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PERSPECTIVE

Infection and inflammation in somatic maintenance, growth and longevity

Elizabeth B. Kopp and Ruslan Medzhitov

HHMI and Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA

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Correspondence
Elizabeth B. Kopp, Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06510, USA. Tel.: +1 203 785 6090; fax: +1 203 785 4461; e-mail: elizabeth.kopp@yale.edu

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Abstract

All organisms must display a certain degree of environmental adaptability to survive and reproduce. Growth and reproduction are metabolically expensive and carry other costs that contribute to aging. Therefore, animals have developed physiologic strategies to assess the harshness of the environment before devoting resources to reproduction. Presumably, these strategies maximize the possibility for offspring survival. Current views of aging reflect a trade-off between reproductive fitness and somatic maintenance whereby environmental stress induces an adaptive metabolic response aimed at preserving cellular integrity while inhibiting growth, whereas favorable environmental conditions (abundance of food and water, and optimal temperature, etc.) promote growth and reproductive maturity but simultaneously increase cellular damage and aging. Here we propose that the prevalence of infectious pathogens in a given niche represents an additional environmental factor that, via innate immune pathways, actively shifts this balance in favor of somatic maintenance at the expense of reproduction and growth. We additionally propose the construction of a genetic model system with which to test this hypothesis.

Introduction: stress resistance strategies

There are many examples of stress-resistant states for various organisms and many identified stress-inducers. Some mammals, for example, may produce thicker fur in the winter, but here we are limiting the discussion to environmental conditions that result in a change in metabolism. There are several known types of extreme metabolic states induced by the environment. Drought and heat induce estivation in many frogs and fish. The lungfish is a well-known example. During times of drought, the African lungfish burrows into the mud and secretes a protective mucous around itself. Its metabolic rate drops and it breathes air until the next rainstorm washes it out of the mud. Anoxia is also a well-known stressor, inducing a dormant state in many invertebrates (mollusks, some insects) and vertebrates (turtles, some fish) (Storey and Storey 1990). Some bacteria can survive dormant as endospores until environmental conditions improve, and invertebrates such as *Caenorhabditis elegans* can enter a dormant alternative developmental state called dauer or diapause when faced with a lack of nutrient availability (Hu 2007). The hibernation in some species of mammals is another well-known example of environmentally induced dormancy; metabolism and body temperatures of hibernating animals are drastically reduced, and they exist in suspended animation until spring when the likelihood of food availability and therefore offspring survival is greatest (Lyman et al. 1982).

Estivation, diapause, spore formation, and hibernation are extreme examples of stress resistance in that they represent discrete life-states of the affected organisms. In all of these cases, this is a dormant life-state in which the animal temporarily forgoes its usual life activities such as movement, foraging, eating, mating, reproducing, young-rearing, etc. It is important to note that when in these 'altered' states, many cellular and physiologic processes are greatly retarded, and cellular and tissue damage (caused by active metabolic states) is minimal. This suspended animation is essentially a nonaging state of being (Roth and Nystul 2005). There is presumably a spectrum of stress-resistant metabolic states, corresponding to a spectrum of stress conditions that do not all result in dormancy. Specifically, we propose that since an infected

animal is less likely to bear and rear healthy offspring, a special mechanism may have evolved to shift the cellular response from growth to maintenance in times of infection-associated stress. We further suggest that the 'infected state' is sensed by the innate immune system which could then coordinate the detection of an infection with an appropriate metabolic response. While our proposal is speculative, we provide some empirical evidence to support such a mechanism and a plausible system with which to test it.

A better understanding of the stressors inducing the anti-aging phenotype, and the genes responsible for transmitting these signals, will be critical to possible intervention in aging-associated human pathologic conditions. One particularly well-studied stress-condition in mammals that results in a reduced but not dormant metabolic state is caloric restriction. Caloric restriction refers to the maintenance of a low-calorie diet. In practical terms, this represents about a 40% reduction in the total calories consumed relative to an animal fed *ad libitum* (Piper and Bartke 2008). It has been known for 70 years that caloric restriction can extend lifespan in mammals (rodents, so far, as these experiments by necessity are very long). Caloric restriction is a form of nutrient stress, essentially conveying the physiologic message that environmental conditions are not conducive for offspring survival. Animals undergoing caloric restriction do not only live longer than *ad libitum* fed counterparts, they are also more resistant to age-related diseases such as heart disease and cancer.

Not surprisingly, there is currently a keen interest in research to develop drugs against aging-related targets, and to devise methods to induce torpidity for the preservation of tissues. Indeed, a brief state of dormancy has been artificially induced in mice by treating them with H_2S gas. Under these conditions, their metabolic rate dropped by 90% and their body temperatures reached ambient levels. Remarkably, when removed from the gas, the mice recovered with no apparent adverse effects (Blackstone et al. 2005). Likewise, much recent work has focused on identifying the gene transcription and translation programs that are activated or subdued in dormant states such as estivation and hibernation. This work is particularly interesting in light of the fact that many of these gene programs are ancient and conserved across phyla opening the possibility that they could be 'reactivated' in humans (Storey and Storey 2007).

Genetic control of longevity in invertebrate model organisms

The genetic control of longevity has been greatly elucidated in model organisms. Long-lived mutant worms (*C. elegans*) and flies (*Drosophila melanogaster*) were developed and the affected genes were subsequently identified. The genes responsible for negatively and positively controlling longevity overlap and come under two broad categories: nutrient-stimulated growth and maintenance of cellular (including nuclear) integrity. The first category comprises the insulin and insulin-like growth factor (IGF) signaling (IIS) pathway. This pathway is also found in vertebrates and is critical for detection of nutrients which leads to the subsequent upregulation of genes involved in anabolism. It also inhibits pathways of metabolic conservation. As characterized in *C. elegans*, the canonical signaling pathway in this response starts with stimulation of the DAF-2 receptor (an insulin receptor homolog) followed by activation of a PI3-kinase (AGE-1) and activation of AKT. Signaling through DAF-2 results in inhibition of the FOXO transcription factor, DAF-16, thereby inhibiting DAF-16 targets. Mutants in signaling proteins in the DAF-2 pathway are long-lived and this longevity requires DAF-16. DAF-16 targets are genes involved in the general stress response and metabolism, such as heat shock proteins, antioxidants, and cell cycle inhibitors (Murphy et al. 2003). Mutations in the DAF-2 signaling pathway, or gain-of-function mutations in the inhibitor of this pathway (DAF-18, a lipid phosphatase) result in long-lived worms.

The second category of 'longevity pathway' mutations identified in *C. elegans* comprise genes encoding proteins involved in the electron transport chain, Kreb's cycle, and mitochondrial carrier proteins (Artal-Sanz and Tavernarakis 2008). It is still unclear exactly why mutations in genes regulating mitochondrial function promote longevity, or whether they are related to the IIS pathway, however, prevailing theories suggest that oxidative damage from mitochondrial activity may be responsible for cellular aging and that a reduction in these activities could be beneficial.

Interestingly, the presence of bacteria in *Drosophila* cultures has been tested with respect to longevity. Brummel et al. found that *Drosophila* grown in an aseptic environment (axenic cultures) had 30% shorter lifespans than flies grown in the presence of bacteria. Specifically, bacterial exposure during the first week of adult life was beneficial for lifespan. Conversely, bacterial exposure during the last part of life was slightly detrimental for lifespan. This phenotype was dependent on the genotype of the fly as the Ecdysone receptor mutant (EcR^{v559fs}) was unaffected by bacteria whereas the long-lived DJ817 mutant had even greater longevity in the presence of bacteria (Brummel et al. 2004). While the authors did not suggest that stimulation of innate immune receptors communicates the stress response (longevity response), the different phenotypes seen in the different mutant strains imply that

the response is dependent on a genetically determined reaction of the host to the presence of bacteria or bacterial products. Similar work has been done in *C. elegans*, however the axenic diet, not the reverse, promoted the longevity phenotype (Garigan et al. 2002; Houthoofd et al. 2002). Conclusions in *C. elegans* however are more difficult to draw as bacteria are the normal food for these worms. Thus, it is difficult to determine whether worms fed axenic diets have a longer lifespan due to lack of innate immune signaling (the opposite of our hypothesis), due to dietary restriction, or due to induction of stress response genes. In either case, the detrimental effect of bacteria seen at the last stage of life is likely due to overabundance of bacteria (microbial pathogenesis) and not to the acceleration of an aging process.

Genetic control of body size and aging in mammals

In mammals, the IIS pathway is conserved and contributes to total body growth and metabolism. When nutrients are abundant, insulin and IGF-1 are secreted and promote the uptake of glucose, anabolic growth, and storage of carbohydrates. Growth hormone itself exerts its effects chiefly by inducing the production of IGF-1 by the liver. Multiple cellular sensors exist that relay the message of nutrient adequacy or inadequacy. These sensors and effectors include both the receptors and intracellular signaling molecules such as the insulin receptor substrates (IRS 1–4), AMP-dependent kinase, TOR, and the NAD-dependent deacetylase, SIRT-1. Many of these gene-products are essential for general metabolic homeostasis or development, but several general and tissue-specific knockouts have been developed that clarify the relationship between the IIS pathway and longevity. For an extensive review of these knockouts see Liang et al. (2003).

Growth hormone and growth hormone receptor mutants have been generated and found to affect lifespan in mice. Ames and Snell dwarf mice carry mutational defects in the growth hormone-IGF-1 axis. These mice have a reduced body size (about 1/3 of wild-type), reduced body temperature and reduced metabolic activity. Ames mice are long-lived (by 49% in men, and 68% in women). Snell female mice are long-lived when on particular genetic backgrounds but the data for the males are more conflicting. Gene ablation in growth hormone releasing hormone also supports a model in which a reduction in growth hormone reduces body size and increases longevity. When growth hormone receptor activity is ablated in the livers of mice (the GHR/BP knockout) the resulting animals are small and long-lived. Interestingly, while delayed in sexual maturation, female mice are not infertile indicating that regulation of lifespan and fertility can be separated.

Transgenes and knockouts in mitochondrial enzymes and repair proteins in mice have been disappointing with respect to anti-aging phenotypes (Kregel and Zhang 2007). This may be due to functional redundancy in these factors or due to the likelihood that aging results from many different genetic and environmental factors. However, the p66Shc knockout mouse line lives approximately 30% longer than wild-type mice, and cultured cells from this line have reduced cellular oxidative damage and production of reactive oxygen species (ROS) (Migliaccio et al. 1999; Trinei et al. 2002). P66Shc is postulated to promote oxidative-stress-induced apoptosis by at least two mechanisms and therefore the deletion of this gene is thought to increase longevity by preventing this apoptosis (Pinton and Rizzuto 2008).

Some insight into mechanisms (and potential therapies) of aging may also be learned from the study of age-accelerating disorders. While controversial whether progeria disorders in humans are appropriate models for studying aging, it is interesting to note that where identified, the function of the gene-products encoded by the affected mutations are generally monitors of DNA integrity. These include nuclear lamins, the transcription repair factor subunits XPD and XPB, and several DNA excision repair proteins (Pereira et al. 2008). A study on dermal fibroblasts comparing young, middle aged, old, and cell lines from Hutchison–Guilford progeria syndrome found that the Progeria syndrome cells and the older cells had a similar downregulation of genes involved in mitosis and extracellular matrix formation (Ly et al. 2000). It has also been shown that certain enzymes involved in ROS scavenging are produced in greater levels in human centenarians than in most younger (but still elderly) individuals (Paolisso et al. 1998) suggesting the possibility that increased levels of antioxidants may contribute to extreme longevity.

The innate immune system as an environmental sensor

In all of the stress-conditions mentioned above, the austerity of the environment is detected by biologic sensing systems and relayed to the relevant cells and tissues either directly by small molecules like H_2S or indirectly by soluble ligands (hormones, growth factors, neurotransmitters, etc.). In its most basic sense, the innate immune system is a sensitive environmental sensor and relay system. Tissue macrophages are located in virtually every tissue and are therefore uniquely suited to report on local environmental conditions. Other cells of the innate immune system reside in the blood and as mobile units are able to

transmit messages throughout the body. Furthermore, the innate immune system has its own hormone-like relay signal in the form of cytokines. Cytokines in turn have numerous effects not only on other hematopoetic cells, but also on major metabolic tissues such as the vascular endothelium, muscle, liver, and adipose tissue. In addition, the major proinflammatory cytokines, TNF-α, IL-1, and IL-6 act on the hypothalamus to alter the set-point for body temperature and appetite.

The innate immune system detects infection via germline-encoded receptors recognizing conserved molecular features characteristic of microbes (Janeway 1989). These features are required for the survival of the microbe (i.e. mutations in them would render the microbe nonviable) and include not only surface molecules, but also genetic material. By recognizing microbe-specific features, the innate immune system avoids inadvertently targeting host cells and tissues. Furthermore, because the receptors exist in both intracellular and extracellular compartments, the response can be tailored to the specific microbe and its niche. In other words, the signals emanating from each type of receptor can convey information for an appropriate response against a specific class of microorganism. It is important to note that these recognized invariant features are not specific to pathogens *per se* but are conserved features of entire classes of microorganisms, pathogenic or not. Thus, in principle, like pathogens, commensal microorganisms can and are indeed recognized by innate immune effectors, and defects in controlling the access or extent of this recognition can lead to inflammatory disorders such as inflammatory bowel diseases.

The receptors of the innate immune system detect conserved molecular structures characteristic of microorganisms, such as lipopolysaccharide, lipoteichoic acids, peptidoglycans, flagellin, and viral RNA. The best characterized families of innate immune receptors are the Toll-like receptors (TLRs) and the NOD-like receptors. Upon recognition of their microbial ligands, these receptors activate pro-inflammatory signaling pathways, NF-κB, and mitogen-activated protein kinase (MAPK) and induce expression of hundreds of genes involved in inflammation, antimicrobial defense, and activation of adaptive immunity. These receptors thus function as sensors of microbial infection and induce production of inflammatory cytokines (TNF, IL-1, and IL-6) which trigger a wide range of effects on different tissues to prepare them for defense against infection. The inflammatory response induced upon innate immune recognition of pathogens is essential for the protection of the host, but can have a detrimental effect if it becomes dysregulated.

We hypothesize that innate sensors of microbial infection may determine whether the environment is favorable (in terms of pathogen threat) and communicate this message (in the form of inflammatory cytokines) to the critical control centers, including the hypothalamus, endocrine organs, and other relevant tissues (adipose, liver, etc.). Perception of the 'infectious threat' by these tissues and organs, in turn, may alter the balance between somatic maintenance and reproductive fitness. This does not necessarily require a rerouting of scarce resources from growth and reproduction to immune function; rather, even when resources are not limiting, immune system induction may actively shut off growth and reduce metabolism, perhaps by co-opting an existing molecular strategy as by inhibiting the IIS pathway.

Effects of parasitic infection on growth and reproductive maturity

The idea of balancing immunoactivity with other adaptive traits is of course not new. Indeed, life-history theory proposes that organisms have competing life functions which require resources. These functions include growth, somatic maintenance and repair, reproduction, and immunocompetence, and resources allocated to any of these functions result in a fitness tradeoff relative to the other functions. This hypothesis has been tested in various organisms. In one study, supplementary-fed female Ural owls, for example, benefitted by an improved ability to resist leucocytozoan infection which resulted in earlier egg-laying and bigger clutches. This result suggests that resources devoted to immunity are limiting (Karell et al. 2007). In another study, medicated female Blue Tits were shown to increase their reproductive effort, which correlated with a reduction in parasitic burden (Tomas et al. 2007). Again, this indicates that the energy normally devoted to fighting infection is redirected to reproductive activity as a result of remediation of the pathogen. In breeding male ground squirrels, provisioning them with food at the start of breeding resulted in greater numbers of leukocytes (Bachman 2003). Studies of this type, however, do not illustrate whether the immune system itself directs a growth or reproductive inhibition phenotype. It is also predicted by life-history theory that the anticipated costs of pathology resulting from parasite infection should result in an alteration of the timing or absolute number of offspring, that is, in fecundity compensation (Agnew et al. 2000). Deer mice (*Peromyscus maiculatus*) that were experimentally infected with *Schistosomatium douthitti*, for example, were shown to delay breeding and give birth to heavier (more fit) offspring. Likewise, in a study with great tits, exposure of mother birds to an ectoparasitic flea induced a maternal response (deposition of IgG) in their eggs which led to greater body weight of their young (Gallizzi et al. 2008). This study demonstrates that a

signal (the maternal response) indicating infection resulted in an altered life history in the absence of infection in the young. While these ecologic studies provide important empirical evidence in support of the reallocation of resources and of fecundity compensation during parasitic infection, the mechanism of the resource partitioning or fecundity alteration is unknown. In addition, the tremendous potential variability in the exposure of these animals to parasites and the genetic variation within field populations would render the discovery of these mechanisms very difficult.

Effects of chronic inflammation on growth and reproductive maturity in mammals

If inflammation promotes an anti-stress response that favors somatic maintenance over growth, then one would predict that the constitutive secretion of inflammatory cytokines should correlate with small body size and perhaps longevity. There are some examples in humans that support the possibility of the former. Specifically, in chronic inflammatory diseases like *Helicobacter pylori* infection (Raymond et al. 1994; Perri et al. 1997; Choe et al. 2000; Cuoco et al. 2000; Demir et al. 2001; Bravo et al. 2003; Sood et al. 2005; Windle et al. 2007), Crohn's disease (Motil et al. 1993; Sawczenko and Sandhu 2003; Sawczenko et al. 2006), and juvenile idiopathic arthritis (Simon et al. 2002; MacRae et al. 2006), many studies have shown a correlation between infection or inflammation and short stature. The delay of puberty in these patients is also well-documented (Simon 2002). Unfortunately, these types of studies are at best correlative, as there are usually confounding factors, not the least of which is the pathogenicity of the infection itself. Chronic infection is also commonly associated with poor-living conditions and substandard nutrition, which, as noted above, can inhibit growth through a reduction in IGF-1. In addition, undernutrition itself can result from chronic inflammation as gut diseases often result in malabsorption of nutrients. Moreover, drugs such as steroids used to treat disorders like juvenile chronic arthritis, can inhibit growth themselves. Nevertheless, in a rat model of colitis, an IL-6-dependent decrease in circulating IGF-1 was shown to be independent of malabsorption, suggesting that the inflammation itself contributes to an alteration in the release of a growth factor (Ballinger et al. 2000).

Cytokine regulation of the IGF-1 axis and metabolism

The relationship between an inflammatory cytokine and the IGF-1 axis has been directly tested in a transgenic mouse model in which the pro-inflammatory cytokine, IL-6 is over-expressed (De Benedetti et al. 1997). IL-6 is normally secreted by activated macrophages during an immune response. During an infection, this pleiotropic cytokine is a major inducer of acute phase response proteins from the liver. The acute phase proteins circulate in the blood at extremely high levels and act to opsonize bacteria and activate complement thus contributing to bacterial disposal by phagocytosis. In addition to responding to infection, IL-6 can control whole body temperature. IL-6 has been implicated in a number of chronic inflammatory diseases such as atherosclerosis, arthritis, and Type II diabetes. The latter, a disease of metabolism, is characterized by the persistence of serum cytokines, glucose intolerance, and insulin resistance; although insulin is available, the IIS signaling pathway is inhibited. The serum cytokines have been shown to exacerbate the dysregulated state (Pickup and Crook 1998), and various therapies rely on antagonizing individual cytokines and reducing inflammation.

In the IL-6 transgenic model, IL-6 is constitutively over-expressed and detectable in the serum. These transgenic mice were 30–50% smaller than control mice and had lower levels of circulating IGF-1 (De Benedetti et al. 1997). In addition, transgenic females were either infertile or gave birth to small litters (De Benedetti et al. 2001). Neutralization of the IL-6 by passive immunization with an IL-6 antagonist corrected the IGF-1 levels and reversed the growth defect (De Benedetti et al. 2001). While these studies did not address longevity, they did demonstrate a link between the overproduction of an inflammatory cytokine and fertility and body size indicating that an assumed infection can influence the IGF-1 axis.

Other pro-inflammatory cytokines (and signaling molecules controlling their expression) have been shown to affect metabolic status without affecting body size. Obesity and type II diabetes are chronic inflammatory diseases that are characterized by low-level constitutive secretion of pro-inflammatory cytokines. These cytokines have been shown to contribute to the insulin resistance manifested in these disorders. For example, TNF-α is known to inhibit insulin signaling in adipose tissue (Hotamisligil et al. 1994), and deletion of TNF-α, or the TNF receptor, TNFR1, in both genetic (TNFR1) and high-fat diet-induced (TNFR1 and TNF-α) obese mice results in greater insulin sensitivity (Hotamisligil 1999). As mentioned above, the production of many cytokines is controlled by the inducible activation of the transcription factors, NF-κB, and members of the MAPK family. NF-κB induction depends on the controlled phosphorylation and activation of an upstream kinase, IKK-β. Constitutive activation of IKK-β in the liver in a mouse transgene model (LIKK) led to the production of IL-6, TNF-α, and

IL-1β and caused hepatic and systemic insulin resistance (Cai et al. 2005). Deletion of IKK-β in hepatocytes or in myeloid cells had an opposite effect, resulting in increased sensitivity to insulin for mice on a high fat diet (Arkan et al. 2005). JNK is a member of the MAPK stress signaling pathway, and it is activated during infection via TLRs and cytokines. Once JNK is activated, it phosphorylates and activates transcription factors of the AP-1 family, which induce genes encoding, for example, cytokines. JNK has been shown to contribute to insulin resistance by enhancing the phosphorylation of the insulin receptor signaling molecule, IRS-1, and thereby inhibiting its activity and that of the insulin receptor in adipose tissue. Mice lacking JNK-1 are resistant to diet-induced obesity, and have improved insulin sensitivity on a high fat diet (Hirosumi et al. 2002). These examples illustrate how TLR signaling and the production of cytokines during an infection could turn down the anabolic activity of the IIS signaling pathway.

Evolution of aging

Aging is often viewed as the consequence of increased cellular damage accumulated over time (Balaban et al. 2005). Cellular damage can occur collaterally through oxidative processes necessarily tied to processes required for growth and reproduction (cell division, protein synthesis, storage, etc.), and by stochastic events induced by the environment including DNA damage, replication error, nutrient stress, and infection. In many organisms, resources can be diverted to maintenance and repair programs to retain cellular integrity to the extent needed to ensure offspring birth and survival. This theory of aging is called the disposable soma theory (Kirkwood 1977; Kirkwood and Holliday 1979) and makes several reasonable predictions about the genetic control of longevity (Kirkwood 2008). Its underlying assumption is that selective pressure has enforced the evolution of mechanisms that are competent enough to preserve the germline under the stressful conditions that would be typically expected for each organism. It predicts that somatic cells are more expendable than germ cells and indeed act to protect germ cell viability to the degree necessary to reliably ensure reproductive success. Different organisms have different strategies for maximizing reproductive fitness, and the degree to which longevity can be genetically controlled differs by a host of factors including each organism's lifecycle, ecologic niche, reproductive strategy, extent of mitotic versus postmitotic tissue, etc. As for most organisms (humans and captive animals excepted), environmental conditions such as cold, disease, starvation, or predation will determine their lifespan, and the plasticity of the longevity response need only provide acceptable protection long enough to generate self-sufficient progeny. For humans, the prevalence of age-related physical disorders is likely a recent phenomenon owing to the large degree of control we have over the potentially lethal environmental conditions noted above. Therefore, the degree of plasticity in human stress responses affecting longevity and/or whether maintenance and repair processes can be improved at older ages in humans is largely unknown.

It is perhaps not surprising that the IIS pathway has emerged as a central ancient and conserved system for regulation of organismal longevity. This pathway is concerned with detecting and appropriately allocating nutrient resources essential for cellular and organismal survival. It makes sense then that perturbations in this pathway resulting from intrinsic or extrinsic insults would result in inhibition of further growth and promotion of repair and maintenance. It is unclear whether all or even most anti-aging strategies employ some aspect of the IIS pathway, but given the tendency of parsimonious evolution this is a strong possibility; other signals emanating from sensory systems (detecting temperature, sustained lack of water, seasonal changes in light–dark cycles, for example) need only send a relay into this established hub to perform the similar task of defense until environmental conditions improve.

We have proposed here that infection may be another relevant unfavorable condition that could trigger an anti-aging, cellular maintenance program, whether through a pathway that impacts the IIS pathway, through a damage-sensing circuit (similar to the DNA repair response pathway), or through some other uncharacterized pathway. We have supported this hypothesis with anecdotal information suggesting that activation of the innate immune system by chronic infection in humans correlates with small body size and reduced IGF-1 secretion. The innate immune system is well-suited to convey information about the type and degree of 'infectious' stress encountered by the organism because it communicates via soluble effectors (cytokines) that can have profound consequences on both individual cells and on total body metabolism. This stress response could be considered a form of 'hormesis' in which a sub-lethal 'dose' of infection could temporarily promote a more stress-resistant state.

It should be noted that while beneficial for clearing an infection, the pro-inflammatory cytokines produced in an acute infection can also cause damage to tissues. The fact that sepsis is often fatal demonstrates this point as it is not the infection itself, rather it is the host response to the infection that actually kills the sepsis patient. As a result, there are powerful negative feedback mechanisms that control the magnitude and

duration of the inflammatory response. The notion that infection may promote maintenance at the expense of growth may seem counterintuitive, given that infectious diseases are the major cause of morbidity and mortality in most organisms (certainly in humans until the advent of antibiotics). Indeed, retrospective mortality studies have shown that early-life infections and infant mortality of a cohort correlate with earlier morbidity and mortality of that cohort (Finch and Crimmins 2004). In other words, epidemiologic conditions experienced during childhood could have life-long deleterious effects for those surviving past childhood. This phenomenon however may be related to permanent tissue damage sustained during these infections whether by the pathogen or by immunopathology incurred during clearance of the infection. If, however, infection and inflammation do have a hormetic effect, it is likely to be temporary as it would only have evolved to permit postponing reproduction until conditions are more favorable, in this case until the infection is cleared. For this reason, chronic infection may provide a more significant effect. Interestingly, the effect of chronic infection may be mimicked by constitutive stimulation of the innate immune system by commensal microflora. Results from our laboratory demonstrate that proper maintenance and renewal of gut epithelium require recognition of commensal bacteria by the innate immune system (Rakoff-Nahoum et al. 2004). Gut epithelial cells are in constant contact with commensal bacteria, and therefore gut innate immune receptors receive tonic stimulation. It is tempting to speculate that this maintenance program is taking advantage of a hormetic system linking microbial recognition and stress resistance.

Determining the mechanism of infection-induced stress resistance

An obvious shortcoming to the available empirical data on this subject is that longevity associated with immune activity could be due to the clearance of pathogen or to an enhanced stress response or both. Likewise, commensal populations provide several functions as mentioned above including aid in digesting food. Thus, experiments in which commensals are eliminated would provide confusing results with respect to growth, reproductive development, and longevity. To test our hypothesis, mammalian models will therefore need to be developed that replicate the 'assumption' of infection by the innate immune system without actual pathogens. This type of model should trigger not only one cytokine (like the IL-6 transgene) but an appropriate array of cytokines to mimic an actual infection but in the absence of real pathogen. In this way, we would be able to discriminate between the detrimental effect of the infectious burden and the effect rendered by the immune system's interpretation of that burden. One way to approach this problem would be to design transgenic animals expressing constitutively active TLRs or their ligands. Many TLR ligands, like LPS for example, are not proteins and therefore are not easily amenable to genetic engineering, however, both flagellin (the TLR5 ligand) and profilin (a TLR11 ligand) are gene products, and the former is a TLR ligand in both mice and humans. A flagellin-expressing transgene could possibly mimic chronic infection and be used as a model to investigate the metabolic reaction to perceived infection.

Conclusions

We propose here that similar to nutrient availability, temperature, and other key environmental factors, infectious agents, in addition to triggering the appropriate host defense reaction, may be sensed to indicate an unfavorable environment. Infection is sensed by the innate immune system, which, through the induction of inflammatory cytokines may control the key growth and maintenance pathways, including the IIS pathway. In this way, infection detected at certain critical periods may promote stress-resistant tissue maintenance states at the expense of reproduction and growth. In some cases, it may even increase lifespan to delay reproduction until the environment becomes more favorable.

Term	Glossary of terms
IIS pathway	Insulin and Insulin-like growth factor signaling pathway. Signaling pathway conserved from insects to humans. Growth factors released after feeding (insulin and insulin-like growth factor, IGF-1) stimulate receptors of this pathway and promote cellular and oraganismal anabolic growth
DAF-2	The *Caenorhabditis elegans* ortholog of the insulin and insulin-like receptor. Mutations in DAF-2 have been shown to increase longevity in *Caenorhabditis elegans*. DAF-2 negatively regulates DAF-16, a FOXO transcription factor
PI3 kinase	Phosphoinositide-3 kinase. Important kinase in the IIS signaling pathway. This kinase phosphorylates phosphatidyl inositol which promotes targeting of cellular signaling proteins to various membranes through phosphoinositide binding domains. The *Caenorhabditis elegans* ortholog is called AGE-1

DAF-16 (FOXO)	In *Caenorhabditis elegans*, the DAF-16 transcription factor is required for the longevity phenotype in IIS pathway mutants. DAF-16 regulates genes that promote cellular homeostasis rather than anabolic growth. In mammalian cells, insulin signaling results in the sequestration of DAF-16 in the cytoplasm where it cannot interact with DNA targets
IGF-1	In mammals, IGF-1 is a hormone produced by the liver in response to growth hormone. In addition, IGF-1 can be produced by other cell types and can act on cells in a paracrine or autocrine manner. IGF-1 signals through both the IGF-1 receptor and the insulin receptor and effects many cell types to induce growth and inhibit programmed cell death. IGF-1 is made throughout life but is produced to the greatest extent during the pubertal growth phase
AMPK	AMP-dependent kinase . AMPK can sense the lack of availability of cellular nutrients by its sensitivity to a high AMP: ATP ratio. When activated AMPK phosphorylates and inactivates genes responsible for
GHRH/GHR	Growth hormone releasing hormone/growth hormone receptor. Growth hormone releasing hormone produced by the hypothalamus induces release of growth hormone in the anterior pituitary. Growth hormone acts on growth hormone receptors and confers much of its growth promoting activities through the induction of IGF-1 by the liver
P66Shc	A signaling adaptor that can shuttle between the nucleus and the cytoplasm. P66Shc is thought to play a role in the negative control of forkhead transcription factors during oxidative stress. It has been shown to promote apoptosis, possibly explaining the mechanism of longevity in p66Shc knockout mice
XPD and XPB	Xeroderma pigmentosum complementation group D or B. Genes involved in DNA excision repair (maintenance of DNA integrity). Patients with mutations in this gene have multiple disorders including immature sexual development, short stature, and skin and hair shaft lesions
IKK-β, MAPK/JNK	I kappa B kinase beta, Mitogen activated protein kinase, jun-N-terminal kinase. Kinases important in the signal transduction pathways leading from intracellular or extracellular stress receptors (including infectious detectors) to nuclear effectors of transcription. Generally these pathways involve a cascade of phosphorylation events ultimately resulting in the upregulation of hundreds of genes involved in stress responses
TLR	Toll-like receptor. Transmembrane receptors containing a TIR domain. These receptors detect conserved features of microorganisms (bacteria, fungi, viruses) and relay this information through a signal transduction pathway to relevant transcription factors
NLR	NOD-like-receptors. Some of the receptors of this family are still orphan receptors, however they are believed to be involved in activation of proinflammatory genes
TNF IL-1	Tumor necrosis factor. A pleiotropic inflammatory cytokine released upon infection. Also implicated in apoptosis
IL-6	Interleukin-6. A pleiotropic inflammatory cytokine released upon infection. Causes fever and induces the production of acute phase proteins by the liver
Crohn's disease	An inflammatory bowel disease exacerbated by autoimmune activation perhaps by recognition of gut commensal bacteria by the immune system. Patient's with mutations in the NLR, NOD2 are more susceptible to Crohn's disease
Juvenile idiopathic arthritis	A form of arthritis seen in childhood with symptoms including arthritis, spiking fever, rash, acute phase response proteins, and IL-6
Progeria syndromes	Syndromes of accelerated aging many of which are caused by mutations in genes involved in maintenance of DNA integrity
IRS-1	Insulin receptor substrate-1. An intracellular signaling molecule phosphorylated during ligand engagement of the insulin receptor. Phosphorylation renders IRS-1 incompetent to signal, thereby shutting off the response

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