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**THEORETICAL ARTICLE**

**Neurons vs germline: a war of tradeoffs and the ‘Indispensable Soma’ hypothesis**

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**Abstract**

The process of human ageing is significantly dependent upon evolutionary events which are currently shaping humanity. One such event is the seemingly inexorable progress of technology, and specifically, digital communications technology (internet). Technology and biology are tightly interconnected, and this has a direct relevance on how our own ageing mechanisms are evolving and adapting to the change. One way technology may affect biological ageing is based on the concept of information exposure which up-regulates neuronal stress response pathways. This may have an impact on germline repair, with two consequences: 1. Neurons become increasingly more likely to acquire repair resources and function for longer, and 2. The fidelity of repair mechanisms in the germline may have to be downgraded, in order to accommodate a corresponding escalation of repairs in neurons. This is the Indispensable Soma hypothesis (essentially the disposable soma theory in reverse): A purposeful integration with technology, which hormetically challenges our cognition, may initiate a shift in evolutionary priorities, rebalancing the conflict between the soma and the germline, and resulting in an eradication of age-related dysfunction in participating humans.

Introduction

In a progressively technological world, it seems inevitable that the biological and the digital domains will increasingly merge (1). This bio-digital symbiosis is reflected in the emergence of a novel ecosystem, an interacting amalgamation of humans and the internet (2). This ecosystem is a self-organising complex adaptive system (3, 4) a distributed, sustainable, scalable, open socio-technical construct (5). Within this environment, existing evolutionary realities begin to alter, and what was considered normal or natural until now, may not be so in the near-term future (6). Aside from practical benefits associated with a human-machine merge (such as knowledge creation and information mining), there are also socio-cultural benefits such as reduction of redundant and repetitive work, which ultimately results in improved health (7). But the most relevant impact on our health comes from a biological perspective. We know that sensory perception cues can affect longevity, at least in model organisms (8), but it is also likely that external perceptions which improve neuronal health can also affect survival (1). Below I describe a mechanism (the Indispensable Soma Hypothesis) by which participating humans may experience elimination of age-related degeneration, based on a reversal of the repair resource trade-offs between the germline and the soma.

Discussion

In biological terms, I will argue that we may now begin to witness a shift in evolutionary priorities, and specifically, a transition from the current emphasis on the germline, to an increased emphasis on the somatic neuron, i.e. a shift of importance from the physical to the cognitive. This may have a direct bearing upon human ageing and degeneration. Here, I define ageing as ‘time-dependent dysfunction’.

It is slowly becoming better appreciated that there is important cross-talk between the soma (specifically the neuron) and the germline (9-12). It is also becoming clear that there are several mechanisms which create a flow of repair resources from the soma to the germline in order to safeguard the survival of the species (13-15). For instance, it has been suggested that sequence-specific regulatory information in the form of dsRNA can be transferred from neurons to the germline in order to cause transgenerational silencing (16).

There is a brutal competition for resources between the germline and the neuron (for instance: 17, 18). Here, the discussion is relevant to any neuron, not only with regards to the central nervous system but also with regards to the autonomic and the enteric nervous systems (19, 20). I have argued (6) that this competition, this war of trade-offs, can be ‘won’ by the neuron, if the neuronal stress response is up-regulated to such a degree that it causes continual apoptosis in the germline (21). Levi-Ferber et al. (22) have shown that the neuronal stress response interferes with germline survival, because it induces apoptosis in the germline. One possible mechanism for this, is mediated through the IRE-1 (inositol-requiring enzyme 1) factor, an endoplasmic reticulum stress response sensor, which initiates the apoptotic cascade in the germline (22). It is worth pausing for a minute to ponder on the significance of this and similar mechanisms. Stress response in neurons may be initiated through hormetic exposure to cognitive stimulation of the magnitude and quality we encounter in our modern technological environment. Hormesis is a phenomenon whereby mild, positively stressful stimuli or challenges entice the organism to act and adapt (23). Stress response elements originating from neurons may cause apoptosis in the distant germline cells, and this re-balances the resource allocation process with a resulting improvement of neuronal repair (6). Thus, there appears to be a direct relationship between a hormetic application of cognitive challenges and somatic survival (Figure 1).

The environment, i.e. a ‘context-dependent’ epigenome, influences not only a soma-to-germline, but also a germline-to-soma flow of resources (24). In other words, the trade-offs between the soma and the germline are not immutable, but are flexible and can be reversed (6). One such trade-off was studied in C. elegans and involves the mobilization of lipids from somatic cells to the germline in order to improve fecundity. This comes at a cost of poor survival (25) and it is a typical example of how allocation of resources currently favours the germline in order to ensure survival of the species in times of environmental pressures. This example also shows that the allocation mechanism is not unchallengeable, but it depends on environmental and evolutionary necessities: it can be reverted if somatic health becomes a more likely survival strategy (26).

There is another example of a potential communication pathway between the germline and the neuron. Germline (spermatogonial) stem cells may act as a source of neuron-like cells (27) and definitive neural stem cells (28). Multipotent neural and glial precursors can be derived from multipotent adult germ line stem cells (29). These neurons then undergo full maturation and efficient integration within the existing neural network. The possibility that the germline may act as a source of fully functional neurons (30-32) is a remarkable finding, necessitating further research and consideration. For instance, it is necessary to establish under what circumstances can the germline allow the provision of neural stem cells, what the interrelationship between these two elements are, and if external cognitive challenges which activate the stress response in neurons may have an impact (and what impact) on spermatogonial germ stem cells.

The impending merge of humans with the digital realm may reverse or interfere with the priorities of the above processes. As we are witnessing a shift of the current evolutionary emphasis from the physical to the cognitive (i.e. as we become increasingly more embedded in an information-rich, cognitive techno-cultural environment) we experience a new stage in the gene-culture co-evolution process, which may result in reversal of resource allocation from the germline to the soma, and specifically the neuron. Exposure to a hormetic-style cognitive information enhances the process of superior pattern processing (SPP) (33) in humans and this ensures a continual process of adaptation to increasingly more complex cognitive challenges. Stress response factors which may be active in modeling such an adaptation are PERK- (Protein kinase RNA-like endoplasmic reticulum kinase), ATF6 (activating-transcription-factor-6), c-Jun N-terminal kinase 1 (JNK), and ATF4. Several other markers such as the Mitogen-activated protein kinases (MAPK) MEK-1 and SEK-1 may initiate germline cell apoptosis depending on the level of sensed damage, and can thus be used as biomarkers of a cognitive stress response, which may then affect germline function (34).

We know that the DNA Damage Response (DDR) has effects which not only affect by-stander elements (i.e. neigbouring cells) but also distance elements, and may operate through apoptosis gradients (i.e. the same stressful event may cause a strong response near the damage, in addition to a lesser response far away from the damage). Thus, stress responses may not only affect the cells where the stress is being applied at, but also may have by-stander and even distant effects (35). Therefore it is quite conceivable that application of a local neuronal hormetic stress, can affect the distant germline, as discussed above.

This scenario makes it increasingly more difficult to explain why there is a continual need for germline repair: highly cognitive human agents may be more conducive to improving the overall evolutionary process, and are thermodynamically costly to replace, compared to what was an appropriate evolutionary reality until now (36).

Conclusions

In this paper, I am suggesting that a hormetic (dose-response), positively challenging exposure to a more cognitively-biased environment will activate neuronal stress response systems and this will lead to in improved repair of neurons, with a consequent down-regulation of germline repairs. By ‘cognitive’ I refer to a tendency to engage in creative, imaginative, divergent and abstract thinking (37) and enhanced brain activities such as those exhibited by the default network, as well as goal-directed, self-generated cognition (38). Some of these activities involve activation of the prefrontal cortex (39). This is significant because the prefrontal cortex is involved in assessing risk and governs conscious perception. An enhanced amount of self-generated thinking can be both beneficial (in evaluating possible threats and in increasing creativity and visionary thinking) and possibly detrimental, as it may result in neuroticism and anxiety (40). Therefore an ideal between the two must be found, a typical dose-response, hormetic situation.

By becoming active contributors within a techno-cognitive ecosystem, our soma stops being ‘disposable’, and it becomes ‘indispensable’ to the overall evolution and adaptability of the ecosystem: therefore it lasts longer. The ‘war of trade-offs’ between the soma and the germline is a race for survival which reflects a wider evolutionary conflict: the survival of individual cognition and ‘self’ vs the survival of the species. Our technology may now be placing us in such a position that we may be able to win this ‘war of trade-offs’ and ensure our own personal survival through the elimination of age-related somatic degeneration in participating humans.

**BOX Summary**

**\***  Information technology is placing an increased cognitive burden on our biology

\* As a result, human neurons are under continual pressure to repair themselves

\* Thus, repair resources must be allocated preferentially to the soma (neuron)

\* This hormetic cognitive stress may result in a reduction of age-related degeneration

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**References**

1. Kyriazis M. Systems neuroscience in focus: from the human brain to the global brain? Front Syst Neurosci 2015; 9: 7.

2. Gershon N. Wearables, Humans, and Things as a Single Ecosystem! November 9, 2015 <http://iot.ieee.org/newsletter/november-2015/wearables-humans-and-things-as-a-single-ecosystem.html> (accessed 22 March 2016)

3. Buckley W. Society as a Complex Adaptive System. Emergence : Complexity and Organization 2008; 86-112.

4. Phister PW. Cyberspace: The Ultimate Complex Adaptive System. The International C2 Journal 2010. <http://www.dodccrp.org/files/IC2J_v4n2_03_Phister.pdf> (accessed 24 March 2016)

5. Briscoe G, De Wilde P. Digital Ecosystems: Evolving service-oriented architectures. In Conference on Bio Inspired Models of Network, Information and Computing Systems. IEEE Press, 2006.

6. Kyriazis M. The Indispensable Soma Hypothesis. Figshare 2016; <https://dx.doi.org/10.6084/m9.figshare.3079732.v1> (accessed 8 April 2016).

7. Kyriazis M. Engagement with a technological environment for ongoing homoeostasis maintenance. In Challenging Ageing: The anti-senescence effects of Hormesis, Environmental Enrichment, and Information Exposure. Bentham Science Publishers, UAE 2016. In press.

8. Linford N, Kuo TH, Chan TP, Pletcher SD. Sensory Perception and Aging in Model Systems: From the Outside In. Annu Rev Cell Dev Biol 2011; 27: 759–785.

9. Avise JC. The evolutionary biology of aging, sexual reproduction and DNA repair. Evolution 1993; 47: 1293-1301.

10. Gracida X, Eckmann CR. Mind the gut: Dietary impact on germline stem cells and fertility. Commun Integr Biol 2013; 6(6):e260040.

11. Khodakarami A, Saez I, Mels J, Vilchez D. Mediation of organismal aging and somatic proteostasis by the germline. Front. Mol. Biosci 2015; <http://dx.doi.org/10.3389/fmolb.2015.00003>.

12. Qian Y, Ng CL, Schulz C. CSN maintains the germline cellular microenvironment and controls the level of stem cell genes via distinct CRLs in testes of *Drosophila melanogaster*. Dev Biol 2015; 398(1):68-79.

13. Douglas PM, Dillin A. The disposable soma theory of aging in reverse. Cell Research 2014; 24:7-8.

14. Ermolaeva MA, Segref A, Dakhovnik A, Ou HL, Schneider JI, Utermöhlen O, Hoppe T, Schumacher B. DNA damage in germ cells induces an innate immune response that triggers systemic stress resistance. Nature 2013; 501(7467):416-20.

15. Zimmerman SM, Hinkson IV, Elias JE, Kim SK. Reproductive Aging Drives Protein Accumulation in the Uterus and Limits Lifespan in *C. elegans*. PLoS Genet 2015; 11(12):e1005725.

16. Devanapally S, Ravikumar S, Jose AM. Double-stranded RNA made in C. elegans neurons can enter the germline and cause transgenerational gene silencing. Proc Natl Acad Sci U S A 2005; 112(7): 2133–2138.

17. Parlato R, Otto C, Begus Y, Stotz S, Schütz G. Specific ablation of the transcription factor CREB in sympathetic neurons surprisingly protects against developmentally regulated apoptosis. Development 2007; 134(9):1663-70.

18. Muotri AR. L1 Retrotransposition in Neural Progenitor Cells. Methods Mol Biol 2016;1400:157-63.

19. Costa M, Brookes SJH, Hennig GW. Anatomy and physiology of the enteric nervous system. Gut 2000; 47:iv15-iv19.

20. Furness JB, Callaghan BP, Rivera LR, Cho HJ. The enteric nervous system and gastrointestinal innervation: integrated local and central control. Adv Exp Med Biol 2014; 817:39-71.

21. Labbadia J, Morimoto RI. Repression of the Heat Shock Response Is a Programmed Event at the Onset of Reproduction. Mol Cell 2015; 59(4):639-50.

22. Levi-Ferber M, Salzberg Y, Safra M, Haviv-Chesner A, Bülow HE, Henis-Korenblit S. It's all in your mind: determining germ cell fate by neuronal IRE-1 in C. elegans. PLoS Genet 2014; 10(10):e1004747.

23. Mattson MP. What doesn’t kill you… Scientific American 2015; 313: 40-45.

24. Leseva M, Knowles BB, Messerschmidt DM, Solter D. Erase-Maintain-Establish: Natural Reprogramming of the Mammalian Epigenome. Cold Spring Harb Symp Quant Biol. Jan 13 2016; pii: 027441. [Epub ahead of print].

25. Lynn DA, Dalton HM, Sowa JN, Wang MC, Soukas AA, Curran SP. Omega-3 and -6 fatty acids allocate somatic and germline lipids to ensure fitness during nutrient and oxidative stress in Caenorhabditis elegans. Proc Natl Acad Sci U S A 2015; 112(50):15378-83.

26. Johnson EL, Cunningham TW, Marriner SM. Resource allocation in a social wasp: effects of breeding system and life cycle on reproductive decisions. Mol Ecol 2009; 18(13):2908-20.

27. Wang X, Chen T, Zhang Y, Li B, Xu Q, Song C. Isolation and Culture of Pig Spermatogonial Stem Cells and Their in Vitro Differentiation into Neuron-Like Cells and Adipocytes. Int J Mol Sci 2015; 16(11):26333-46.

28. Teichert AM, Pereira S, Coles B, Chaddah R, Runciman S, Brokhman I, van der Kooy D. The neural stem cell lineage reveals novel relationships among spermatogonial germ stem cells and other pluripotent stem cells. Stem Cells Dev 2014; 23(7):767-78.

29. Glaser T, Opitz T, Kischlat T, Konang R, Sasse P, Fleischmann BK, Engel W, Nayernia K, Brüstle O. Adult germ line stem cells as a source of functional neurons and glia. Stem Cells 2008; 26(9):2434-43.

30. Kim BJ, Lee YA, Kim KJ, Kim YH, Jung MS, Ha SJ, Kang HG, Jung SE, Kim BG, Choi YR, Do JT, Ryu BY. Effects of paracrine factors on CD24 expression and neural differentiation of male germline stem cells. Int J Mol Med 2015; 36(1):255-62.

31. Streckfuss-Bömeke K, Vlasov A, Hülsmann S, Yin D, Nayernia K, Engel W, Hasenfuss G, Guan K. Generation of functional neurons and glia from multipotent adult mouse germ-line stem cells. Stem Cell Res 2009; 2(2):139-54.

32. Yang H, Liu Y, Hai Y. Efficient Conversion of Spermatogonial Stem Cells to Phenotypic and Functional Dopaminergic Neurons via the PI3K/Akt and P21/Smurf2/Nolz1 Pathway. Mol Neurobiol 2015; 52(3):1654-69.

33. Mattson M. Superior pattern processing is the essence of the evolved human brain Front. Neurosci 2014; 22 August, http://dx.doi.org/10.3389/fnins.2014.00265.

34. Salinas LS, Maldonado E, Navarro RE. Stress-induced germ cell apoptosis by a p53 independent pathway in *Caenorhabditis elegans*. Cell Death Differ 2006; 13(12):2129-39.

35. Nikitakia Z, Mavragania IV, Laskaratoua DA, Gikaa V, et al. Systemic mechanisms and effects of ionizing radiation: A new ‘old’ paradigm of how the bystanders and distant can become the players Seminars in Cancer Biology. Science Direct 2016. <http://www.sciencedirect.com/science/article/pii/S1044579X16300049> (accessed 23 March 2016)

36. Kyriazis M. Reversal of informational entropy and the acquisition of germ-like immortality by somatic cells. Curr Aging Sci 2014; 7(1):9-16.

37.Beaty RE, Benedek M, Silvia PJ, Schacter DL. Creative Cognition and Brain Network Dynamics. Trends Cogn Sci 2016; 20(2):87-95.

38. Beaty RE, Kaufman SB, Benedek M, Jung RE, Kenett YN, Jauk E, Neubauer AC, Silvia PJ. Personality and complex brain networks: The role of openness to experience in default network efficiency. Hum Brain Mapp 2016; 37(2):773-9.

39. O'Callaghan C, Shine JM, Lewis SJ, Andrews-Hanna JR, Irish Ml. Shaped by our thoughts--a new task to assess spontaneous cognition and its associated neural correlates in the default network. Brain Cogn 2015; 93:1-10.

40. Perkins AM, Arnone D, Smallwood J, Mobbs D. Thinking too much: self-generated thought as the engine of neuroticism. Trends Cogn Sci 2015; 19(9):492-8.

Figure 1 Legend:

Cognitively-challenging information initiates the neuronal stress response, which results in damaged germline and a consequent increased flow of repair resources back to the neuron.