The brain–body energy conservation model of aging

Shaulson ED, Cohen AA, Picard M. *Nat Aging* 2024

Peer Reviews

Reviewer #1 (Remarks to the Author):

Comment 1: This is a lovely perspective piece on an energetic model of aging and how aging manifests. The text is peppered with little gems of insight that readers of Nature Aging should find thought provoking and scientifically valuable (e.g. Adaptive recalibration). I may be biased but I am absolutely a proponent of energetics as a driver in aging and the importance of signaling integrity to direct energy use toward maintenance, adaptation, and survival. The authors have done a terrific job of synthesizing and integrating complex ideas and providing compelling evidence for the reader to consider. The paper is strongest in the biological arguments and some of the more psychological aspects detract, not having as firm a basis in terms of evidence. I have only a few things that the authors might address but overall, this is a great match for the journal and a welcome addition to the Aging literature.

Response 1: Thank you for your time reviewing this piece, the positive comments, and for the useful criticisms. We appreciate that the reviewer feels the biological arguments are strong. One of our objectives with this piece is to help bridge the existing divide between the biological and psychological literatures in geroscience, so we have opted to preserve most of the section on psychological and stress factors. We are now explicit about the fact that this is an underdeveloped area and needs further research, consistent with a recent perspective piece published in Translational Psychiatry (Faria et al., 2024; PMID: 38816369), which we now cite.

Comment 2: The authors are using the word senescence in the old-fashioned sense (age, aging, becoming aged) and might at the outset define what they mean by the use of the word. The ubiquity of "senescent cell" reports, reviews, and perspectives, has led to some ambiguity in how the work "senescence" is understood. This could be added to the box but the least a working definition should be articulated in the main text.

Response 2: Thank you for raising this important point and for the helpful suggestion. We have added a "senescent cell" entry to Box 1 (Definitions and Key Concepts) to resolve ambiguity. We have also included a new perspective on the contentious and physiological roles of senescence (Gems and Kern, 2022, PMID: 36068483) (Magalhaes, 2024, PMID: 38900869). We limit our use of the term to refer to the cellular state.

"SENESCENT CELL: cellular state marked by cell cycle inhibition and a growth arrest phenotype. Senescence is now recognized to play several key roles in normal development and physiology, including the active synthesis and secretion of SASP factors [213], among other behaviors [26,97]."

Comment 3: On p6 section on in vitro aging trajectories the authors talk about reversible senescence and a bit of hair-splitting is in order. The paper they cite describes senescence-like cells. Perhaps some consideration of the semantics would be in order here.

Response 3: Great point, thank you for pointing out the ambiguity in this section. We have revised this section of the text to clarify in line with the previous comment.

Comment 4: On p7 section on metabolic flux there is a statement about quiescence and senescence being misnomers – this is not really true – these terms came from an older discipline investigating regulation of cell cycle and factors involved in cellular proliferation. The terms were not specifically linked to metabolism at all and distinctions about metabolic status were not part of that. The authors might make the point (that a cessation in cell division does not mean a decline in energetic demand or use) without getting tangled up in what those terms mean.

Response 4: Another good catch. We've revised the text such that the word "misnomers" is replaced with "misleading".

The text now reads:
"From a metabolic standpoint, the terms *quiescence* and *senescence* are misleading because for most scientists they imply that these cells serve little useful purpose and are inactive [26,97]. But on the contrary, these complex cellular states are implicated in normal physiology [26] and are in fact marked by the upregulation of several energetically costly processes."

Comment 5: P10 In the section on energy constraints as drivers the argument about hearing loss is a bit of a stretch. As written the authors give the impression that the brain "chooses" to sacrifice hearing to spare energetic cost, this argument does not add up. There is a strong genetic component to age-related hearing loss and the idea that hearing is "dispensable to survival" has no support in evolutionary terms.

Response 5: Thank you for the productive critique of this claim. We partially agree that this argument is a stretch. For one, we agree that there is no evidence to support the dispensability of hearing to survival and have therefore removed the related language from the text (see excerpt below). That said, the fact that there is a strong genetic component to age-related hearing loss is compatible with the notion that age-related hearing loss *can* be driven by energy constraints. For example, a genetic mutation/polymorphism that causes hearing loss may do so via a mechanism that involves excessive energy demand from the hair cells (perhaps secondary to accelerated damage accumulation or metabolic dysregulation). In fact, genetic oxphos defects have been linked to hearing loss in humans (eg. MIDD = maternally inherited diabetes and deafness). However, metabolic distress in hair cells could cause hearing loss independent of energy constraints if it simply too damaging to overcome.

Ultimately the argument we are making is certainly a stretch from the accepted order of things, but adopting an energy constraints perspective makes it a possibility. Accordingly, we retain a shorter version of this section that is now framed in terms of a question – how specific are brain-driven energy conservation responses? This new wording/framing raises the possibility without overstating the available evidence:

"How specific are brain-driven energy conservation responses?

Since we currently lack a comprehensive mapping of all the potential compensatory responses that the brain can trigger, it is unclear how specific the brain's energy conservation responses can be. The major energy conservation responses discussed above are general brain outputs (stress hormones, fatigue, etc.) that are fine-tuned in the periphery by tissue-specific responses. These general responses allow for simultaneous suppression of many low priority processes, including seemingly trivial expenditures (e.g. hair pigmentation) that when combined and summed over time, might represent significant energy savings.

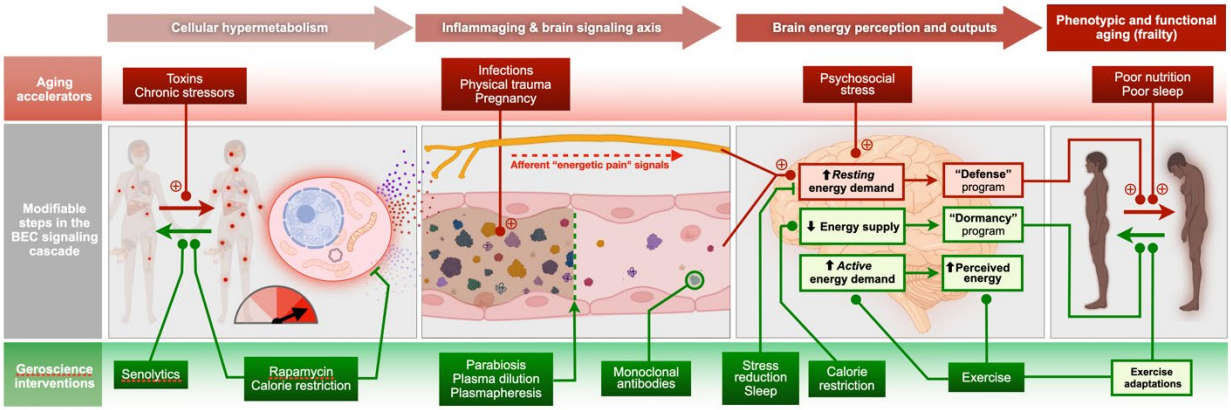
The brain may also have more specific control mechanisms at its disposal. In fact, the brain was recently shown to have surprisingly specific feedback control over systemic inflammatory responses [201]. The brain may also possess feedback control over its own functions, which collectively account for roughly 25% of TDEE [202]. For example, the aging brain undergoes a learning-to-prediction shift, which may represent an adaptive attempt to leverage existing knowledge to save on the energetic cost of processing raw inputs, learning, and creating new memories [203,204]. By the same logic, age-related cognitive and sensory "deficits" may at least partially represent consequences of psychobiological energy conservation responses. Thus, although it's unlikely that the brain is capable of selectively shutting down single cells when they become defective (if it could, cancer and senescence would be non-problems), it may be able to selectively withdraw energetic resources from specific physiological and/or biological processes (see **Table 1**)."

Comment 6: P10/11 anti-aging section the theme is a reduction in the brain's "perception of cytokine based signaling" – later on it is clear that the authors do appreciate the difference between actually lower levels of signaling (CR, rapa) and lower ability to detect signaling (biologics to blunt cytokine communication) but that might be brought up sooner. The authors appropriately describe the potential risk in disabling the brain's ability to receive these inputs, making it more important to clarify between reduced capacity to detect signals and reduced levels of signals being conveyed. The placement of rapa and CR to the right of figure 5 first panel seems odd – really these interventions prevent the person with dots transitioning to a person with more dots.

Response 6: We fully agree that the distinction between "lowering the production rate of the signal" and "lowering the ability to detect the signal" should be made more explicitly. We modified the paragraph below accordingly:

" From a longevity point of view, inflammaging-driven energy conservation responses and frailty may in fact be *adaptive*. If so, depriving the brain of information about *cellular* hypermetabolism could, in the long-term, promote unsustainable *whole-body* hypermetabolism, accelerate somatic damage accumulation, and hasten mortality. In fact, whole body hypermetabolism in midlife predicts earlier mortality [196,197]. This is less likely to be a concern for interventions that work via upstream causes to reduce the rate of cytokine production/secretion than interventions that interfere with or dilute cytokine signaling downstream of their production."

With regards to the placement of CR and rapa within figure 5, we have modified the figure (see below) such that 1) CR and rapa are no longer to the right of the green arrow, and 2) there are now two lines projecting from the "CR/rapa" textbox, one targeting the hypermetabolic cell itself (to represent inhibitory effects on protein synthesis and secretion) and a second line targeting the green arrow connecting the two silhouettes on the left-hand side of the figure (to represent suppression of senescent cell accumulation).



Comment 7: P12 section on exercise the authors suggest that there are "longevity benefits" of exercise. This is another idea worthy of hair splitting. There is no doubt that exercise conveys health benefits and certainly reduces incidence of what might be termed premature death but there is no evidence of lifespan extension being conferred. The gold standard for "enhanced longevity" is an increase in median and maximum lifespan.

Response 7: Agreed. We included the section on exercise to clarify that not all energy conservation responses contribute to accelerating aging (ie. exercise and calorie restriction). To avoid improper usage of terms, we replaced "longevity benefits" with "doesn't accelerate aging".

"The distinction between "supply-side" and "demand-side" energetic threats is insufficient to explain why exercise, which poses a "demand-side" threat, doesn't accelerate aging like stress and inflammaging do (see Figure 5)."

Reviewer #2 (Remarks to the Author):

This is a well-written "idea" paper proposing that a key player of aging is the allocation of energy cellular energy (focusing on OX-PHOS of the mitochondria) via signaling by energy stressed cells to the brain which then regulates energy expenditure in the periphery. Specifically it asserts that inflammation at the SASP have evolved to signal excessive cellular energy consumption to the brain. The idea that the brain is a master regulator of aging is an old one, but the focus on energetic allocation, signaling by cells to the brain with the brain in turn regulating energy consumption by tissues, gives it a new twist. I find the idea a nice corrective to the overemphasis on intracellular processes of the Hallmarks (all interaction among cells relegated to one of twelve hallmarks – altered intercellular communication). I think the idea is original enough, and well-enough described to lead to rich discussion in the field. One thing I wish it had contained were some predictions about observations that might falsify the hypothesis. Not to be too Popperian but falsifiability is the defining characteristic of a scientific hypothesis. Some nod to that idea would be useful.

Response 1: We appreciate the reviewer's comments. We have added a small section to the latter portion of the manuscript to highlight key falsifiable predictions:

"Are energetic tradeoffs causes or consequences of aging?

If inflammatory cytokines cause energetic tradeoffs that accelerate phenotypic aging, then genetic knockout of inflammatory cytokines (or their receptors) should slow phenotypic aging. Consistent with this, knockout of the anti-inflammatory IL-10 causes upregulation of pro-inflammatory IL-6 and shortens lifespan [205]. However, double knockout of IL-10 and IL-6 also shortens lifespan [206]. GDF15 also plays complex roles in mediating tissue and systemic inflammation [207]. Ultimately, the effects of cytokine knockouts on lifespan are difficult to interpret for several reasons. For one, cytokine signaling is highly redundant, pleiotropic and interactive, so manipulating a single cytokine without understating the full "cytokine code" tends to have widespread effects across cytokine families. Cytokines also play key roles in development, making it difficult to rule out lifespan effects caused by early-life events. Finally, cytokine knockouts manipulate signaling in both the periphery and brain, blurring the contributions of peripheral vs brain-driven responses. Inducible, brain-specific knockouts of cytokine *receptors* may afford greater specificity in testing predictions of the BEC model.

Overall, the BEC proposes that inflammaging causes energy conservation responses that accelerate phenotypic aging. Implied by this claim is the falsifiable prediction that inflammaging *precedes* lean tissue loss, endocrine deficits, and other manifestations of aging. Testing this prediction (and others like it) in humans will require studies involving repeated quantitative measures of REE, TDEE, physical activity, functional capacities, and a diverse set of protein and metabolite biomarkers to establish within-individual trajectories of energetic and functional tradeoffs. Harnessing within-person temporal variation in body-brain signaling, including during the restorative state of sleep, also could offer new fundamental insights into how the aging body manages its energetic resources over time."

Reviewer #3 (Remarks to the Author):

Comment 1: An interesting hypothesis that aims to explain aging and frailty from a purely energetics perspective, driven by cellular hypermetabolism driven by molecular damage, which is sensed by the brain and leads to a decline in energy expenditures on non-critical functions. While generally interesting and worth further discussion, a few points to consider:
I fully appreciate the suggestion that aging and frailty might be a physiological adaptive response, and thus addressing them without the overall context might even be detrimental, but what the authors fail to address is why do cells go into hypermetabolism in the first place. The simplistic "it's because of damage accumulation" is not satisfactory: why do they accumulate damage? Is it because the cell's resilience is reduced? then why is it reduced? In the same line, it is difficult to understand from the evolutionary perspective: why do mouse cells go into hyperactivity so much sooner than human or whale cells? Again, the ultimate cause of aging is not addressed in the BEC model, which only provides a framework to understand how the brain may modulate energy expenditure during aging (I say 'only', but I don't mean to diminish the value of the hypotheses proposed), but it does not explain why the process is initiated. The authors suggest initiation is from damage accumulation, but this is not supported by evidence: in many systems and levels, damage doesn't simply 'accumulate' linearly: there's often a sharp inflection in the curve, where damage starts indeed accumulating. Why is that? What triggers the change in slope?

Response 1: We are delighted that the reviewer finds this perspective on aging and frailty interesting and worth further discussion. Among the spectrum of questions from the fundamental causes of aging to the functional and phenotypic manifestations of aging, this model addresses the latter part and is agnostic as to what the ultimate cause of aging is, and why damage accumulates in living cells. The competing hypotheses on this topic have been covered elsewhere (Medvedev, 1990, PMID: 2205304) (Gladyshev, 2016, PMID: 27060562) (Gems and Magalhaes, 2021, PMID: 34271186) (Cohen et al., 2020, PMID: 32949595) (Finch, U Chicago press, 1994), which we reference in the BEC model. Cross-species comparisons on the rate of damage accumulation, allometric scaling of body size, metabolic rates, and rates of development/aging also are better covered elsewhere (Promislow, 1993, PMID: 8315214) (Magalhaes and Church, 2007, PMID: 17339640) than our piece could do justice in the limited space allotted. The editor also has asked us to cut words, so we can't expand the breadth…

Comment 2: The authors are advised against making sweeping statements such as "of course, the cascade starts in the nucleus, as all things biological are assumed to do", or "cells exist as an energetic collective managed by the brain"… this last statement is what they are proposing, but they state it as an acknowledged and known fact.

Response 2: Point well taken – we've removed these (and a handful of other) sweeping statements from the text.

Comment 3: The figures should be simplified, if nothing else, to allow other researchers to discuss these ideas in their own presentations. A simplified, aesthetically pleasing and clear model would help.

Response 3: We appreciate that clear, simple figures are essential to enable further discussions. We have aimed, in discussion with the editor, to provide two types of figures – simple, general figures that illustrate the model in simple terms that can be used by other researchers (e.g., Figures 1 and 2), and more complex figures that provide concrete examples of processes, bringing substance to the arguments (Figures 3-5). We would encourage others to use these figures in parallel to show the overall model to raise questions about specifics, then present the more complex versions one piece at a time, then coming back to the general figures for discussion.

Reviewer #4 (Remarks to the Author):

This is an interesting idea but I don't think it really holds water. Here are some comments major and minor accumulated while reading the paper, culminating with my main 3 objections.

Comment 1: Lines 42-3 : also sensory outputs

Response 1: Good catch – we changed the text to say: "… responds with neuroendocrine and sensorimotor outputs"

Comment 2: Line 46: I would suggest survival rather than 'health' since you are discussing evolutionary concepts.

Response 2: Agreed. We have revised the text accordingly.

Comment 3: Line 49: The idea the energy supply is limited is frequently stated but as far as I am aware there is very scant evidence to support it. The cited reference for example just states it as If it's a fact without providing any evidential support. Can the authors actually provide any direct evidence that energy supplies were limited. It seems an important part of the argument that is developed so it would be good to have something more than just an assertion. See for example the arguments in Speakman and Krol (2010 Int. Comp. Biol. 50: 793-807) about why energy supply is probably often not limited.

Response 3: Another good catch – a limited energy supply is not a necessary feature of the model. The constraints on total energy expenditure are what impose the trade-offs discussed in the piece. We have therefore removed this sentence on line 49 from the piece

Comment 4: Line 52: Is it necessary to postulate shortages to have this trade-off. I don't think so. For example if the total ability to expend energy was limited then there would be the same requirement for a trade-off. That would be independent of resource supply. (see paper cited above).

Response 4: Exactly. See further discussion immediately below in Response 5.

Comment 5: Line 86. As above the presence of energy shortage or energy threats may not be a necessary feature of the model. It can work if there is just a total limit on expenditure ability.

Response 5: Agreed. However, a semantic point must be made to justify our usage of the term "energetic threats". Energetic threats can exist in the absence of "energy shortage" (ie. low energy supply) because of the limit on metabolic rate. The activated immune system, for example, poses an energetic threat not because it brings the organism to the maximal limit of energy expenditure, but because other energetic expenditures must be reduced to stay within the limits of metabolic rate. The notion that energy tradeoffs take place at submaximal levels of energy expenditure is reviewed in (Pontzer and McGrosky, 2022, PMID: 35728556), and includes evidence from (Halsey et

al., *Functional Ecology,* 2018), (Careau et al., 2021, PMID: 34453886), (O'Neal et al., 2017, PMID: 28111149*),* and (Jasienska and Ellison, 2004, PMID: 15368604), among others. These studies show that submaximal increases in physical activity are associated with suppression of BMR and/or tradeoffs with reproduction. This point also was discussed in (Hammond and Diamond, 1997, PMID: 9087402). The threat here is almost completely independent of energy supply – it is a function of competition between energy demands, which cannot all be met at the same time, even at submaximal levels of EE.

Comment 6: Line 108. Step 3. It is unclear why this is unsustainable. Why for example can the animals not just eat more food. I am unclear about the rheostat analogy. In what way does the brain act like a variable electrical resistance?

Response 6: Organisms can increase EE up to 20x BMR for short periods of time, but integrated over longer periods of time, organisms cannot sustain high EE, for reasons that are unclear. Digestive limitations have been proposed (Thurber et al., 2019, PMID: 31183404) but this we think is unlikely to account for the type of limitation and the timeframe we are discussing. Limitations to heat dissipation in animals (Zhao et al., 2022, PMID: 35288719) and Gibbs free energy dissipation (Niebel et al., 2019, PMID: 32694810) also have been proposed – both of which are compelling.

In humans, it is clear that eating more does not increase the energy budget in proportion with the ingested calories. Submaximal increases in PA-related energy expenditure suppressed progesterone levels in rural Polish women independent of nutritional status, body weight or body composition (Jasienska and Ellison, 2004, PMID: 15368604). These women *did* increase their energy intake to compensate for the increased demand, yet the tradeoff between activity and reproduction still occurred. Another case in point is critically ill patients (where hypermetabolism is a frequent clinical feature) in whom feeding additional calories with aggressive parenteral nutrition – in a rational attempt to curtail weight loss and loss of fat free mass – can end up being damaging and increasing mortality in adults (Casaer et al., 2011, PMID: 21714640) and children (Fivez et al., 2016, PMID: 26975590) rather than increasing the budget to sustain hypermetabolism more easily. Some factor(s) that remains to be identified limit(s) the human energy budget, such that eating more does not afford additional energy allocated to growth, maintenance and repair processes that would prevent or delay biological aging.

The nature of energy constraints and *reasons* why high EE is unsustainable – and why the brain runs a tight economy of energy – is a broad topic partially covered elsewhere that is not necessary to our argument that the brain sense peripheral energy demand and deploys physiological changes to compensate for their energy costs.

In the revised version of the manuscript, we have added references to useful papers documenting the existence of limits to human EE, evidence of physiological energy constraints in cells and organisms, and evidence that heat dissipation limits may be involved. The reviewer's excellent question as to why hypermetabolism is unsustainable requires additional empirical work at the intersection of three fields: i) life history research, ii) human energy expenditure, and iii) cellular biophysics.

We removed the rheostat analogy because it was vague and not necessary to make our point.

Comment 7: Line 111. Steps 4 and 5. Why does the brain not just selectively switch down metabolism in the cells where it happens to be increased thereby avoiding the issue. The suggested things that are described as increasingly powerful catabolic adaptations include things like hair pigmentation loss that likely have trivial to zero effects on energy demands.

Response 7: The argument here is a good challenge to our model – if the brain is "bidirectionally connected to every cell" (we removed this line from the text), then the easiest way to solve the problem (energetic threat) posed by hypermetabolic cells would be to selectively shut them down - why doesn't the brain do that?

For one, the brain may not be able to specifically switch down metabolism in the hypermetabolic cells. If the brain had this level of specific control, cancer and senescence would be non-problems. Regardless, your question raises an important point about the specificity of brain-driven energy conservation responses that we discuss below.

The objection to the hair pigmentation argument is strong in that it is likely true that the energy cost of maintaining hair pigmentation is tiny. That being said, withdrawal of energetic resources from hair pigmentation may be a byproduct of a broader energy conservation response. For example, stress hormone signaling is a fairly non-specific response by the brain that is fine-tuned in the periphery by cell-type specific responses. Accordingly, many low priority processes are likely to be affected. In this framing, the energy savings from suppressing maintenance of hair pigmentation is likely to be trivial, but the combined energy cost of suppressing many "cheap" processes, may in fact result in large savings, especially over long time periods.

We've added brief discussion of this point towards the end of the text:

"Since we currently lack a comprehensive mapping of all the potential compensatory responses that the brain can trigger, it is unclear how specific the brain's energy conservation responses can be. The major energy conservation responses discussed above are general brain outputs (stress hormones, fatigue, etc.) that are fine-tuned in the periphery by tissue-specific responses. These general responses allow for simultaneous suppression of many low priority processes, including seemingly trivial expenditures (e.g. hair pigmentation) that when combined and summed over time, might represent significant energy savings."

Comment 8: Lines 123-161. These things that are enumerated in this section are for sure not free. But for the argument to hold water you need to quantify how much these things actually cost relative to the whole organism energy budget. To make an analogy. Buying ice cream costs me money. But there is a big flaw if I made the argument that the cost of buying ice-cream is traded off against the type of car I can afford. So rather than say these things have an energy cost (which all biological processes do) what we need to know is what % of the total energy budget do they consume. Are they realistic parts of a trade-off as you propose.

Response 8: Fully agree with the argument being made here (stating process-specific energy costs in relation to the total budget is superior to simply stating things have an energy cost). Unfortunately, process-specific energy cost estimates are extremely scarce in the literature and the methods used to produce those estimates are severely limited. Even so, if energetic trade-offs

occur at submaximal energy expenditures, then small increases in energy demand could impose a need for (similarly small) tradeoffs that may become significant over long timescales.

For example, in young-adult men, non-febrile immune activation causes an 8-14% increase in REE and is associated with a 10-30% reduction in circulating testosterone (Muehlenbein et al., 2010; PMID: 20309883). This finding is consistent with the notion that even relatively small immune-related energy costs can impose significant trade-offs on competing processes. We've included reference to this paper in our now explicit discussion of energetic tradeoffs at the organismal level:

"Life history theory holds that prolonged increases in immune-related energy costs ("defense") can compromise energetic investment in other primary life tasks (growth, reproduction, etc.). Indeed, during human development, even mild increases in immune activity can cause up to 49% growth reduction [147]. Similarly, in young adult men, non-febrile immune activation caused an 8-14% increase in resting energy expenditure alongside a 10-30% reduction in testosterone, indicating 1) a trade-off between defense and reproduction [148], and 2) again, that energetic tradeoffs occur at submaximal levels of energy expenditure [7]. But how do energetic tradeoffs shape phenotypic aging?"

Comment 9: Line 203-240. Great. Some numbers. But hard to relate these in vitro data to whole animal energy expenditures. Might be nice to try.

Response 9: We strongly agree that it is hard to relate the in-vitro energy costs to organismal energy expenditures. To avoid being overly speculative, we've modified a portion of text that acknowledges that quantifying energetic costs imposed by aging cells remains an open area research to include explicit references to in-vitro (Bobba-Alves et al., 2022; PMID: 37423094), in-vivo (Lee et al., 2023; PMID: 37186827)(Brace et al., 2016; PMID: 28721274) and longitudinal cellular aging experiments (Sturm et al., bioRxiv, 2022; https://www.biorxiv.org/content/10.1101/2022.05.10.491392v4) that provide indirect evidence in support of the claim that stressors and senescense *may* consume significant energetic resources.

Brace et al. (PMID: 28721274) show that a DNA repair deficient mouse model of Cockayne syndrome display ~96% higher VO2 (normalized lean mass) than age-matched controls while dermal fibroblasts from these Cockayne syndrome mice have ~30% higher OCR (normalized to protein content) than controls. To the extent that this model of endogenous genotoxic stress is a model of accelerated cellular aging, these findings support the notion that 1) stressors and senescence *may* consume significant energetic resources and 2) in-vitro models may underestimate systemic energy costs.

It should be pointed out that the ~96% increased VO2 in the Cockayne syndrome mice is likely an overestimation due to improper normalization (Fernandez-Verdejo, 2019, PMID: 31391589). The authors express the VO2 data as a simple ratio of VO2/lean mass, rather than using a regression approach for correction. Since the Cockayne syndrome mice are considerably smaller than the controls (16-18g vs. 22-28g), using the ratio of VO2-to-lean mass likely overestimates the true difference in TDEE between Cockayne mice and controls. If necessary, we are happy to modify the text below to acknowledge this potential limitation.

"Quantifying the energetic costs imposed by aging cells remains an open area of research [124]. In many cases, the excess energetic costs of different processes and stress responses remain largely unknown. That said, *in vitro* [125] and *in vivo* studies [62,126], and longitudinal cellular aging experiments [15] suggest that the energy cost of stressors and senescence could be sufficiently large to impose meaningful energetic and functional tradeoffs. In fact, dermal fibroblasts isolated from progeroid DNA repair-deficient mice display ~30% higher oxygen consumption rates than control fibroblasts, while the DNA repair-deficient mice display ~96% higher TDEE than control mice [62]. The recruitment of cell non-autonomous, physiological mechanisms could contribute to whole-body hypermetabolism beyond the excess energetic costs of impaired cells [73]."

Comment 10: Lines 272-280. These seem to be a disconnected set of processes to the things happening within cells you have called hypermetabolic states. At least the link seems to me to be pretty tenuous. Can this be firmed up more.

Response 10: Agreed. Conceptually, the sources of energetic inefficiency listed in lines 272-280 need not be the result of the same processes as cellular senescence-related hypermetabolism to impose energetic tradeoffs – these "other sources of energetic inefficiency", like hypermetabolic cells, are energy sinks. We therefore moved lines 272-280 and recontextualized them in the newly added "Age-related changes in whole-body energy expenditure and efficiency" section:

"Consistent with this, we propose that cytokines inform the brain not only of the direct energy costs of cellular senescence, but also of the broader ensemble of energetic inefficiencies that accumulate across levels of biological organization with age. Indeed, as organisms age, their behaviors and organ systems become progressively less energetically efficient. This includes locomotor efficiency [127,128], cardiovascular efficiency [129], and inter-organ metabolic coupling [130, 131]. So called "futile cycles" serving homeostatic or anabolic roles may also contribute to age-related energetic inefficiency [132]."

Comment 11: Lines 290-294. This seems a fairly critical lack of knowledge for the argument to hold water. If these accumulated effects are actually trivial at the whole body level then the brain is unlikely to need to enable any things to counteract them. Reference 21 doesn't seem to provide the necessary information as it is not a whole organism level determination.

Response 11: It is true that magnitude of the energy costs imposed by aging cells is critical missing piece of information in the model. That said, these costs have never been directly quantified (to our knowledge) and our appraisal of the indirect evidence is that it at least directionally supports the hypothesis that the *direct* costs of cellular senescence are sufficiently large to impose meaningful trade-offs. These direct costs, however, are not the whole story. Senescence-associated hypermetabolism is one player in a broader ensemble of age-related energetic inefficiencies that are present across levels of organization.

As discussed in response to Comment 9 above, we now include explicit, quantitative discussion of the findings from (Brace et al., 2016 PMID: 28721274) in the text. Immediately following this, we discuss age-related changes in bioenergetic efficiency and the possibility that cytokines inform the brain not only of the direct energy costs of cellular senescence, but also of the indirect costs associated with various age-related energetic inefficiencies:

"Quantifying the energetic costs imposed by aging cells remains an open area of research [124]. In many cases, the excess energetic costs of different processes and stress responses remain largely unknown. That said, *in vitro* [125] and *in vivo* studies [62,126], and longitudinal cellular aging experiments [15] suggest that the energy cost of stressors and senescence could be sufficiently large to impose meaningful energetic and functional tradeoffs. In fact, dermal fibroblasts isolated from progeroid DNA repair-deficient mice display ~30% higher oxygen consumption rates than control fibroblasts, while the DNA repair-deficient mice display ~96% higher TDEE than control mice [62]. The recruitment of cell non-autonomous, physiological mechanisms could contribute to whole-body hypermetabolism beyond the excess energetic costs of impaired cells [73].

Consistent with this, we propose that cytokines inform the brain not only of the direct energy costs of cellular senescence, but also of the broader ensemble of energetic inefficiencies that accumulate across levels of biological organization with age. Indeed, as organisms age, their behaviors and organ systems become progressively less energetically efficient. This includes locomotor efficiency [127,128], cardiovascular efficiency [129], and inter-organ metabolic coupling [130, 131]. So called "futile cycles" serving homeostatic or anabolic roles may also contribute to age-related energetic inefficiency [132]."

Comment 12: Line 308. I couldn't find any whole organism data in ref 119 to support the statement that energy expenditure is doubled.

Response 12: Apologies for the oversight. We included the wrong reference number– the correct reference is Uehara et al., Crit Care Med, 1999 (PMID: 10446823). We have revised the text accordingly.

Comment 13: Line 322-3. I really don't like these unquantified statements. Physical activity in humans costs about 40% of the energy budget. Why not state that.

Response 13: We appreciate the preference for quantified over unquantified statements in general and have modified this section of the manuscript accordingly:

"Sickness-associated anorexia and inactivity are especially potent energy conservation responses. Food-seeking behaviors are probably the predominant activities of most animals [143], requiring substantial energetic investment (AEE accounts for ~30% of TDEE in adult humans, but varies widely [144]). Digesting and assimilating food also comes at a cost (thermic effect of food; TEF), accounting for ~10% of TDEE [145]. Sickness-associated anorexia and inactivity therefore minimize both activity and digestion costs, saving up to ~40% of the typical energy budget. Even so, severely ill, bedridden humans often display elevated TDEE [139], reflecting substantial increases in resting energy costs. It follows that the brain responds to high concentrations of circulating cytokines by withdrawing energetic resources from lower priority (and potentially risky [146,147]) processes."

Comment 14: Line 324-327. Sickness induced anorexia maybe serves more to prevent the individual becoming food themselves if they attempt to forage while ill, rather than as an energy conservation mechanism (see e.g. arguments in Speakman 2018 Journal of Experimental Biology 221. E167254).

Response 14: Energy conservation/reallocation is one of many proposed reasons for the existence of sickness-induced anorexia. Protection from predation is another. Another is to promote metabolic tolerance to systemic inflammation (Wang et al. 2016; PMID: 27610573). In this paper, anorexia protects mice from death during systemic listeriosis (caused by glucose oxidation-related neurotoxic seizures) by maintaining "fasting physiology" (ie. high concentrations of circulating ketone bodies, FFAs and TAGs). Strikingly, feeding increased mouse mortality during bacterial sepsis yet reduced mortality during viral sepsis.

To sum up: 1) there are likely to be multiple reasons for sickness induced anorexia, 2) there is no consensus on what these reasons are, and 3) whatever the reasons may be, many are likely related to energy metabolism, possibly including energy conservation/reallocation. Even so, we've added references to both the Wang et al., 2016 piece (PMID: 27610573) and the Speakman 2018 piece (PMID: 29514887) to the text:

"Sickness-associated anorexia and inactivity are especially potent energy conservation responses. Food-seeking behaviors are probably the predominant activities of most animals [143], requiring substantial energetic investment (AEE accounts for ~30% of TDEE in adult humans, but varies widely [144]). Digesting and assimilating food also comes at a cost (thermic effect of food; TEF), accounting for ~10% of TDEE [145]. Sickness-associated anorexia and inactivity therefore minimize both activity and digestion costs, saving up to ~40% of the typical energy budget. Even so, severely ill, bedridden humans often display elevated TDEE [139], reflecting substantial increases in resting energy costs. It follows that the brain responds to high concentrations of circulating cytokines by withdrawing energetic resources from lower priority (and potentially risky [146,147]) processes."

Comment 15: Line 340-341. I don't buy that at all. The energy sink of the fetus-placenta is really trivial. Metabolic rates of pregnant females barely shift the needle in metabolic rate until late in the second trimester. Yet morning sickness is often an early pregnancy event.

Response 15: This is a strong argument if we assume that there is no tradeoff at play during pregnancy. Could it be that the fetus-placenta cost "is not moving the needle" on TEE and BEE because there is compensation and other physiological processes that cannot at this point experimentally be dissected out, are turned off? Perhaps spontaneous activity is suppressed (we're not aware of any studies quantifying this across trimesters or in relation to plasma GDF15).

While we remain interested in the possibility that GDF15 may signal the excess energy cost of the fetal-placental unit, we agree that there is insufficient evidence to justify our claims. We have therefore removed this speculative section of text from the manuscript.

Comment 16: Lines 354-426. If I understand this correctly the argument is that the brain detects the hypermetabolic state from senescent cells and then responds by creating a hypometabolic compensation response. A key issue for me is why the brain over does the response. Why does it not just downregulate some costly things to produce an overall balance.

Response 16: Thank you for the incisive critique. We relied on the juxtaposition of hyper- and hypo-metabolism too strongly in our writing, giving the impression (and sometimes explicitly

stating) that the brain's response to cellular hypermetabolism is to overcompensate, resulting in whole-body hypometabolism. We agree that the brain-driven overcompensation is unlikely to occur. What the model seeks to explain is why despite aging/senescent cells becoming hypermetabolic, the whole body does not. Accordingly, we reframed the relationship between our model and the counter-intuitive finding that cellular energy demand increases while TDEE decreases. The model now emphasizes the simultaneous decline in TDEE and rise in cellular energy demand as drivers of increasingly severe energy conservation responses with age.

This change is reflected in the text in two main ways.
First, in the new abstract:
"Aging involves seemingly paradoxical changes in energy metabolism. Molecular damage accumulation increases *cellular* energy expenditure, yet *whole-body* energy expenditure is stable or decreases with age. We resolve this apparent contradiction by positioning the brain as the mediator and broker in the economy of energy within the organism. As somatic tissues accumulate damage over time, costly intracellular stress responses are activated, causing aging/senescent cells to secrete cytokines that convey increased cellular energy demand (hypermetabolism) to the brain. To conserve energy in the face of a shrinking energy budget, the brain deploys *energy conservation responses,* which suppress lower priority processes, producing fatigue, physical inactivity, blunted sensory capacities, immune alterations, and endocrine "deficits"..."

Second, in the newly added section on "Age-related changes in whole body energy expenditure and bioenergetic efficiency":
"Age-related changes in whole-body energy expenditure and bioenergetic efficiency

Starting around age 60, size-adjusted TDEE decreases by ~7% per decade [122]. This decline in TDEE is usually attributed to age-related reductions in organ metabolism or altered cellular energy metabolism [17,122,123], but is not yet fully understood. The BEC model suggests that this could be driven at least partially by the brain. Similar to TDEE, REE (typically ~50-60% of TDEE) also starts to decline in the 6th decade of life, but not as rapidly as TDEE [122]. This results in an age-related increase in the ratio of resting to total energy needs (REE/TDEE) that may at least partially reflect the escalating energy costs of senescent cells and inflammaging.

Quantifying the energetic costs imposed by aging cells remains an open area of research [124]. In many cases, the excess energetic costs of different processes and stress responses remain largely unknown. That said, *in vitro* [125] and *in vivo* studies [62,126], and longitudinal cellular aging experiments [15] suggest that the energy cost of stressors and senescence could be sufficiently large to impose meaningful energetic and functional tradeoffs. In fact, dermal fibroblasts isolated from progeroid DNA repair-deficient mice display ~30% higher oxygen consumption rates than control fibroblasts, while the DNA repair-deficient mice display ~96% higher TDEE than control mice [62]. The recruitment of cell non-autonomous, physiological mechanisms could contribute to whole-body hypermetabolism beyond the excess energetic costs of impaired cells [73].

Consistent with this, we propose that cytokines inform the brain not only of the direct energy costs of cellular senescence, but also of the broader ensemble of energetic inefficiencies that accumulate across levels of biological organization with age. Indeed, as organisms age, their behaviors and organ systems become progressively less energetically efficient. This includes locomotor efficiency [127,128], cardiovascular efficiency [129], and inter-organ metabolic coupling [130, 131]. So called "futile cycles" serving homeostatic or anabolic roles may also contribute to age-related energetic inefficiency [132].
Thus, aging organisms face a converging set of energetic threats. As the organismal energy budget diminishes, inflammaging-associated energy costs ramp up, and bioenergetic efficiency declines.

Aging organisms therefore have smaller energy budgets to spend on increasingly expensive cellular and physiological tasks. The BEC model suggests that this results in progressively stronger brain-driven functional and anatomical tradeoffs, allowing the organism to operate within its energy budget."

Comment 17: Lines 443-454. If this is true then KO of these cytokines or their receptors should increase lifespan. Is that known? It was recently shown increasing TLR5 increases IL-22 and leads to elevated lifespan (Lim et al 2024 Nature communications 15: 46). Double KO of IL-6 and IL-10 increases mortality (Ma et al 2021 J. Gerontol. 76: 211-215. But I am not familiar with studies of other cytokines.

Response 17: In theory, yes, the model predicts that KO of inflammatory cytokine and/or cytokine receptors could increase lifespan. While the studies you cite do contradict this prediction, other studies are in line with it. For example, (Ko et al., 2012: PMID: 21633802) show reduced lifespan in IL-10 KO associated with increased serum IL6 in midlife and skeletal muscle deficits.

In practice, the effects of cytokine/cytokine receptor KO on lifespan are difficult to interpret. Since cytokine signaling is highly redundant, pleiotropic and interactive, single (or double) cytokine KOs tend to have widespread effects across cytokine families. KO of anti-inflammatory IL-10, for example, leads to upregulation of (generally) pro-inflammatory IL-6. Since KO of all cytokines is not possible, interaction and compensation effects are unavoidable. Furthermore, cytokines play key roles in development, so KO models may have compromised or extended lifespans by virtue of changes that occurred early in life. Finally, these model systems manipulate cytokine signaling in the periphery and CNS, making it difficult to isolate the effects of brain-driven responses. We've added brief discussion of these points towards the end of the piece in a section that discusses falsifiable predictions of the BEC model:

" If inflammatory cytokines cause energetic tradeoffs that accelerate phenotypic aging, then genetic knockout of inflammatory cytokines (or their receptors) should slow phenotypic aging. Consistent with this, knockout of the anti-inflammatory IL-10 causes upregulation of pro-inflammatory IL-6 and shortens lifespan [205]. However, double knockout of IL-10 and IL-6 also shortens lifespan [206]. GDF15 also plays complex roles in mediating tissue and systemic inflammation [207]. Ultimately, the effects of cytokine knockouts on lifespan are difficult to interpret for several reasons. For one, cytokine signaling is highly redundant, pleiotropic and interactive, so manipulating a single cytokine without understating the full "cytokine code" tends to have widespread effects across cytokine families. Cytokines also play key roles in development, making it difficult to rule out lifespan effects caused by early-life events. Finally, cytokine knockouts manipulate signaling in both the periphery and brain, blurring the contributions of peripheral vs brain-driven responses. Inducible, brain-specific knockouts of cytokine *receptors* may afford greater specificity in testing predictions of the BEC model"

Comment 18: Lines 474-476. Yet exercising more which must surely have a much greater impact on whole body energy demands seems to lengthen not shorten lifespan. Ah. I see you come to that at line 510...

Response 18: Yes, thank you. To draw sharper contrast between the responses to inflammaging/stress and exercise/CR, we have now moved the sections on exercise and calorie restriction into their own section earlier in the manuscript.

Comment 19: Lines 510-534. The fact the brain can respond differently to exercise however weakens the argument that this is an inevitable requirement to balance a trade-off within an overall budget. With elevated exercise the brain responds by telling the organism to eat more. Why does it not just do the same when faced with signals of cellular hypometabolism?

Response 19: Energy balance and energy constraints are related, but exert distinct influences on physiology on behavior in response to increases in energy demand. The limit on metabolic rate is ultimately the driving force responsible for the conservation responses discussed in the paper. Eating more (to match increased expenditure/demand) solves the energy balance problem, but not the constraint problem (see above discussion of the rural polish women studied in Jasienka and Ellison, 2004, PMID: 15368604).

The constraint problem is handled differently by the brain depending on the source of increased demand. Our understanding is that the key distinction between the exercise- and cellular hypermetabolism-related energy demands is that exercise is an "active" expenditure while senescence-associated cellular hypermetabolism is a "resting" expenditure. Active and resting expenditures trigger distinct energy conservation responses. Resting expenditures (whether from hypermetabolic senescent cells, the activated immune system, or stress hormone signaling) stimulate "emergency" energy conservation responses that withdraw energetic resources away from low priority processes in favor of higher priority processes. We expand on this point in a previous paper (Bobba-Alves et al., 2022, PMID: 37423094). Active expenditures trigger withdrawal of energetic resources from lower priority processes (immunosuppression, reduced oxygen delivery to brain, etc.) in the present, but they also stimulate adaptations that increase future bioenergetic efficiency and capacity. This future benefit is driven by exercise adaptations that are *initiated* independent of the brain (such as mitochondrial biogenesis and myofibrillar hypertrophy) but become relevant to the brain's appraisal of active energy demands during future bouts of activity.

Comment 20: Lines 510-638. The weakest points of this model are
1) the lack of any quantitative comparison of how big the hypermetabolism effect is at the whole animal level compared to the hypometabolic response. In other words is this like saying individuals sell their cars and buy bikes instead to pay for two more ice-creams a month.

Response 20: As discussed above, it is true that magnitude of the energy costs imposed by aging cells is critical missing piece of information in the model. That said, these costs have never been directly quantified (to our knowledge) and our appraisal of the indirect evidence is that it at least directionally supports the hypothesis that the costs are sufficiently large to impose meaningful trade-offs. We've modified a portion of the text accordingly:

"Quantifying the energetic costs imposed by aging cells remains an open area of research [124]. In many cases, the excess energetic costs of different processes and stress responses remain largely unknown. That said, *in vitro* [125] and *in vivo* studies [62,126], and longitudinal cellular aging experiments

[15] suggest that the energy cost of stressors and senescence could be sufficiently large to impose meaningful energetic and functional tradeoffs. In fact, dermal fibroblasts isolated from progeroid DNA repair-deficient mice display ~30% higher oxygen consumption rates than control fibroblasts, while the DNA repair-deficient mice display ~96% higher TDEE than control mice [62]. The recruitment of cell non-autonomous, physiological mechanisms could contribute to whole-body hypermetabolism beyond the excess energetic costs of impaired cells [73]."

Comment 21: 2) Its really unclear why the hypometabolic response over compensates. If its a compensation for cellular hypermetabolism then why doesn't the energy expenditure stay constant.

Response 21: As discussed above, we have changed the framing of our model and descriptions to reflect our agreement with you that the brain is unlikely to overcompensate (ie. produce whole body hypometabolism) in response to increased cellular energy demand.

Comment 22: 3) If the organism can respond to other hypermetabolic demands like exercise by just eating more food, why does it not do the same for cellular hypermetabolic states. Incidentally the fact intake can increase when some demands increase shows that supply is unlikely to be limited.

Response 22: As discussed above, increases in energy demand can cause tradeoffs *even when energy intake increases to compensate*. Jasienka and Ellison (2004, PMID: 15368604) measured TEE, food intake, body size/composition and female reproductive hormones in rural Polish women during the summer (high workload/harvest season) and winter (low workloads). The ~10% reduction in mean luteal progesterone in August (compared to January) occurred alongside a ~18% increase in mean TEE and a mean ~6% increase energy intake. While energy intake did not increase in proportion with energy expenditure in the summer, energy intake exceeded energy expenditure during both the winter and summer (by ~20% and ~8%, respectively). More importantly, statistical models revealed that only the increase in TDEE could explain the reduction in progesterone.

We agree that energy supply limits are not a necessary feature of the model – energy constraints and trade-offs are consequences of limits on metabolic rate, regardless of the cause(s) of the limit.

To avoid confusing readers about energy balance and energy constraints, we included in the text a short paragraph discussing their distinct influences during periods of increased energy demand:

"Energy *constraints* and energy *balance* are interrelated, but they exert distinct influences on physiology and behavior, especially in response to increases in energy demand. Increases in energy demand cause compensatory increases in energy intake [120]. This resolves the energy balance problem, but not the energy constraints problem. Resolving the energy constraints problem requires tradeoffs between subsystems to balance the limited energy budget. Accordingly, some systems are constrained even before reaching the maximal energy budget. For example, in adult women, submaximal increases in physical activity (AEE) suppressed ovarian function even when energy balance and body composition were maintained [121]. It follows that increases in energy demand impose energetic tradeoffs that are not meaningfully alleviated by compensatory increases in energy intake. Eating more does not eliminate physiological energy constraints."

Reviewer #5 (Remarks to the Author):

Comment 1: Metformin, a senotherapeuitic, seems to increase metabolic activity while lowering inflammation.

Response 1: Interesting point that is relevant to our model in at least two ways. First, since metformin may exert its effects by partially inhibiting the ETC, the finding that it "increases metabolic activity" is in line with our data showing hypermetabolism in OxPhos deficient cells, mice and humans. However, the fact that inflammation is lowered alongside the increased metabolic activity is inconsistent with our model – at least at first glance. The conflict may be resolved by the fact that cytokines come from many different sources, and that metformin enhances insulin sensitivity. If insulin resistance (in adipose tissue, for example) causes increased cytokine production/release, this could explain the inflammation suppressing effects of metformin.

Insulin resistance itself exists at the intersection of at least three hallmarks of aging: inter-cellular signaling, nutrient sensing, and mitochondrial "dysfunction". The implications of this convergence are fascinating to think about. We considered discussing the role of insulin resistance in the aging process (in the context of the Healthspan-extending effects of exercise in obesogenic environments), but did not have the space for it.

Comment 2: The new incretin-mimetics (such as Eli Lilly's retatrutide, a triple agonist targeting receptors for GLP-1, GIP, and glucagon) seem to promote metabolism of long stored fat (ie. in the liver) perhaps by countering glucagon insufficiency. This glucagon insufficiency may be driven by the brain, perhaps as part of the BEC, and is related to the age-old question of why older people seem to gain fat that they can't lose. Does inflammaging (possibly driven by adipose tissue) lower metabolic activity specifically in these areas? Could it be to reduce the energy cost of body temperature maintenance? Long story short – I think you have an opportunity to add something about obesity with aging and regulation of insulin-glucagon axis as an anti-aging pharmacological target.

Response 2: This is a wonderful example of a possible BEC phenomenon driven by age- and obesity-related endocrine dysregulation. It would have fit nicely with the paragraphs we drafted describing the role of insulin resistance in aging! Unfortunately, the editor was brutal on length and we didn't have the space to include it in this manuscript.

Reviewer #6 (Remarks to the Author):

Comment 1: The "hypermetabolism" term really started tripping me up towards the end. In the immune cell scenarios, when cells are responding to infection, is the increased metabolism really "hyper" or is it the level of metabolism that is needed for the required/programmed response. Many of the examples of "hypermetabolism" seemed like they could be viewed as "normal" or "expected" physiologic responses.

Response 1 & 2 (Combined): Thank you for this constructive critique! Others have expressed related concerns about the term "hypermetabolism" and we have done our best to clarify our usage of the term in the piece and have significantly revised the parts of the piece dealing with organism level energy conservation responses.

The question you pose (do the increased energy demands of the immune response during infection constitute "hypermetabolism" or are these "normal/expected" energy costs?) is incisive. The key component of our definition of hypermetabolism is the elevation of energy expenditure above the cost of sustaining *normal* basal functions. In the BEC model, the costs of the immune response are not considered "normal" because 1) under basal conditions, immune cells are not nearly as active as they are during infection, and 2) the immune response likely competes with normal basal functions for energetic resources

In the context of acute infection, the hypermetabolism of immune cells is linked, via cytokines and the brain, to a reordering of biological priorities that results in sickness behavior and withdrawal of energetic resources from activity, feeding, digestion, and at least some "normal basal processes". However, this energy conservation response does not necessarily lead to a reduction in total energy expenditure. In some cases, total energy expenditure remains significantly elevated despite near zero expenditure on activity and feeding (2 of the 3 components of total energy expenditure), reflecting a massive increase in resting energy expenditure (the 3rd component) that we refer to as "hypermetabolism".

We've also been asked whether frailty is characterized by hypo- or hyper-metabolism. In our model, frailty is mechanistically linked to *cellular* hypermetabolism (i.e., increased energy costs associated with aged/senescent cells) by a centrally driven energy conservation response (promotion of lean mass loss) that can but does not necessarily lead to whole body hypometabolism (i.e., reduced whole body energy expenditure relative to predicted).

But what about exercise? Are the added energy costs considered "normal/expected" or "hyper"? In the context of our model, exercise-associated expenditures are considered "hyper" for the same reasons the costs of the immune response are considered "hyper" – the costs of exercise come in addition to and competes with basal/normal costs. We have added a new section on exercise and calorie restriction that addresses this point more carefully (see response to Comment 2).

Comment 2: The initial discussions of in vitro studies were solid, but it seemed to start stretching and grasping when extended to the tissue and organism levels and pulling together every loose end in aging biology. The SEC predictions of calorie restriction and exercise seemed particularly weak.

We appreciate the critique of the CR and exercise sections. To address this we fundamentally re-worked these sections to highlight that different energetic threats (exercise, CR, stress, inflammaging) trigger distinct energy conservation responses with divergent effects on the rate of aging.

"BEC responses do not necessarily accelerate phenotypic aging

Calorie restriction vs inflammaging and stress: "supply-side" vs "demand-side" energetic threats

The BEC model posits that brain-driven energy conservation responses drive the manifestations of aging, yet calorie restriction (CR) induces energy conservation responses and extends lifespan [170]. This seeming contradiction is resolved by the fact that CR, stress and inflammaging trigger distinct energy conservation responses with divergent effects on phenotypic aging.

CR is a *supply-side* energetic threat that engages cellular and organismal "dormancy" programs [28]. Inflammaging and stress are *demand-side* threats that engage "defense" programs (see Figure 5). Both the "dormancy" and "defense" programs suppress non-essential functions to conserve energetic resources, but the "dormancy" program saves these resources for later, while the "defense" program mobilizes and burns available resources (muscles, other reserves) for immediate investment in energetically expensive emergency processes [28]. This distinction is reasonable considering that "dormancy" programs in wild animals (e.g., hibernation) are adaptive responses to prolonged nutrient scarcity (e.g., winter) – energetic resources are conserved until conditions improve. In contrast, defense programs in the wild are adaptive responses to more acute survival threats that can be more quickly resolved (e.g., infection, predators, wound), justifying extreme "defense" measures.

CR forces the major metabolic organs (including the brain) to protect the body's energy reserves and lean tissues while maintaining sustainably low concentrations of circulating fuels [171]. In response to low circulating nutrient availability, cellular energy and nutrient sensing mechanisms enforce a set of metabolic priorities that promote quality control processes and bioenergetic efficiency while minimizing entropy production [115,172]. The "dormancy" program therefore preserves lean tissues and likely counteracts the SASP [173]. In contrast, inflammatory cytokines and stress hormones stimulate the mobilization of stored fuels to support immune proliferation, signaling, and other energetically demanding processes, likely at the expense of longevity promoting processes. The "defense" program therefore accelerates lean tissue loss while creating a metabolic environment that is more permissive to damage accumulation and inflammation.

Exercise: not all "demand-side" energetic threats are created equal

The distinction between "supply-side" and "demand-side" energetic threats is insufficient to explain why exercise, which poses a "demand-side" threat, doesn't accelerate aging like stress and inflammaging do (**Figure 5**). A further distinction must be made between "demand-side" threats that are caused by increases in the *active* (AEE) versus *resting* (REE) components of TDEE. Increases in AEE but not REE trigger energy conservation responses that 1) increase bioenergetic capacity and efficiency, and 2) redistribute energetic resources in favor of longevity-promoting growth, maintenance, and repair processes.

At the level of the muscle cell, multiple signaling pathways couple the *present* perception of increased ATP demand to investments in *future* bioenergetic capacity and efficiency (e.g., mitochondrial biogenesis) [174]. At the level of organ systems, exercise adaptions increase the capacity and efficiency of the cardiovascular and neuromuscular systems [175] while enhancing inter-organ cross-talk [174] and improving the overall *efficiency* of the system [119]. One interpretation of this is that high physical activity is the norm for our species, and energetic efficiency is therefore optimized under these conditions. Accordingly, the more sedentary lifestyles typical in industrialized societies represent a deviation from our evolved norm that compromises energetic

efficiency. Therefore, at the level of the organism, exercise adaptations may in part counteract the "sickness behavior" effects of inflammaging- and stress-induced energy conservation responses, effectively delaying the vicious cycle of inactivity, deconditioning and frailty.

The constrained model of TDEE holds that increases in the active component of TDEE (AEE) cause compensatory decreases in the resting component (REE) [118,119]. Depending on the exercise workload, activity-mediated suppression of physiological processes that contribute to REE can either delay or accelerate aging-related processes [176]. Excessive workloads cause overtraining syndrome/RED-S, marked by fatigue, immunosuppression, endocrine deficits, and lean tissue loss [177]. These changes likely reflect prolonged tradeoffs between activity and longevity-promoting growth, maintenance and repair processes within REE [16]. On the other hand, more moderate increases in activity compress REE in a manner that suppresses inflammation [178], dampens stress reactivity [179,180], promotes hippocampal neurogenesis [181], and may beneficially reshape the proteome of aging muscle [182]. Thus, active expenditures compress REE while redistributing energetic resources within it, prioritizing growth and repair over "defense"."

Comment 3: The SEC (now BEC) predicts that imperfections/stress cause hypermetabolism and the brain responds by lowering whole body energy expenditure. I would expect that in brain dead individuals, who have very high levels of stress/inflammation, the lack of brain function would result in run-away hypermetabolism, but less potentially less aging because the brain is not there to mediate a "hypometabolic" response. However, it seems that patients who are clinically brain dead have lower REE and VO2, so I'm not sure how this fits with the model.

Response 3: This is a fascinating test case for the model – thank you for bringing it to our attention!

Your prediction (that brain dead patients may lack the energy conservation responses described by the model, which could lead to runaway hypermetabolism, possibly alongside a reduced rate of aging) is logically sound and does seem to be at odds with the findings of the paper you cite (reduced REE in braid dead patients). That said, brain death is not simply the absence of responses to hypermetabolic signals. For one, brain death is associated with a reduction of brain energy metabolism, which is usually a significant contributor to whole body EE. Similarly, these patients are unconscious, which further reduces EE (sleep EE is about 20-30% lower than resting EE). Furthermore, the brain-dead patients in the study you cite also have reduced thermoregulatory capacity, possibly accounting for further reductions in EE.

Moreover, the presentation of "brain death" mostly relates to the death of the conscious mind portion of the system, whereas vegetative centers and subcortical nuclei could still be highly active and able to manage the economy of energy. Ultimately there are too many unknowns and potential confounders to make sense of these findings in the context of our model (still a fun test case to think about though!)

Reviewer #7 (Remarks to the Author):

Comment 1: Is frailty characterized by hypermetabolism or hypometabolism?

Response 1: This is an excellent and incisive question that we did not address clearly enough in earlier drafts of the manuscript – thank you for pointing it out and providing relevant and interesting references.

Frailty *can* be characterized by both hypermetabolism and hypometabolism, but at different levels of organization (cellular vs. whole body). More specifically, frailty is mechanistically linked to *cellular* hypermetabolism (ie. increased energy costs associated with aged/senescent cells) by a centrally driven energy conservation response (promotion of lean mass loss, suppression of activity, etc.) that can but does not necessarily lead to *whole body* hypometabolism (ie. reduced whole body energy expenditure relative to predicted).

The observation that frailty is associated with increased RMR is consistent with the notion inflammaging-associated energy costs are part of the "resting" component of total energy expenditures (TEE). According to the classic 3-component model of TEE (activity, thermic effect of food, and resting), it is possible for an individual to have significantly increased RMR without an increase in TEE if expenditures associated with activity and feeding/digestion are reduced. In this case, a frail individual with RMR above predicted but TEE slightly below predicted can be said to be both hyper- and hypo-metabolic. The person is hypermetabolic in so far as the cellular hypermetabolism associated with senescence/inflammaging is contributing to increased RMR, but hypometabolic insofar as their TEE is reduced.

The manuscript could have been clearer on these points, so we refined our explanations accordingly in the new version.

The whole body hypermetabolism observed in ALS is fascinating to consider in the context of the BEC model. One possible explanation is that the increased metabolic activity of dysregulated/degenerating neurons contributes to an increase in whole body EE that is not compensated for by energy conservation responses. Another possibility is that the whole body elevation in EE is the result of dysregulated energy homeostasis. These possibilities are not mutually exclusive. It may be the case that the metabolic abnormalities that cause degeneration in motor neurons are also present in neuronal subpopulations that play critical roles in the regulation of energy intake and expenditure (such as AgRP and/or POMC neurons in the arcuate nucleus of the hypothalamus). In fact, mutations in mitochondrial proteins restricted to these hypothalamic neuronal subpopulations can have profound effects on energy balance-related physiology and behaviors in mice (for example, see Dietrich Cell 2013, PMID: 24074868 and Jin Elife 2021, PMID: 33689681)

Comment 2: Why doesn't cell-level hypermetabolism add up to organism level hypermetabolism? I suspect the answer is in the description of "aging cells" being "sparsely scattered across somatic tissues", but it would be useful to know estimates of how common they are, especially SASP cells which are implicated in inflammaging by inducing energy consuming inflammation in nearby cells.

Response 2: We think the reason why cellular hypermetabolism does not result in organismal hypermetabolism is twofold: 1) the aging cells are sparsely scattered across somatic tissues, and 2) the brain is capable of responding to circulating signals of cellular hypermetabolism with energy conservation responses that dial down energy expenditure from dispensable process to stay within a limited energy budget, easily offsetting the relatively unknown increase in EE from scattered senescent cells.

It would indeed be useful to know how aging/SASP cells are distributed within and across tissues – this is highly relevant to quantifying the magnitude of age-associated cellular hypermetabolism, which remains unknown.

Comment 3: Is the BEC model applicable to the entire lifecourse? Research on the developmental origins of health and disease clearly links many aging and especially frail phenotypes with early life adversity (ELA) beginning prenatally, with mitochondria of course having central roles – as per the 2022 paper you co-authored with Gyllenhammer and others. In fact infants can be born already on a course of accelerated biological aging (e.g., Quinn, et al. 2023).

It therefore seems the BEC model should be applicable across the lifecourse? After all, the same allostatic mechanisms are operative. E.g., the BEC model article as a section on inflammaging as characteristic in aging individuals – but this can start much earlier in highly distressed individuals. The figure below from Merz and Turner 2021 shows that frailty is associated with inflammaging that can start well before elderhood. ELA is depicted as increasing inflammation early in life which initiates a lifelong course of immunosenescence associated with accelerated aging. Regarding allostatic systems, Merz and Turner (2021, p.1) proposed that "ELA acts as an accelerator for inflammageing and age-related diseases" because it "shapes the developing immune, endocrine and nervous system in a non-reversible way, creating a distinct phenotype with accelerated immune-senescense and systemic inflammation."

Response 3: This a great question and the references you provide are fantastic. Yes, the model applies across the lifecourse. We have discussed the role of stress, and more indirectly of adversity, on energy demand and long-term consequences across the lifespan in Bobba-Alves et al. PNEC 2022 (PMID: 36302295).

Additional evidence relevant to your question comes from two recent papers demonstrating that the rate of embryonic development and cell differentiation scales with metabolic rate and maximal lifespan (Diaz-Cuadros et al. Nature 2023, and Iwata et al., Science 2023). Clearly energy/mitochondrial metabolism is related to both development and aging, but the BEC model doesn't apply in the absence of a brain to drive energy conservation responses. That being said, early developmental events (prior to brain development) certainly could set the stage for hypermetabolism (and brain-driven energy conservation responses) later in life. The quote you cite from the Merz and Turner paper describes this possibility quite convincingly – we've included this point in the section of the manuscript that discusses stress – thank you for bringing it to our attention!

We haven't given much thought to the point in development at which brain-driven energy conservation responses become relevant to the organismal management of allostatic load, but the Quinn et al. paper you cite is highly relevant and suggests that it may be in utero. The fact that low

birthweight predicts the rate of epigenetic aging over the first 3 years of life suggest that energetic threats in utero may trigger energy conservation responses that shape the entire lifecourse. It is fascinating to consider how the in-utero responses to different types of energetic threats (supply-side vs. demand-side, for example) might differ and the extent to which they are (mal)adaptive.

Comment 4: I'd appreciate hearing insights into a common observation in the stress literature: chronic glucocorticoid hypersecretion typically transitions to chronic hyposecretion, which is often assumed to reflect transitioning from hyper- to hypo-metabolism (although the relationship between GC and energy metabolism is not clear in this context). "Hypo" phenomena were not explicitly addressed in the Bobba-Alves dissertation, yet Figure 1 shows "hypo- and hyper-activation of organ systems" as both possible responses to allostatic load/overload, but there's no further discussion. Using Google Scholar I failed so far to find *in vitro* research on hypo-hyper or hyper-hypo transitions, I wonder if such research exists or is even possible?

Response 4: This is a great question. We are not sure either what evidence there if for this type of transition. Some recent evidence in the brain on its way to Alzheimer's disease seem to show this hyper-hypo transition: in late stage AD the brain is hypometabolic (low glucose utilization), but recent work shows affected areas are in fact hypermetabolic before symptoms (and energy constraints perhaps) set in. This data is consistent with the wild idea that there may be deliberate pulling of energy resources from certain organs and brain areas to promote survival, but that this then directly causes symptoms.

Reviewer #8 (Remarks to the Author):

Comment 1: Is the brain a precise? Or is it a blunt instrument? One of the repeated notions is that the brain, as you state, captures the "Gestalt state" and mobilizes a response. The manuscript gives the impression that the brain is quite precise in which processes are fueled and which are sacrificed. However, I'm skeptical about the brain's capacity to fine-tune the function of a cell inside a discrete organ.

The mental model I have (and again, perhaps I'm ignorant) is that of functional sympatholysis, which is best exemplified during exercise. During exercise, the sympathetic nervous system is activated and thus causes vasoconstriction in vessels with alpha adrenergic receptors. If this was all that would happen, working skeletal muscle would be deprived of oxygen. However, a milieu of local factors (nitric oxide, pH, O_2, CO_2, potassium, among others) override the sympathetic output to vasodilate the vessels that deliver blood to working muscle. Is it reasonable to expect the brain to have finer control over other organ/cellular processes especially in the context of hormonal output, which affects the whole organism?

In Box 1: you suggest that blood flow "is diverted" away from organs unnecessary for exercise. The follow up is, "to what?" which are the working muscles. Overall, the use of passive voice begs the question of "is diverted by what?" The answer there is not by a single organ (i.e. brain) but by a mixture of central and peripheral factors.

In the third paragraph of the first page, you suggest that the brain has superseding outputs that ultimately controls systemic energy metabolism, but here is one case that might not be the case (though writing this, I have to remind myself of the brain's control over fatigue and exertion, so perhaps I just refuted my own idea that brain can't supersede organ function)…

Response 1: Thank you for the excellent question and useful example. Ultimately the brain can act as both a blunt and precise instrument. That said, we agree that we overstated the precision with which the brain controls peripheral processes in earlier drafts. The brain-driven energy conservation responses described by the model are general, "whole body" responses (HPA axis activation, fatigue, etc.) that are "uniquely processed by each organ" (as you say in a later comment). You are also right to point out that this organ specific processing is modulated by the local milieu.

The brain is however capable of more precise outputs. For example, discrete populations of glucose sensing neurons in the hypothalamus directly modulate sympathetic outflow to the liver and pancreas during hypoglycemia to increase blood glucose levels. There are many examples like this, but they are generally not the type of brain responses we are describing in the piece. A particularly striking example is described in a recent Nature paper that presents a body-brain feedback control circuit with surprisingly specific central control of systemic inflammatory responses.

Your comment helped us formulate a short section discussing the specificity of the brain's energy conservation response (see below) – thank you!

"How specific are brain-driven energy conservation responses?

Since we currently lack a comprehensive mapping of all the potential compensatory responses that the brain can trigger, it is unclear how specific the brain's energy conservation responses can be. The major energy conservation responses discussed above are general brain outputs (stress hormones, fatigue, etc.) that are fine-tuned in the periphery by tissue-specific responses. These general responses allow for simultaneous suppression of many low priority

processes, including seemingly trivial expenditures (e.g. hair pigmentation) that when combined and summed over time, might represent significant energy savings.
The brain may also have more specific control mechanisms at its disposal. In fact, the brain was recently shown to have surprisingly specific feedback control over systemic inflammatory responses [201]. The brain may also possess feedback control over its own functions, which collectively account for roughly 25% of TDEE [202]. For example, the aging brain undergoes a learning-to-prediction shift, which may represent an adaptive attempt to leverage existing knowledge to save on the energetic cost of processing raw inputs, learning, and creating new memories [203,204]. By the same logic, age-related cognitive and sensory "deficits" may at least partially represent consequences of psychobiological energy conservation responses. Thus, although it's unlikely that the brain is capable of selectively shutting down single cells when they become defective (if it could, cancer and senescence would be non-problems), it may be able to selectively withdraw energetic resources from specific physiological and/or biological processes (see **Table 1**)."

Comment 2: How much has the brain evolved to control aging? Or is it a matter of driving development to promote organismal success (i.e. reproduction)?
I found the notion that the brain coordinates and facilitates multi-organ bodies compelling. However, I'm not sure how a brain has served an organism in the context of aging. Rather, in the context of development and evolution, it is rather compelling. As you stated in Box 1, the brain is tuned towards a "young, maximally efficient state." However, is there not evidence to suggest this is at odds with longevity?
Additionally, aren't cells equipped with the capacity to sense energy? Is the brain only there to try to be[er coordinate the response to stress? I generally view cellular metabolism as divided into three categories: metabolism, growth/reproduction, and somatic maintenance. Metabolism, as you stated, is prioritized. Growth/reproduction and somatic maintenance are nearly tied in cellular priority.
However, in light of evolutionary pressures, growth/reproduction seems to win in prioritization. Thus, organisms (and cells?) prioritize growth/reproduction at the tradeoff of processes related to maintenance. I think the brain is but a passive agent to evolutionary pressures. One example of this is from a paper by Steve Austad on an insular population of opossums. Compared to their mainland counterparts who faced greater predation, these opossums reproduced less and at a later age and lived longer. I do not think it was the brain the coordinated this extension in life. Rather, I think it was the external and somatic signals that alleviated the burden and impetus to grow and reproduce quickly. The brain just happened to not signal to the soma to mature so quickly. It seems the brain integrates peripheral signals and translates this into behavior and whole-body signals.

Response 2: This is another incisive question that helped to refine our thinking. Thank you! Our understanding is that the brain evolved to promote both survival and reproduction by enforcing a dynamic hierarchy of competing needs. The rank order of growth, reproduction, and maintenance (the three "life history programs") within this hierarchy changes over the life course and in response to survival threats. The brain's role in detecting acute survival threats (infection, famine, etc.) and orchestrating the re-ordering of organismal priorities in response is undeniable. However, the brain's role is not as clear in the context of age-related re-ordering of organismal priorities (during inflammaging, for example).

While the brain likely did not evolve to control the rate of aging, its evolved ability to enforce a dynamic hierarchy of competing energy needs may endow it with adaptive responses to survival threats that are unique to old age. The BEC model posits that the brain's response to circulating cytokine signals of senescence-associated hypermetabolism is a low-grade variant of its evolved response to systemic inflammation during acute infection. Sickness behaviors are characterized by a re-ordering of organismal priorities in favor of "defense" and "dormancy" (both components of the "maintenance" program), which promotes survival, at least in part, by maximizing the immune system's ability to clear the invading pathogen. According to the proposed model, lower levels of the same cytokines trigger a similar but less severe re-ordering of priorities (and related redistribution of energetic resources) that we propose 1) drives the manifestations of aging and 2) *may* be adaptative.

Inflammaging-induced energy conservation responses can be seen as adaptive because they address the energetic threat. However, chronic deployment (which would be unusual outside the context of aging) is likely to have deleterious effects

Comment 3: Miller's hypothesis suggests that the issue is that there is hyper-metabolism (protein synthesis) of the wrong proteins. Speculation would be lifespan extending interventions (CR, mTOR inhibitors, exercise) modulates the proteome to a "healthier" state (that evolution would not have not selected for).
Finally, given that exercise is perhaps the most effective healthspan (and lifespan) extending intervention for humans, I think there ought to be more space dedicated to it. Arguably, it's a perfect example of a hormetic signal that reprograms the cellular transcriptional and translational landscape that improves cellular function. What's interesting is that despite it's very large energy costs (the ACSM recommends the equivalent of ~1200 - 1500kcals/week of exercise), it causes cellular and organismal changes that increases muscle function and cardiorespiratory fitness even beyond the age of 100. Are any of these adaptations mediated (or coordinated) by the brain?

Response 3: Miller's hypothesis is fascinating to consider in the context of the BEC model and energetic constraints more generally. One interpretation of the hypothesis is that the lifespan extension associated with CR, mTOR inhibitors, and exercise is caused, at least in part, by a reordering of the muscle cell's protein synthesis priorities, culminating in "healthier" muscle proteome. Perhaps the reordering or muscle protein synthesis priorities is the result of myocellular energy conservation responses to energetic threats associated with CR (a "supply side" energetic threat) and exercise (a "demand side" energetic threat). mTOR inhibitors could be thought of as mimetics for CR and/or exercise – the commonality between the three being signaling of low cellular nutrient and ATP availability, which may force the cell to be more selective about which proteins it synthesizes to promote metabolic efficiency.

With respect to exercise, the revised manuscripts now gives it more space by integrating our discussion of exercise (a "demand-side" energetic threat driven by "active" expenditures) with inflammaging (a "demand-side" energetic threat driven by "resting" expenditures), and CR (a "supply side" energetic threat). The theme of the section is that the energy conservation responses to each type of energetic threat are different and have divergent effects on the rate of aging. The relevant section is copied below:

"BEC responses do not necessarily accelerate phenotypic aging

Calorie restriction vs inflammaging and stress: "supply-side" vs "demand-side" energetic threats

The BEC model posits that brain-driven energy conservation responses drive the manifestations of aging, yet calorie restriction (CR) induces energy conservation responses and extends lifespan [170]. This seeming contradiction is resolved by the fact that CR, stress and inflammaging trigger distinct energy conservation responses with divergent effects on phenotypic aging.

CR is a *supply-side* energetic threat that engages cellular and organismal "dormancy" programs [28]. Inflammaging and stress are *demand-side* threats that engage "defense" programs (see Figure 5). Both the "dormancy" and "defense" programs suppress non-essential functions to conserve energetic resources, but the "dormancy" program saves these resources for later, while the "defense" program mobilizes and burns available resources (muscles, other reserves) for immediate investment in energetically expensive emergency processes [28]. This distinction is reasonable considering that "dormancy" programs in wild animals (e.g., hibernation) are adaptive responses to prolonged nutrient scarcity (e.g., winter) – energetic resources are conserved until conditions improve. In contrast, defense programs in the wild are adaptive responses to more acute survival threats that can be more quickly resolved (e.g., infection, predators, wound), justifying extreme "defense" measures.

CR forces the major metabolic organs (including the brain) to protect the body's energy reserves and lean tissues while maintaining sustainably low concentrations of circulating fuels [171]. In response to low circulating nutrient availability, cellular energy and nutrient sensing mechanisms enforce a set of metabolic priorities that promote quality control processes and bioenergetic efficiency while minimizing entropy production [115,172]. The "dormancy" program therefore preserves lean tissues and likely counteracts the SASP [173]. In contrast, inflammatory cytokines and stress hormones stimulate the mobilization of stored fuels to support immune proliferation, signaling, and other energetically demanding processes, likely at the expense of longevity promoting processes. The "defense" program therefore accelerates lean tissue loss while creating a metabolic environment that is more permissive to damage accumulation and inflammation.

Exercise: not all "demand-side" energetic threats are created equal

The distinction between "supply-side" and "demand-side" energetic threats is insufficient to explain why exercise, which poses a "demand-side" threat, doesn't accelerate aging like stress and inflammaging do (**Figure 5**). A further distinction must be made between "demand-side" threats that are caused by increases in the *active* (AEE) versus *resting* (REE) components of TDEE. Increases in AEE but not REE trigger energy conservation responses that 1) increase bioenergetic capacity and efficiency, and 2) redistribute energetic resources in favor of longevity-promoting growth, maintenance, and repair processes.

At the level of the muscle cell, multiple signaling pathways couple the *present* perception of increased ATP demand to investments in *future* bioenergetic capacity and efficiency (e.g., mitochondrial biogenesis) [174]. At the level of organ systems, exercise adaptions increase the capacity and efficiency of the cardiovascular and neuromuscular systems [175] while enhancing inter-organ cross-talk [174] and improving the overall *efficiency* of the system [119]. One interpretation of this is that high physical activity is the norm for our species, and energetic efficiency is therefore optimized under these conditions. Accordingly, the more sedentary lifestyles typical in industrialized societies represent a deviation from our evolved norm that compromises energetic efficiency. Therefore, at the level of the organism, exercise adaptations may in part counteract the "sickness behavior" effects of inflammaging- and stress-induced energy conservation responses, effectively delaying the vicious cycle of inactivity, deconditioning and frailty.

The constrained model of TDEE holds that increases in the active component of TDEE (AEE) cause compensatory decreases in the resting component (REE) [118,119]. Depending on the exercise workload, activity-mediated suppression of physiological processes that contribute to REE can

either delay or accelerate aging-related processes [176]. Excessive workloads cause overtraining syndrome/RED-S, marked by fatigue, immunosuppression, endocrine deficits, and lean tissue loss [177]. These changes likely reflect prolonged tradeoffs between activity and longevity-promoting growth, maintenance and repair processes within REE [16]. On the other hand, more moderate increases in activity compress REE in a manner that suppresses inflammation [178], dampens stress reactivity [179,180], promotes hippocampal neurogenesis [181], and may beneficially reshape the proteome of aging muscle [182]. Thus, active expenditures compress REE while redistributing energetic resources within it, prioritizing growth and repair over "defense"."