REVIEW
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Probing Pedomorphy and Prolonged Lifespan in Naked Mole-Rats and Dwarf Mice

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Pedomorphy, maintenance of juvenile traits throughout life, is most pronounced in extraordinarily long-lived naked mole-rats. Many of these traits (e.g., slow growth rates, low hormone levels, and delayed sexual maturity) are shared with spontaneously mutated, long-lived dwarf mice. Although some youthful traits likely evolved as adaptations to subterranean habitats (e.g., thermolability), the nature of these intrinsic pedomorphic features may also contribute to their prolonged youthfulness, longevity, and healthspan.

naked mole-rat; neoteny; protracted development; thyroid hormone; longevity; dwarf mouse

Introduction

Species lifespan varies by more than four orders of magnitude across the animal kingdom and 100-fold among mammals (6, 26, 121). This range dramatically surpasses observed extensions of longevity by genetic or environmental manipulations in any one model organism (109, 131, 132). Maintaining processes critical to early life development may be linked to both prolonged lifespan and prolonged health span. Retention of these early life traits may confer youthful properties (e.g., sustained proliferative potential), more efficient physiological function, and sustained species fitness. These juvenile traits may also facilitate better tolerance of stressors and foster metabolic plasticity. Preservation of juvenile traits in adult animals, termed "pedomorphy," has been observed throughout the animal kingdom (e.g., insects, amphibians, reptiles, and mammals), including humans (50, 81, 106, 137, 151, 196) and naked mole-rats (1a, 22, 83, 118, 128, 156, 191), and may contribute to prolonged longevity. Long lifespans necessitate a suite of molecular and biochemical mechanisms to maintain cellular and organ system homeostasis, thereby delaying the functional declines that typically occur during the aging process. Pedomorphosis and the mechanisms that regulate this process may play a pivotal role in protracted good health and prolonged longevity.

What Is Pedomorphosis?

Developmental processes in multicellular organisms are complex, requiring tight regulation of key milestones in development and maturity within a precise timeline. Altered timing or rates of developmental processes in an organism is called heterochrony, an expansive term with multiple subcategories beyond the scope of this review (summarized in Table 1). One such category is pedomorphosis, a type of heterochrony that refers to the retention of immature traits into adulthood, such that these traits in mature adults resemble the juvenile forms of the ancestral species (94). Originally, this phenomenon was labeled "neoteny," a term that has "evolved" multiple, contentious meanings (Table 1) within the fields of evolutionary and developmental biology (for reviews, see Refs. 81, 170, 187). Neoteny has been used to describe the general phenomenon of youthful traits appearing out of context in adult organisms or multiple sub-categories of the very same phenomenon (e.g., decreased rate or delayed timing of developmental processes). Neoteny has also been defined as very specific types of developmental events, like becoming reproductively active while retaining larval morphology (130). To avoid any potential confusion associated with multiple definitions, we will eschew the word "neoteny" altogether and exclusively use "pedomorphy" to refer to the general phenomenon of maintaining youthful traits into adulthood.

Small changes in developmental processes due to both genetic and environmental influences can lead to large changes in phenotype and can impact survival both in utero and postnatally (212). After birth, newborn mammals encounter a very different environment compared with that in utero and exhibit a markedly different physiology to that of fetuses and mature adults. Compared with adults, both the fetus and the newborn show remarkable

Table 1. *The language of heterochrony*

Pedomorphosis Mechanisms	Peramorphosis Mechanisms
Decreased rate of developmental processes (rate hypomorphosis, neoteny, deceleration)	Increased rate of developmental processes (rate hypermorphosis, acceleration)
Decreased duration of developmental events (time hypomorphosis)	Increased duration of developmental events (time hypomorphosis)
Timing of developmental events is delayed relative to that of ancestors (post-displacement, neoteny)	Timing of developmental events is earlier than observed in ancestors (pre-displacement)

Heterochrony is the variation in the timing of developmental processes compared with the ancestral form. Pedomorphosis, or neoteny, is the retention of youthful traits into adulthood. Peramorphosis, or recapitulation, is the exaggeration of adult characteristics. Both pedomorphy and peramorphy occur via a variety of mechanisms, including genetic alterations and environmental perturbations. For more discussion regarding the language of heterochrony and associated processes, see Refs. 1, 73a, 81, 170, 187. Note that the term "neoteny" has been applied to various specific mechanisms of "pedomorphosis," as well as being generally used to mean "pedomorphosis."

tolerance to numerous physiological stressors, including hypoxia, thermoregulatory stressors, and lack of nutrients (189). These age-dependent differences may be attributed to juvenile-specific traits and their concomitant protective developmental phenotypes essential for early life environment.

The potential origins for development of a pedomorphic trait include both genetic and environmental influences (FIGURE 1). Humans have commonly practiced genetic selection of pedomorphic features in dog breeding, creating a variety of small dog breeds that exhibit sociability, subservient behavior, longer lives, and other traits often associated with playful puppies compared with their adult wolf-like ancestors (59). Beyond Mammalia, pedomorphy has been extensively studied in amphibians (50, 176), where, under non-favorable environmental conditions, metamorphosis can be paused, as observed in the tiger salamander (182). Genetic mutations altering endocrine function may similarly slow or stop maturation to the adult phenotype, as seen in the Mexican axolotl (*Ambystoma mexicanum*) (43).

The hypothalamic-pituitary-thyroid axis is the most widely known endocrine system involved in species maturation. It alters gene expression networks facilitating the onset of metamorphosis in lower vertebrates. Retention of larval characteristics into the adult stage in the Mexican axolotl (*Ambystoma mexicanum*) is attributed to low activity of the hypothalamic-pituitary-thyroid axis and attenuated tissue sensitivity to these hormones (130). Similarly, thyroid hormone is thought to be the master regulator of cardiomyocyte proliferation in multiple phylogenetic clades, including fish and mammals (47, 92).

Progression into adulthood can also be delayed by perturbation of the insulin/IGF/FOXO axis (15). Like the tiger salamander, when roundworms (*Caenorhabditis elegans*) encounter sub-optimal conditions that may negatively impact reproductive success (e.g., reduced nutrient availability), they remain in a juvenile-like dauer state (111) for many months, with reduced insulin/IGF signaling. Thereafter, they resume normal development into healthy, fertile adults (109, 172). Genetic mutants that reduce insulin/IGF/FOXO signaling (e.g., *daf-2*) constitutively stimulate dauer formation, even under optimal conditions (109, 117), and foster the juvenile traits of enhanced stress resistance, energy conservation, and increased longevity (108).

Although there are multiple potential origins for pedomorphic traits, benefits associated with these traits may have resulted in their positive selection in long-lived organisms. These benefits include energy conservation (by preventing development if conditions are too harsh to support the adult organism), metabolic and reproductive plasticity (e.g., switching between glucose and fructose metabolic substrates or retaining the ability to reproduce throughout life), and maintenance of youthful attributes in cells, tissues, and/or organs (e.g., higher functionality, ability to regenerate, and stress resistance).

Long-Lived Rodent Models

Here, we evaluate pedomorphic traits of two long-lived rodents: naked mole-rats and spontaneously mutated dwarf mice (FIGURE 2). We question whether these two rodents, one a natural extremophilic subterranean-dwelling species (179) and the other an experimental model of extended longevity (8), share similar traits and whether these may be regulated by evolutionarily conserved pathways directly pertinent to extended longevity.

The Naked Mole-Rat

The naked mole-rat (*Heterocephalus glaber;* Rodentia, Heterocephalidae; FIGURE 2A) is the

smallest (~40 g) of the >50 known subterranean rodent species but is the longest-lived, living at least a decade longer than other species (123). Strikingly, unlike other mammals, naked mole-rats maintain a constant risk of dying even at ages many-fold greater than their allometrically predicted maximum lifespan and at ages >25-fold their age at sexual maturity (174). This trait is observed in both the dominant, breeding individuals and their reproductively suppressed subordinates, although those that breed, in defiance of the disposable soma theory of aging (58), live longer than subordinates (174). Rather, as is observed in juveniles of other mammalian species, death in this species is stochastic, with lifetime maintenance of physiological and biochemical function, as well as tissue homeostasis (25, 84, 146). Age-associated chronic diseases, including cancer, neurodegeneration, and cardiovascular disease, are extremely rare (51, 63, 183), with similar incidences in both young and old individuals.

The naked mole-rat is a prime example of an organism exhibiting extreme biology. It is one of only two eusocial mammals, with a similar social structure to that of termites and bees. Naked mole-rats live in large colonies of up to ~300 individuals, with only one dominant breeding female who suppresses reproduction, sexual maturation, and sex steroid hormone levels in her offspring (103). She mates with 1–3 males. Her offspring are sexually monomorphic (160) and rarely leave their natal colony, but rather perform cooperative tasks for the colony and remain non-reproductive, regardless of their age (103). Females show no menopause and can continue to produce young beyond the age of 33 yr, with the older breeders often producing larger litters than the newer, less-established breeders, although pup survival is commonly lower.

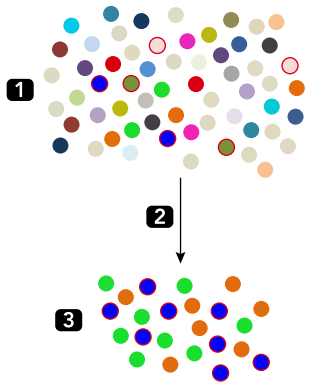

FIGURE 1. **Emergence of pedomorphic traits**
1: each circle color represents an independent trait available in the ancestral gene pool of any organism; some of those traits are pedomorphic (indicated by red outline), whereas others are not. *2*: over time, environmental pressures (food availability, temperature, pH, toxins, predation, etc.) select from among available traits for those that are most fit in an ecophysiological niche. *3*: in this example, among the traits providing high fitness is one pedomorphic trait. This youthful trait, as an example, may be advantageous for providing organisms the ability to digest an abundant form of sugar that adult organisms typically cannot digest, such as lactose.

Naked mole-rat colonies reside in a maze of underground burrows; this sealed niche is physiologically challenging, with limited options for heat and gas exchange, the latter resulting in hypoxic and hypercapnic conditions within the deep nests. Naked mole-rats also have high metabolic demands associated with tunneling through soil while blindly foraging for underground plant roots and tubers, their main source of nutrients and water (121). These animals exhibit numerous adaptations to their harsh habitat (23), which, nevertheless, provides protection from widely fluctuating climatic conditions, airborne infectious agents, and predators, thereby attenuating many common causes of extrinsic mortality. Evolutionary theory suggests that long-lived species would have evolved in relatively protected habitats where evolutionary tinkering could amend molecular pathways that indirectly influence lifespan (101). Benefits from acquiring this extreme longevity must outweigh the costs involved in attaining this trait without compromising species fitness. Not only should long-lived species exhibit greater resistance to environmental threats they encounter in their milieu, but they should also have the capacity to maintain youthful levels of repair and regenerative mechanisms to facilitate better somatic maintenance throughout life (78, 179).

Considerable evidence from postmortem analyses of older animals reveals numerous signs of tissue regeneration and remodeling; nevertheless, numerous age-associated pathologies are evident, including sarcopenia, osteoarthritis, and cataracts, as well as signs of cardiovascular, renal, and peridontal disease (63). Because naked mole-rats are typically housed at high ambient temperatures, necrosis rapidly sets in, impeding assessments of cause of death. Despite extensive necropsies, no consistent pattern of age-associated causes of death are evident, and most age-associated common causes of mortality (e.g., cancer and cardiovascular disease) are rarely observed (27, 51, 63). Rather, like that observed in young animals, naked mole-rat causes of death appear to be random and stochastic (174).

The German naturalist Edward Rüpell first published a description of naked mole-rats in 1842. He thought these "sand puppies" were juveniles of a larger, haired adult mammal (175). This misconception was based on their newborn-like physical appearance, notably their small size, absence of an insulatory pelage, and the fact that their eyes predominantly remain closed even when the animals are active (FIGURE 2). Since that first suggestion

that these small mammals may retain juvenile traits into adulthood, there have been many other reports documenting perinatal or pedomorphic traits (FIGURE 3) in this species (1a, 22, 83, 105, 118, 128, 154, 156, 192). For instance, naked mole-rats have disproportionately large heads relative to their body size; maintain a flexible, unfused mandibular symphysis that allows the lower incisor teeth to move independently (33); and have high levels of body fat (146). Naked mole-rats lack ear pinnae, and the males are cryptorchid, lacking descended scrotal sacs. The absence of sexually dimorphic external genitalia, evidence of sexually monomorphic traits in male and female subordinates, similar number and arrangement of the motor neurons innervating the phallus, and the striated perineal muscles associated with the phallus are more akin to early developmental stages in utero (158). Additionally, like juveniles of other species, their vomeronasal organ, essential for pheromone detection, is an order of magnitude smaller than observed in similar-sized adult mice and shows no signs of neuroepithelial postnatal development and folding. This is possibly indicative of the lack of sexual activity in adult subordinate naked mole-rats, similar to what has been observed in juveniles from other species (54, 195).

Dwarf Mice

Regardless of the genetic manipulation (i.e., *Pit1* or *Prop1* mutations), dwarf mice are a third of the size of their normal-sized counterparts (FIGURE 2B) and live about a year longer, a lifespan extension approximately equivalent to 30 yr in humans (20, 131). Dwarf mice typically have a deficit in growth hormone (GH) or its receptor (GHR) (GHR knockout mice). Although the well-characterized Ames mouse phenotype is driven by a spontaneous point mutation in the *Prop1* gene that is upstream of *Pit1*, Snell dwarf mice exhibit a mutation in *Pit1*, resulting in altered anterior pituitary cell-type expression (8, 125, 197). Both the Ames and the Snell dwarf mice also lack thyroid-stimulating hormone and prolactin (Tables 2 and 3), and live up to 68% and 50% longer than their wild-type siblings, respectively (20, 75). These mice share many characteristics associated with calorically restricted mice (Table 2), a dietary intervention that also extends both lifespan and healthspan while modulating glucose handling and energy metabolism (13). However, caloric restriction further extends dwarf mouse longevity, suggesting that the lifespan-extending mechanisms of these two experimental manipulations may work through different pathways (10).

Dwarf mice, even in old age, retain a juvenile appearance, with pup-like features including flattened, smaller snouts and high levels of body fat. They also exhibit impaired reproduction. Like the naked mole-rat, they maintain cardiac function during aging, are more active than age-matched, wild-type conspecifics (21, 79, 131, 169), exhibit enhanced stress resistance, and have lower incidences of age-associated diseases, including cancer (4, 99, 140, 141). Shared attenuated aging phenotypes between these two models of extended longevity suggest conserved mechanisms may contribute to maintenance of youthfulness and extreme longevity.

Protracted Growth and Development and the Hormones Involved in These Processes

Unlike most other small mammals, particularly compared with other similar-sized rodents, the gestation period of naked mole-rats is exceptionally long [~66–72 days (102)], and more than three times longer than mouse gestation [21 days (55)]. Despite large interspecific differences in the amount of time spent in utero, pup mass at birth is similar between the species (1–1.8 g/pup). The number of pups per litter is more variable, with litter sizes ranging from 1 to 29 for naked mole-rats and from 2 to 12 for mice (202).

Growth, as determined by Gompertz transformation, revealed that naked mole-rat pups have the slowest maximum growth rate (0.207 g/day on average) compared with other mole-rat species and mice (147). Although they can become sexually mature and reproduce at 6 mo, somatic growth continues for the first 18 mo, suggesting that overall growth is considerably slower; naked mole-rats require more developmental time to mature than mice. Similarly, the Ames dwarf mouse shows extended periods of development compared with wild-type counterparts. Born with the same weight as wild-type littermates, adult Ames mice weigh 12–15 g, whereas wild-type mice weigh 35–40 g, illustrating the somatic actions of GH (12). The Ames dwarf phenotype only begins to emerge 10–12 days after birth (193), after which point

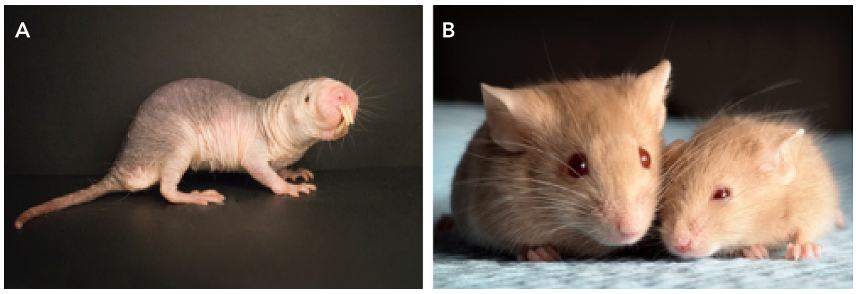

FIGURE 2. **Naked mole-rats and Ames dwarf mice exhibit multiple pedomorphic features**
Both naked mole-rats (*A*) and Ames dwarf mice (mouse on *right* in *B*) exhibit multiple pedomorphic features.

dwarf pups exhibit significantly slower growth rates, delayed eye-opening, and an approximately twofold longer time to reproductive maturity, evident in both males and females (12).

Many of the differences in dwarf mice are attributed to pronounced hormone deficiencies associated with abnormal pituitary gland development, particularly those linked to growth and thyroid hormones (19). Similarly, naked mole-rats have lower levels of both GH and thyroid hormones relative to other mole-rats and mice (28) that may contribute to attenuated growth rates and delayed attainment of adult mass (Table 3). Deficiencies in these tropic hormones and concomitant postponement of tissue maturity likely play a pivotal role in delaying age-associated decline and prolonging health.

Insulin and IGF

The key hormones for growth and development, GH, insulin, and IGF-1, are highly conserved components of pathways that are known to influence the lifespan of most animal models (9, 107). Not only do naked mole-rats have low levels of GH, but transcriptomic evidence suggests that they also exhibit attenuated levels of insulin and mTOR pathway components (110), as do dwarf mice (Tables 2 and 3). Together, these features may contribute to their protracted development and slow growth rates (147, 149, 156).

Fasting blood glucose, plasma insulin, and IGF-1 (24, 25, 110) are also low in naked mole-rats, as in dwarf mice (19). Both models of extended longevity show impaired glucose tolerance responses (11, 114), more in keeping with glucose tolerance profiles associated with either insulin resistance or insulin deficiency. Nevertheless, these low levels of insulin and IGF-1 are associated with delayed aging in multiple species, including humans, rodents, and canids (9, 82, 85).

In contrast to IGF-1, both Kim et al. (110) and Brohus et al. (17) reported that insulin-like growth factor 2 (*IGF-2*) transcript levels, which are typically high in utero, are retained at high levels throughout life in naked mole-rats, underscoring how these animals maintain perinatal traits into adulthood; in certain tissues *Igf-2* levels even increased during aging (17, 110).

Thyroid Hormone

Thyroid hormones have also been implicated in regulation of development, metabolism, and lifespan; many of these actions result from downstream modulation of membrane composition, mitochondrial efficiency, and substrate utilization (96). However, thyroid hormone is also considered critical for maturation from juvenile to adult in vertebrates, including frog and axolotl metamorphosis, and normal organ development in mammals (138, 203). Thyroid hormone only begins to rise late in mammalian fetal development, reaching levels 2,000 times that in utero in the first week of life and declining thereafter to sustained low levels in adulthood (56, 155). Despite the importance of this pleiotropic hormone in development and energy utilization, low levels of thyroid hormone are associated with prolonged longevity in certain animal models, including naked mole-rats as well as long-lived centenarian humans (5, 8, 16, 28). Naked mole-rats have very low circulating levels of thyroid hormone that increase slightly when animals are housed in the cold, although levels never come close to those of mice housed under standard laboratory conditions (29). Similarly, dwarf mice are hypothyroid relative to wild-type conspecifics (Table 3).

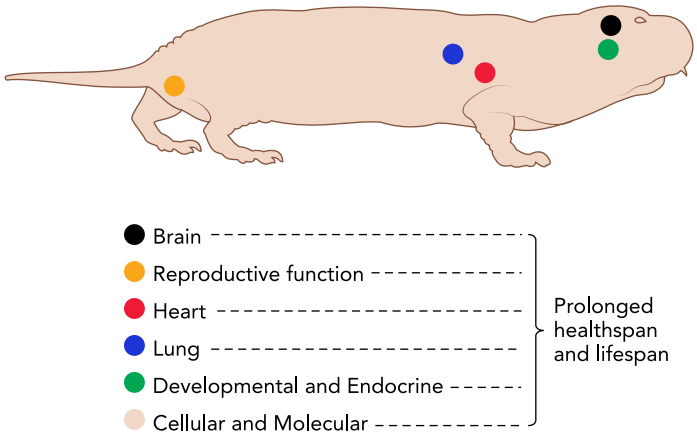

FIGURE 3. **Prominent pedomorphic traits of the naked mole-rat that potentially lead to extreme longevity and healthspan**
Highlighted are various organ and cellular systems that exhibit pedomorphic traits in the naked mole-rat. Note that the "Cellular and Molecular" phenotypes indicated include the entire organism and not just the epidermis. A single pedomorphic trait, or possibly combination of pedomorphic traits, likely contributes to the naked mole-rat's prolonged health- and lifespan.

Sexual Maturity and Reproductive Hormones

Social status affects many aspects of health and reproduction in mammals, including humans (214), by influencing the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes (180). Regardless of age, subordinate naked mole-rats remain in a hypogonadic, "prepubescent" state, with very small gonads and extremely low levels of sex steroid hormones regardless of age (102), and an inactive hypothalamic-pituitary-gonadal axis (73, 102). Subordinate females, like prepubescent animals of other species, regardless of age, are anovulatory, a phenomenon attributed to the inactivity of gonadotropin-releasing hormone (71, 72). Regardless of age, all subordinates can, however, transition into

Table 2. ***Pedomorphic traits in naked mole-rats and dwarf mice***

Naked Mole-Rat	Dwarf Mouse
Visually observable	
Lower body weight than other mole-rats	Lower body weight than wild-type mouse
Absence of hair	Shortened snout
Elastic skin	Small ears
Absence of external auricles	
Small, simple-shaped vomeronasal organ	
Non-descended testes	
Physiology	
Slow growth rates and protracted development	Slow growth rates and protracted development
Low metabolic rate	Low metabolic rate
Thermolability	Thermolability
High levels of heat-shock proteins	High levels of heat-shock proteins
Cardiac and circulatory	
Sustained blood vessel elasticity	Lack of age-related declines in cardiac function
Cardiomyocyte myofilament signature with β-MHC and skeletal troponin	Maintained levels of β-MHC in heart and skeletal muscle
Fetal hemoglobin	
High hematocrit	
Lack of age-related declines in cardiac function	
Skeletal	
Non-fused growth plates	Not known
Maintained cortical bone mineral density	
Pulmonary	
Neonatal-like lung morphology	Not known
Extensive cuboidal epithelium	
Undifferentiated alveolar pneumocytes	
Decreased alveolar septation	
Double capillary pulmonary arrangement	
Neurological	
Hippocampal distribution of calbindin	Signs of increased neurogenesis in adults and aged animals
Absence of age-related decline in cognitive function	Improved spatial memory and short-term learning
Maintenance of neuregulin levels into old age	Resistance to Alzheimer's disease pathologies and phenotypes
Maintenance of both 3R and 4R tau in adults	Slow cerebral growth
Sustained neurogenesis in old animals	
Endocrine	
Low thyroid hormone levels	Low thyroid hormone levels
Low growth hormone levels	Low growth hormone levels
High IGF2 levels and low IGF1	Low IGF1
Cellular and molecular	
Fructose metabolism	Stress resistance
Stress resistance	
Hypoxia and anoxia resistance	
Emergent traits	
Extended lifespan	Extended lifespan
Decreased hazard of death	Decreased hazard of death
Extended healthspan	Extended healthspan

References are highlighted throughout the text.

breeding animals should they be removed from the stimuli of the dominant female when the breeding female dies or if removed from their birth colony. This sexual maturation is not governed by a typical developmental clock and appears to be directly linked to changes in dominance status, occurring in animals as young as 6 mo or as old as 27 yr.

The transition to breeding status is accompanied by an estrogen-dependent "puberty-like" growth surge (53, 148) that continues over the first few pregnancies. After this occurs, the lumbar vertebrae increase in length, and the head-to-tail length increases substantially. Although breeding males have higher levels of testosterone than subordinates, their transition to dominance is

Table 3. *Mouse models of extended longevity share several features with naked mole-rats compared with wild-type laboratory mice*

	Wild-Type Mouse	Naked Mole-Rat	Ames Dwarf Mouse	Dietary Restriction (Mouse)
Maximum lifespan, yr	3	35	4	4
Body temperature, °C	37.5	32	35.5	36
Body mass, g	25	40	10	18
Fasting blood glucose, mg/dl	100	75	80	80
Body fat, %	C	↑	↑	↓
Thyroid hormones	C	↓	↓	↓
Insulin	C	↓	↓	↓
Growth hormone	C	↓	↓	↓
IGF1	C	↓	↓	↓
IGF2	C	↑	↓	↓
Testosterone	C	↓	↓	↓
Fertility	C	↑	↓	↓
Proteasome activity and autophagy	C	↑	↑	↑
Cancer incidence	C	↓	↓	↓

C is the reference value for wild-type mice. Data for other groups are relative to values for wild-type mice.

not accompanied by a significant increase in body size (160). Subordinate males have very small testes that contain fewer Leydig cells and fivefold lower levels of testosterone than observed in breeding males. This is accompanied by low sperm counts and poorer quality sperm, both of which contribute to their impaired fertility (40). Similarly, throughout life, dwarf mice exhibit poorer fertility and fecundity than their wild-type conspecifics.

It is well documented that maintenance of low levels of sex steroids, facilitated by the removal of gonads or the attenuation of reproductive hormone signaling, extends lifespan in numerous species, including humans (77, 87, 95). Although naked mole-rat subordinates maintain low levels of sex steroids, unlike the castrated eunuchs that reportedly live longer than sexually intact men, their longevity is shorter than that of breeding animals regardless of sex, so it is unlikely that sex steroid levels impact their longevity (68, 87, 174). Interestingly, male Ames mice exhibit low circulating testosterone and reduced fertility, whereas female Ames mice exhibit low estrogen levels and sterility due to the lack of prolactin and GH needed for luteal function (34, 35).

Protracted Brain Development and Sustained Neurogenesis

Pedomorphy is unambiguously observed in naked mole-rat brains, and this may be linked to low thyroid hormone levels. Thyroid hormone is imperative in brain development and maturation, regulating neuronal and glial development as well as neuronal connectivity (reviewed in Ref. 96). Hypothyroidism retards the rate of brain growth, as well as the rate of migration of neurons toward synaptic targets (96). Although naked mole-rats are born with more developed and twofold larger brains than those of day-old mouse pups, they continue to show signs of brain plasticity and maturation well into their third decade of life. Newborn naked mole-rat brains have a well-developed hippocampus, a clearly laminated dentate gyrus, and a large proportion of myelinated white matter tracts. These precocial traits are shared with humans and other primates (57, 149, 208). In sharp contrast, the majority of mouse brain growth and dentate gyrus development occurs postnatally, completing brain maturation by 6 wk of age (2, 112).

Despite the presence of a more mature brain at birth, postnatal brain growth is prolonged in naked mole-rats, taking six times longer than mice to attain 90% of adult brain mass (Table 2). Markers of neurogenic potential, synaptic markers, and dopamine expression continue to change substantially until at least 3 years of life (149). Additionally, naked mole-rats continue to express a developmental isoform of Tau, 3R Tau, long after brain growth is complete (150) and, like neonates, also maintain high levels of beta amyloid (62, 64).

Studies in older naked mole-rats indicate that brain plasticity, maturation, and synaptic refinement still occur in old age, with some evidence that neurogenesis declines in the second decade of life (149, 156). Such protracted maintenance of brain pedomorphic traits and delayed brain maturation could contribute to extended plasticity/brain remodeling, thereby enhancing cellular dynamics to maintain structural integrity and prevent cellular senescence and neurodegenerative processes.

In Ames mice, neurogenesis also appears to extend into adulthood, as evidenced by protracted brain development (144). Basal levels of hippocampal neurogenesis were elevated in adult Ames mice compared with age-matched wild-type mice (199). These

animals also produced significantly more new neurons in response to a neurotoxic challenge with kainic acid (185). This enhanced neurogenesis may partially explain the maintenance of spatial learning and memory in old age and following neuronal damage to this brain region (186), as well as the lower incidence of neurodegeneration (166).

Pedomorphic Cardiovascular Characteristics

Cardiac function and molecular composition of adult naked mole-rat hearts show several indications of a protracted perinatal phenotype into adulthood. Day-old mouse pups can regenerate myocardial tissue following myocardial infarction (88) and apical resection (161), but lose this ability within the first week of life; human neonates show similar early life responses (89). Adult naked mole-rats possibly have signs of retained cardiomyocyte proliferative capacity (Buffenstein R, unpublished observations), including a large proportion of centrally localized mononucleated cardiomyocytes with large diploid nuclei (62). The switch to oxidative phosphorylation within a week of life in mice promotes ROS production and may switch off cardiomyocyte self-renewal and alter cardiomyocyte myofilament protein signatures and contractility (165).

The cardiac contractile protein signature of adult naked mole-rats closely resembles the myofilament protein signature in fetal mice and rats. Although fetal mice predominantly express β-heavy chain myosin (β-MHC), adult mice predominantly express α-heavy chain myosin (α-MHC) in their ventricles. This switch occurs shortly after birth and is thought to be regulated, at least in part, by the increase in thyroid hormone in the perinatal period (76). In stark contrast, adult naked mole-rats predominantly express β-MHC in their ventricles (83). β-MHC has lower ATPase activity compared with that of α-MHC and is associated with lower myofilament sliding velocity and contractility (143). Similar to naked mole-rats, adult dwarf mice also have a larger proportion of β-MHC in cardiac tissue (32). This likely contributes to the low basal cardiac function, low heart rates, and concomitant parsimonious energy utilization observed in both species (84).

Adult naked mole-rats also express slow skeletal troponin I (ssTnI) in their ventricles (83). For most mammals, including humans and mice, this protein is only highly expressed in utero (Table 2). This declines shortly after birth with a concomitant increase in cardiac troponin (cTnI). This perinatal cardiomyofilament signature may reflect the low thyroid hormone levels throughout life and functional optimization for the hypoxic, hypercapnic, and more acidic conditions encountered both in utero and in the naked mole-rat's deep underground nest.

Perinatal Lung Phenotype

Lungs of adult naked mole-rats also exhibit a suite of physiological characteristics that are more typically observed in fetal or juvenile stages of development in other vertebrates (Table 2). These are not simply morphological adaptations to life underground since they differ substantially from those of other subterranean rodents (129). For example, their cuboidal epithelium extends further into the respiratory system than observed in other adult mammals. Moreover, there is a greater abundance of undifferentiated alveolar pneumocytes and markedly decreased alveolar septation (129). Adult naked mole-rats also use a double capillary system in the interalveolar septa. These morphological traits are generally observed in immature or developing lungs of other mammalian species (31). It is possible that these adaptations permit more functional flexibility in naked mole-rat lungs, allowing them to effectively deal with low oxygen levels and high levels of both carbon dioxide and water vapor they would likely encounter in their burrow atmosphere. Notably, the pedomorphic lung morphology observed in the naked mole-rat also may be associated with its low thyroid hormone levels; it is well known that thyroid hormone is necessary for alveolar morphogenesis and the completion of postnatal pulmonary development and maturation (204).

Neuroepithelial body morphology is also a pedomorphic trait associated with naked mole-rat lungs. Neuroepithelial bodies detect changes in oxygen availability; these chemosensors typically decline in the first week of life but are maintained beyond weaning in the naked mole-rat. The neuroepithelial bodies of naked mole-rats are larger and more numerous than in comparatively aged rats (152). Immunophenotyping of naked mole-rat neuroepithelial bodies revealed that these cells exhibit signs of active proliferation, suggesting an enduring fetal state. Maintenance of this fetal oxygen-sensing complex into adulthood may enable their plastic tolerance of gaseous atmospheres with variable oxygen availability.

Perinatal-Like Immune System

Naked mole-rats were recently shown to have a very different splenic immune cell repertoire to that observed in mice, with high myeloid (~60%)-to-lymphoid (~40%) cell ratios (91). This ratio is similar to that in humans and deviates considerably from the predominant (90%) lymphoid bias observed in mice (133, 145). A similar myeloid

bias was also observed in circulating immune cells; high myeloid immune populations reflect a greater reliance on macrophages, phagocytosis, and innate immunity, similar to that observed in neonates (188).

A novel, transcriptionally distinct cell population was identified in the naked mole-rat myeloid lineage that expressed high levels of anti-microbial peptides, including lactoferrin and cathelicidin (91), both of which are commonly found in breast milk and on perinatal skin (120, 211). This novel granulocyte population was also found to be lipopolysaccharide (LPS)-responsive. Consistent with these findings, a highly potent novel cathelicidin, an antimicrobial peptide, was identified in the naked mole-rat (Hg-CATH) (37). Naked mole-rat macrophages also have a greater phagocytic ability and higher cytokine secretions induced by toll-like receptor ligands compared with mice (36). Collectively, these studies suggest that naked mole-rats, like perinatal individuals, rely more heavily on myeloid cell-based innate immune responses to infections and tend to develop a more anti-inflammatory profile (188).

Similarly, dwarf mice reportedly have low numbers of lymphoid cells and double-positive T cells but are nevertheless immunocompetent (60, 142). They exhibit decreased proinflammatory activity that is complemented by increased levels of anti-inflammatory molecules (42, 69). Age-related splenomegaly and T-cell-proliferative responses are delayed, whereas age-sensitive immune markers (i.e., CD4+ or CD8+ memory cells) and T-cell function are maintained at youthful levels in aged dwarf mice compared with age-matched wild-type mice, suggesting delayed immunosenescence (70, 74, 75, 86). The delays in aging of immune system components, reduced inflammatory state, and similar lymphopenia may be indicative of pedomorphic features in both species.

Neonatal-Like Tolerance of Thermolability

Naked mole-rats are stenothermic, capable of regulating body temperature over a narrow range of ambient conditions, outside of which pronounced thermolability is evident (30). Like human neonates (97) and adult dwarf mice (90, 98), naked mole-rats have a reduced mass-specific metabolic rate than allometrically predicted for the species and have large brown adipose tissue pads (44, 46, 49) used in the employment of non-shivering thermogenesis, in efforts to endothermically maintain homeothermy (94)—yet they are unable to maintain a constant body temperature. This is attributed to their high surface area-to-volume ratio, low thermal inertia, and high rates of heat loss (especially in dry air). Naked mole-rats also rely heavily on behavioral thermoregulation to reduce the exposed surface area for heat exchange, features that are shared with human neonates and dwarf mice (209).

Perinatal-Like Tolerance and Physiological Responses to Low Oxygen

Like a fetus in utero, naked mole-rats routinely encounter hypoxic conditions in their underground milieu, similar to the atmosphere encountered at the top of Mount Everest. Both neonates and naked mole-rats show striking similarity in many physiological responses to low-oxygen environments (48, 190). Newborn rats and mice show greater tolerance of hypoxia than do adults of each species (134, 181). Hypoxia tolerance decreases with increasing postnatal age, such that newborn rats are able to survive 10–16 times longer (50 min) without oxygen than adult rats (171). Park et al. (154) recently showed that adult naked mole-rats can survive 18 min in pure nitrogen, unlike most adult mammals that can only survive 3–5 min when kept in anoxic conditions. Moreover, naked mole-rats can tolerate prolonged exposure to atmospheres containing only 3–5% oxygen (154), conditions likely encountered in the deep nests they share with up to 300 of their conspecifics, microbes, and other respiring organisms.

Both Mole-Rats and Perinatal Young Show Reduced Heart Function With Hypoxia

In most adult mammals, heart rate increases in response to hypoxia. However, both naked mole-rats and perinatal individuals respond by decreasing heart rate and cardiac output (104, 154), which further decreases energy expenditure and metabolic demands. Hypoxia inducible factor 1α (HIF-1α) plays an active role in this regard in both the perinatal heart and the heart of adult mole-rats, mediating the switch from glucose to fructose (135, 184), bypassing the rate-limiting step in glycolysis.

Retention of Fetal Hematological Parameters

Both naked mole-rats and perinatal mammals (i.e., fetuses and neonates) use a different form of hemoglobin compared with adults (67). Fetal hemoglobin, present in utero from 2 months of gestation until 6 months of age in humans, has a higher oxygen-carrying capacity and is able to more avidly bind oxygen than adult hemoglobin (41). This binding of oxygen shifts the oxygen-hemoglobin dissociation curve to the left, facilitating better transport around the body, and enables both the

fetus and the naked mole-rat tissues to maximally extract circulating oxygen (105). Increases in blood-oxygen affinity and capacity, facilitated by polycythemia and higher hematocrits, prolong aerobic latency and reduce lactate accumulation, providing maximum ATP generation per mole of fuel substrate (3, 93, 136).

Brain Tolerance to Hypoxia Involves Perinatal Mechanisms

High levels of neurotrophic growth factors (61) and protracted neurogenesis (149) both in utero and in adult naked mole-rats may also facilitate chronic tolerance of hypoxia, enabling continuous replacement of damaged tissues. Brain immaturity and reduced brain metabolic activity may also contribute to perinatal metabolic rate reduction in the face of hypoxia. Unlike mouse brain slices kept under identical conditions, naked mole-rat brain slices can tolerate complete anoxia for 30 min, fully recovering after oxygen is restored, whereas those of mice stop functioning in 1–2 min without oxygen and never recover (118). Mouse neuronal cell death is attributed to membrane depolarization and the rapid intracellular influx of calcium and efflux of potassium. Clearly, the naked mole-rat shows extreme tolerance to both a lack of oxygen and possible reperfusion-induced damage thereafter. Naked mole-rats also show a blunted calcium response to hypoxia compared with mice, providing further protection against hypoxia-induced neuronal death (159).

Moreover, naked mole-rats show a lack of synaptic paired pulse facilitation as well as insensitivity to adenosine, features commonly observed in early rodent postnatal development (65, 118). Adenosine and the NMDA receptor play key roles in hypoxia-induced toxicity and modulate intracellular calcium influx. In most mammals, the receptor subunit composition of NMDA receptors in adults differs from neonates. The GluN2D subunit is strongly implicated in hypoxia tolerance, and although adult mouse brains show a precipitous decline in GluN2D (13% of neonate levels), adult naked mole-rats retain 66% of the amounts seen in naked mole-rat neonates, thus retarding intracellular calcium influx and protecting neurons of the brain against hypoxia-induced death (14). Although no data are available in hypoxic conditions, for dwarf mice it has been shown that hippocampal mRNA and protein levels of NMDA receptors (NR)1, NR2A, and NR2B, and the kainate receptor 2 are increased in Ames dwarf mice compared with wild-type controls (185), suggesting potential protection from adverse conditions.

Perinatal-Like Pain Tolerance and Physiological Responses to Low Oxygen

Environments with poor gas exchange also can result in the accumulation of carbon dioxide (CO_2). This can be both lethal and painful. High levels of CO_2 in moist air forms carbonic acid, stimulating pain receptors and inducing burning sensations in both eyes and nasal passages. Naked mole-rats appear unable to sense this pain due to a motif change in the gene for one of the voltage-gated sodium channels (*Scn9a*; Nav1.7), inhibiting spike initiation under acidic stimuli (194). Naked mole-rats also lack expression of substance P and calcitonin-related gene peptide, contributing to their insensitivity to acid burn (66, 153).

Acidic conditions associated with hypercapnia can trigger an inflammatory response in the respiratory membranes of the lungs, and this gives rise to pulmonary edema (45, 162); naked mole-rats do not mount these inflammatory responses. Mice exhibit significant pulmonary edema after a 15-min exposure to 15% CO_2, whereas naked mole-rats show no edema even at a 50% CO_2 exposure (153, 194). This hypercapnic tolerance is also a common feature of newborn mice, where CO_2-induced euthanasia takes 10 times longer than that observed in adults (164). Similarly, human fetuses are also unaffected by exposure to CO_2 (167).

Perinatal-Like Stress Resistance

Naked mole-rats, like long-lived dwarf mice and human newborns, are resistant to a wide range of toxins, including xenobiotic compounds, heavy metals, DNA-damaging agents, and cancer-inducing agents (122, 177). This resistance is observed both in vivo and using skin fibroblasts in culture (121, 141). That dwarf mice and naked mole-rats share this resistance to stressors suggests that the protective pathways facilitating this are integral to their protracted longevity. Both Ames dwarf mice and naked mole-rats exhibit resistance to reactive oxygen species, thought to be due to increased expression of the oxidative radical scavenger glutathione as well as glutathione *S*-transferase (GST), a molecule that is largely regulated by the transcription factor nuclear factor (erythroid-derived 2)-like 2 (NRF2) (18). Naked mole-rat livers have three- to fivefold higher levels of GST, heme oxygenase (HO1), and NQO1 activity than observed in wild-type mice (124), thus maintaining its ability to ward off a number of oxidative stress and xenobiotic compounds. High levels of cytoprotective signaling markers and upregulated xenobiotic pathways are regulated by NRF2 (124). NRF2 is considered essential for normal fetal growth (116) and also regulates the transcription of genes

involved in saccular lung maturation, cell growth machinery, lymphocyte immunity, and alveolarization both in utero and during postnatal lung development (38). NRF2 is upregulated in frogs (198) and domesticated bovids during development (80), and thus high levels of NRF2 that continue into adulthood may very well be considered pedomorphic.

It also is noteworthy that both dwarf mice and naked mole-rats have a lower incidence of cancer than other rodents (52, 63, 75, 100). Furthermore, experimental studies reveal that both models resist experimental cancer induction following carcinogen or oncogenic administration (126, 168).

Maintenance of "Youthful" Protein Homeostasis

In many species, the gradual collapse of a cell's protein quality-control machinery is a widely accepted hallmark of aging (127). Age-related declines in protein quality control can result in the accumulation of damaged proteins and protein aggregates, usually leading to cell death (113). Unlike other species typically studied (7, 39, 119, 178, 200, 210), naked mole-rats do not appear to show impairments in protein homeostasis with advancing age. Many molecular chaperones, including the small heat shock protein HSP25, are present at high levels in both young and old naked mole-rats (Buffenstein R, unpublished observations) (173). Additionally, autophagy and proteasome degradation in naked mole-rats are maintained throughout life at levels observed during the developmental period of a typical mammal (163, 201, 213).

In many model organisms, enhancing proteasomal activity has been shown to extend lifespan while concomitantly reducing protein aggregation and neurodegeneration (115, 139, 205). Due to the elevated levels of autophagy and proteasome activity in naked mole-rats, protein solubility remains relatively unchanged during their long lives, with no build-up of polyubiquitinated proteins (157). Higher levels of autophagy have also been observed in long-lived GH mutant dwarf mice (206, 207). Collectively, these data support the theory that sustained proteolytic degradation during aging is beneficial.

Conclusions and Open Questions

Beyond delayed and attenuated Gompertzian mortality hazard, it is noteworthy that two of the longest-lived mammalian species relative to their body mass, naked mole-rats and humans, maintain a diverse suite of pedomorphic traits well into old age, a fact that is also true, albeit not to the same extent, of long-lived dwarf mice (Table 2). Given the numerous benefits associated with the retention of youthful or early development features into adulthood (pedomorphosis), the obvious unresolved question is why pedomorphosis is not routinely employed across the animal kingdom and what may be the tradeoff such that most other species opt for rapid somatic maturation and possible concomitant greater species fitness. For example, the axolotl has traded pedomorphic traits for the ability to ever become a terrestrial-dwelling animal. Pedomorphosis is presumably favored in more stable and less competitive environments that remove the need for a dispersive adult stage and high levels of reproduction (81).

Physiological systems that can maintain youthful aspects and facilitate faster repair, phenoplasticity, and sustained function with advancing age by definition would counter the effects of aging. This line of thinking can be applied to any individual system for which pedomorphic traits are observed and for which aging would result in degeneration. However, it seems likely that each pedomorphic trait arose as an adaptation to a specific environmental pressure rather than to increase longevity per se. For example, in naked mole-rats, pedomorphic lung functionality was likely an adaptation to the low-oxygen and high-carbon dioxide atmosphere, or their pedomorphic brain plasticity may have been an adaptation to eusociality. Ultimately, we still need to address the question of whether a single factor regulates the "master biological clock" (191) or whether a combination of pedomorphic traits is actually causative in the extended lifespans observed in these models of extended longevity.

Many approaches could be useful to address this question. Comparative biology has a lot to offer by examining organisms that exhibit varying pedomorphic phenotypes and longevity to understand the connection between these traits. Molecular biology will also likely generate useful information by engineering naked mole-rat pedomorphic traits into laboratory mice, whereas long-lived mutant mice will allow tests of causation between pedomorphic traits and longevity. ■

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