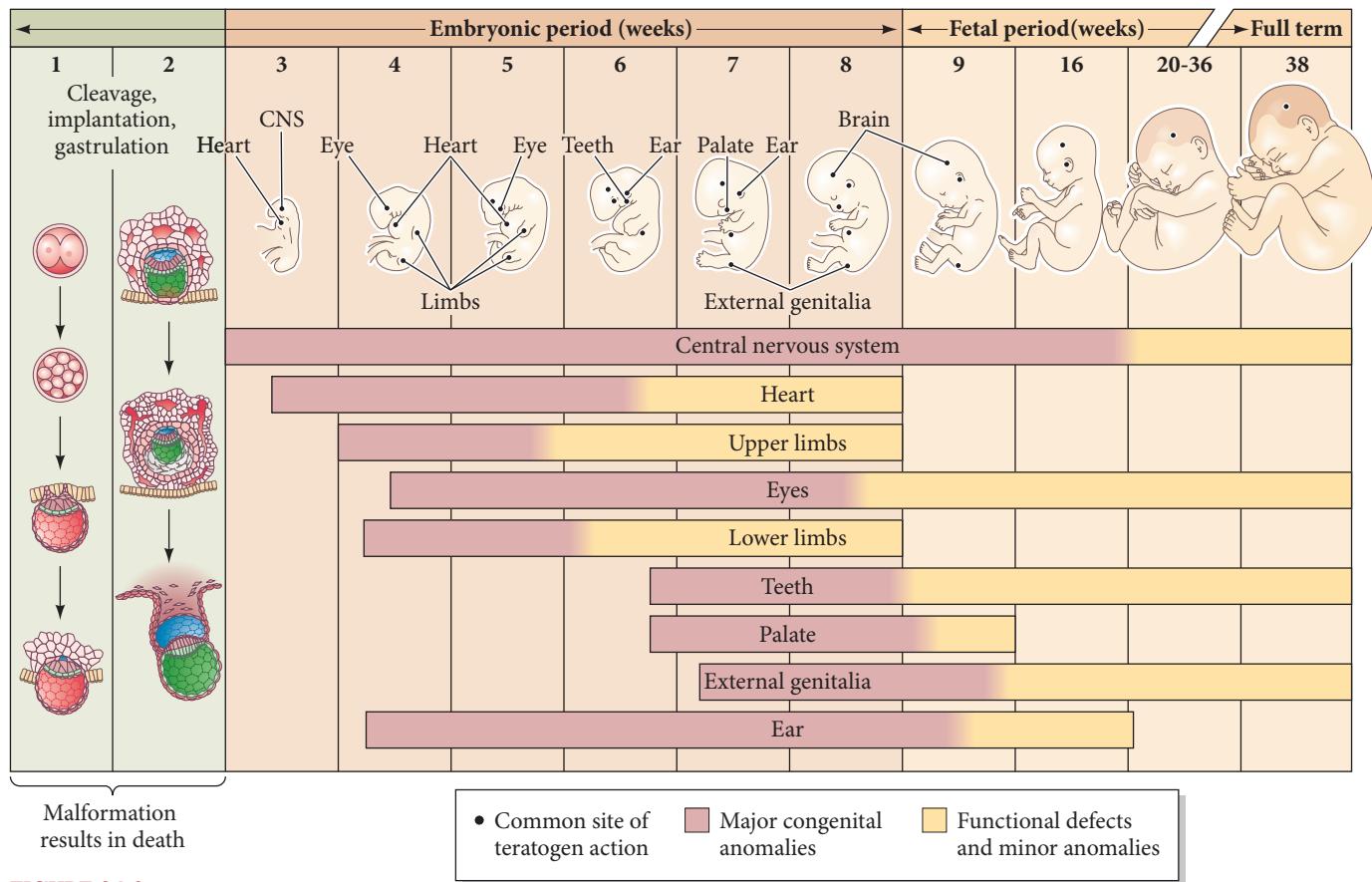
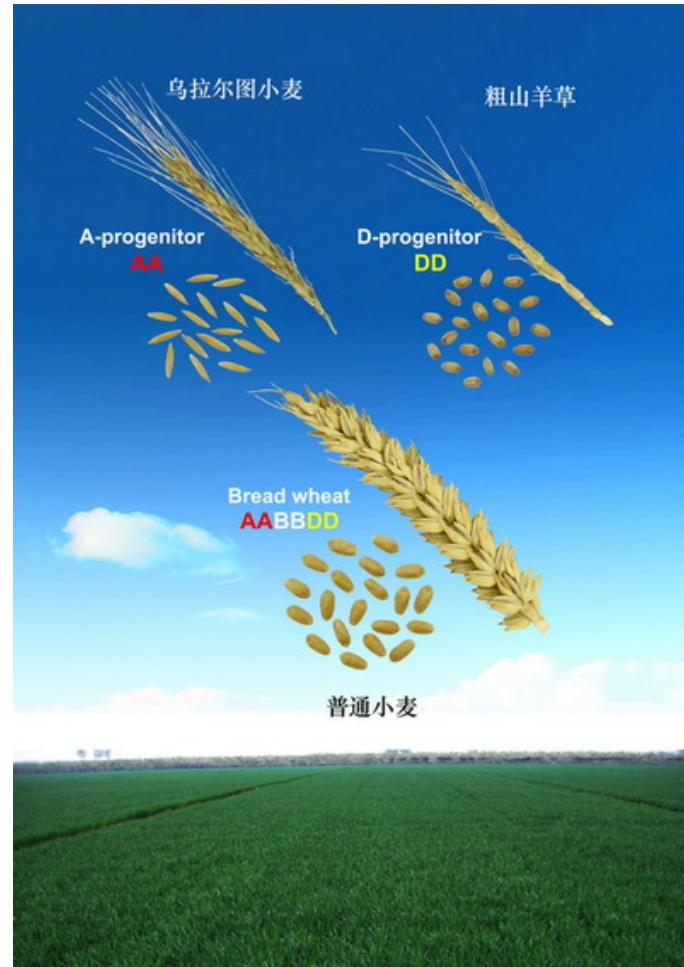


FIGURE 24.3 Weeks of gestation and sensitivity of embryonic organs to teratogens. (After Moore and Persaud 1993.)

- 1. 没有呼吸和循环系统的动物体型极限怎样估算？
- 2. 骨骼支撑力跟其截面积成正比。扔老鼠实验，6楼
- 3. 细胞size的限制，RNA扩散速率计算。

Ploidy of bread wheat



How Is Body Size Controlled?

- Vertebrate body size is controlled by growth hormone and the subordinate insulin-like growth factors (IGFs) (Butler and Roith 2001).
- In invertebrates, growth and body size are also regulated by the insulin/IGF system in response to nutrients.
- In addition, final body size in insects is determined by the number of molting cycles, and these are under the control of the steroid hormone ecdysone and the sesquiterpenoid juvenile hormone.
- In addition to the hormonal control of body size, there are intrinsic genetic constraints to organ and body size.

The amount of nourishment an embryo receives can have profound effects in later life

- In developed countries, smaller size at birth has been associated with an increased risk of developing coronary heart disease, stroke, or type 2 diabetes.
- The “catch-up” growth later may carry a cost, as the body’s resources are diverted from “repair and maintenance” to grow. It seems to promote overweight and even obesity.