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Abstract

During the process of ageing there is canalisation of repair resources which tend to flow from the soma towards the germ line. In the early periods of phylogenetic development there was a time when repair of germ line cells became more efficient compared to the repair of somatic cells. The level of somatic repair became just enough to ensure that the organism reached sexual maturity. It was the biological equivalent of the mathematical bifurcation, when the pathway developed preferentially towards the germ line attractor. We are now looking for evidence that this could be changing, that we may be witnessing a **phase transition** from effective germ line repair to an effective somatic repair. Here I consider mechanisms of fidelity-preservation which may be present in the germ line, and examine the possibility that these may be made to operate upon somatic cells instead. Mechanisms which safeguard the reliability of germ line repair and ensuring robustness/resilience in the germ line may also (or instead) be applicable upon somatic material (cells and molecules, factors) and ensure a continually effective repair of this somatic material. Thus the ability to continually repair and maintain somatic organic material within biological systems is not lost. Continual challenges from the environment ensure that the flow of information remains active and it persistently stimulates the ability to repair the soma. Apart from germ line cells, some unicellular organisms such as bacteria maintain their ability for ongoing repairs, a fact that indicates that, in principle, senescence is not unavoidable.

Keywords: Germ line, Somatic repairs, Trade-offs, Indispensable soma hypothesis, Apoptosis, Environment, Transposons, MicroRNAs, Germ line to soma cross-talk, Immortalisation

Introduction

In this chapter, I will discuss, review and speculate on matters relating to how exposure to information in humans may lead to a situation whereby ageing as a process may be significantly downgraded (or even virtually eliminated, at least in some sections of humanity). Some initial concepts have already been discussed in the previous chapter but I will approach the matter from a variety of angles.

This argument, and most of the conceptual basis of this book, is based upon certain simple evolutionary principles. It is indisputable that the widespread tendency in nature is towards continual life and good function. When a **mildly** stressful (i.e. not excessive or prolonged) event happens, such as famine or starvation, the reproductive priorities in humans are down-graded [1]. The crucial question to ask here is 'why does this happen?' Again, it is undeniable, in my view, that the answer is this: When life is immediately in danger, there is a 'hard-wired' tendency in natural principles to protect the organism as a priority, and allocate to this process whatever resources are necessary for effective repair and maintenance. This may mean a reduced priority for reproductive resources. There exist definite trade-offs between somatic maintenance and reproduction [2], but when somatic elements need repair resources, the first initial objective (i.e. the 'default' option) is to allocate these to the soma. If the danger continues, or if the environment is risky and there is an increased likelihood of the organism dying early, then nature switches to 'option B', the second best option for ensuring survival, which involves the withholding of somatic repair resources and the reallocation of these to the germ line [3]. The point of this argument is to show that the tendency to survive as a discrete organism is **innate and present now** in all of us, and it is the first priority of

most biological processes. Ageing and reproduction are merely secondary processes developed by natural principles in order to assure survival, only as an ancillary, reserve mechanism.

In the co-evolution of the repair mechanisms employed by somatic and germ line cells, there was a certain antagonism, whereby germ line elements have succeeded in modifying the opponent's (somatic) control systems (for instance [4]). Despite several countermeasures deployed by somatic cells in order to acquire sufficient repair resources, there was a relatively rapid divergence of the functionality of the control and regulation systems, resulting in the immortality of the germ line with the mortality of the soma [5]. It is possible to study the basic theoretical mechanisms involved in such co-evolutionary setting, and consider ways to modify or interfere with the processes, in a way that favours the soma instead of the germ line. This may lead to ways to study a fitness landscape where somatic repair mechanisms can evolve rapidly [6]. In this respect, Smelick and Ahmed [7] have suggested that the germ line can antagonise the ageing of somatic cells, and that it may be possible that defects in the mechanisms operating during immortalisation of germ line cells may provide useful repair resources to somatic cells. Germ cells achieve continuous repair and fidelity of replication by ensuring that they maintain robustness - the redundancy that counteracts the effects of random damage. Evolution drives the balance of the appropriate trade-offs between robustness and maintenance resources. The trade-offs between survival of the somatic cells and reproduction could be due to factors such as:

a. The impossibility to maintain all processes within the body indefinitely, due to lack of repair resources

b. The damage to the somatic cells could be incurred during the normal course of reproduction [8].

Germ-line Replicative Fidelity

Under conditions of stress, repair resources are preferentially allocated from somatic to germ line repair in order to safeguard the health of the next generation (see Box 1) [9]. This is essentially the basis of the Disposable Soma theory [3]. Until recently, it was believed that this process is unidirectional, with resources flowing from soma to germ line only. There is evidence however supporting the suggestion that this process is, in fact, *bi-directional*. Under suitable conditions, repair resources can be re-directed from the germ line back to the somatic tissues [10]. This germ-initiated somatic protective response is called 'germ-line DNA-damage-induced systemic stress resistance (GDISR).

****

BOX 1. What is a 'somatic' cell

it is important to emphasise that in the following discussion (and throughout the book) by 'somatic cell' or 'soma' I essentially refer to a **neuron**, or any other relevant cell or organic agent that carries, stores, transmits or elaborates information, AND ALSO to all other cells or tissues which are necessary for the survival of this primary neuron. In essence then:

A). A somatic cell is a neuron plus any other non-germ cell that support the neuron's function, proximally or distantly

B). A germ line cell is a reproductive egg or sperm cell.

****

There is a direct relationship between increasing age and genomic instability in somatic cells. Maintenance resource reallocation favours reproduction at the expense of somatic cell senescence. However, it is possible to encounter soma-to-germ line transformation of gene expression (such as the improved function of the FOXO transcription factor Daf-16) which is normally encountered only in germ-line [11]. There is a substantial body of evidence showing that the rejuvenation process encountered in germ line erases the age-related damage that accumulates over the years. Three mechanisms have been suggested to account for the functional stability of the genome in germ line [7]:

1. A generally more efficient and increased rate of cellular repair and maintenance, as well as specific repair and rejuvenation mechanisms. It is known for example, that DNA repair systems including GG-NER (Global Genome Nucleotide Excision Repair) are specifically active in germ line cells and contribute towards the effective repair of the germ DNA, but these are also active in somatic cells [12]

2. Efficient selection of fully functional germ cells which are allowed to propagate at the expense of less efficient germ cells [13]. A relevant concept here is that of apoptosis regulation, which may also depend on neuronal inputs as will be discussed below

3. Non-autonomous contributions of the soma to germ line rejuvenation [14].

Such strategies may also be present in somatic cells, but are significantly down-regulated. The aim here is to examine the possibility that this rejuvenation process can be driven to operate effectively in somatic cells. It is important to highlight that certain mechanisms of germ line rejuvenation could be dependent upon epigenetic modifications and factors that regulate transcription. Thus it is also conceivable that careful epigenetic co-ordination may have certain rejuvenating effects upon somatic cells, as discussed in the previous chapter.

The above facts raise the possibility that somatic cells lines may, under certain circumstances, withhold any ‘immortality’ contributions for their own repair instead. This may happen when somatic cells are under powerful pressure to maintain themselves (following, for example, intense information inputs and challenges). Fontana [15] has suggested that when ‘good’ (i.e. immortality-affording) matching sequences are not present in the germ line genome, then these ‘good’ sequences are created in the somatic cell and subsequently migrate to the germ line through the bloodstream, a process he termed Germ Line Penetration. In this case, he suggests that transposition of genomic elements in somatic cells drives differentiation in germ cells that drive evolution. As a consequence, it can also be argued that this process can conceivably be arrested, with somatic cells retaining the immortality-affording sequences and using these for their own repairs, if this is beneficial to the overall evolutionary process.

Recent findings that neurons may influence germ line survival lends support to this line of thinking. Levi-Ferber et al. [16] have shown that neuronal stress induces apoptosis in the germ line. This process is mediated by the IRE-1 factor, an endoplasmic reticulum stress response sensor, which then activates p53 and initiates the apoptotic cascade in the germ line. Phosphorylated IRE-1 also activates tumour-necrosis factor (TNF)-receptor-associated factor 2 (TRAF2) which is another apoptosis-initiating factor [17]. Therefore, germ cells may die due to a stress response originating from the distantly-located neurons. The process of apoptosis depends on a large number of converging inputs but it is significant that there is an apparent conflict between neurons and germ cells. If this is confirmed to be the case, it will become a crucial supporting element and will help the entire thrust of the arguments promulgated in this book: **that cognitive stimulation, initiates stress**

response in neurons which then may effect apoptosis of (or other damage in) germ line cells thus ensuring their own continual survival and function, changing the current patterns of human biological evolution (Figure 1).

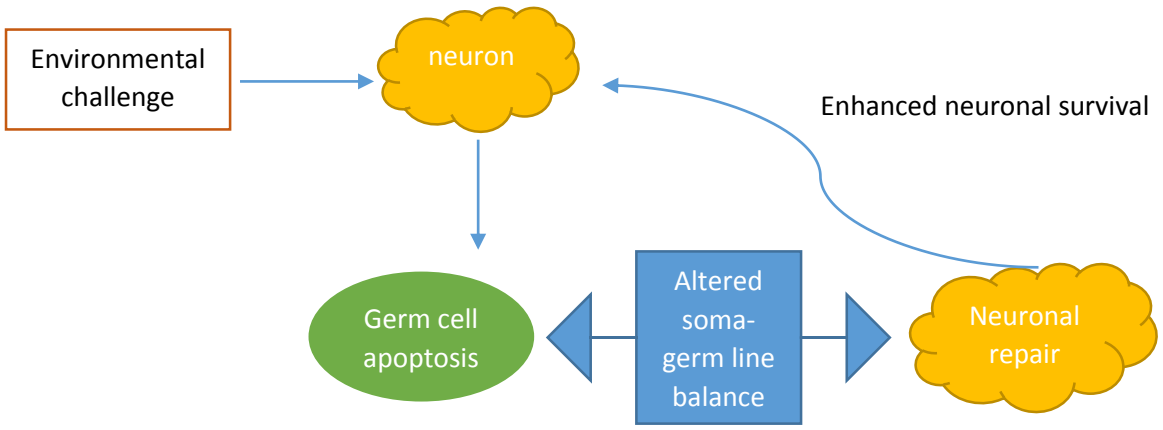

Figure 1. How information ensures neuronal survival. Environmental factors such as sharing meaningful information-that-requires-action, impact positively on the neuron, which may initiate germ cell apoptosis and change the balance between germ line– somatic repair resource allocations. The result is that neurons are better maintained and continue to survive in tandem with diminished germ cell survival. The energetic balance is maintained and the compliance with the second law of thermodynamics remains intact.

On the opposite side of the coin, it was recently shown that germ line cells 'fight back' and increase degeneration of the neurons. Initially, researchers Wu et al. [18] were studying the effects of pathogen infection upon the initiation of neuronal degeneration in C.elegans. Their hypothesis was that the immune response following infection results in neurodegeneration. But they also found that germ line loss resulted in resistance to neurodegeneration following infection. In other words, germ line factors facilitate degeneration of the neurons, and when these germ line factors are lost, then neural degeneration decreases. These effects are mediated by the maternal sterile gene *mes-1* which encodes a receptor protein that is needed for the essential (from the germ line point of view) unequal cell division in embryonic germ line stem cells. This division is required in order for gamete selection, to segregate mutation-carrying material and eliminate it so that it will not interfere with the future health of the germ line cells. In their research, they found that the gene *pgl-1* which is required for healthy germ line cell development, was also affected.

The significance of these findings is staggering. It is as if neurons are targeting the germ line and aim to damage it (through apoptosis and the IRE-1 example mentioned above), but the germ line deploys countermeasures targeting neurons and aims to destroy **them**. Are we witnessing a kind of war of trade-offs between the germ line and the neurons? It is tempting to answer 'yes', although these are results that need confirming. This speculation is intriguing and, if true, it may prove a crucial

mechanism which we may try to manipulate - I posit that we can indeed manipulate it through information that causes neuronal up-regulation. The results of this manipulation could be the rebalancing of trade-offs between soma and germ line (and thus the reduction of age-related dysfunction).

Soma-to-germ line communication

As a general principle, it can be assumed that exposure to an information-rich environment results in an increase in the information content of the individual. This information impacts on (and may influence) biological processes as discussed above. It is known that one of the ways information can be transmitted from the environment to the genome (and, reciprocally, from the genome to the phenotype and thus back to the environment) is through microRNAs. This has been discussed in the previous chapter and will be discussed again here.

Any suitable environmental challenge can cause epigenetic effects which can influence inheritance of certain features through microRNA mediation. This characteristic is encountered in plants, worms and also mammals [19]. The study of "transgenerational systems biology" is concerned with identifying elements involved in heritable epigenetic changes, and it can also provide us with valuable clues about the behaviour and properties of information transfer between the soma and the germ line [20]. However, the suggestion that there is transfer of heritable information from soma to germ line is against conventional and established knowledge, confounded by the fact that epigenetic memory needs to be maintained throughout the process. Nevertheless, research is now providing answers to these conundrums. Sharma ([21] has shown that new evidence now supports the transfer of heritable epigenetic information from soma to germ line and highlights the role of microRNAs and exosome during this process.

Several epigenetic factors have been implicated in germ line transmission of information, and, although some details are discussed below, the full details regarding the mediators of this information transfer from soma to the germ line are still poorly understood. Germ cells are resistant to age-related degeneration, but the exact mechanisms of this resistance are not yet fully known. What is known is that one germ line-specific mechanisms depends on microRNAs and PIWI (P-element Induced WImpy testis) proteins that regulate the function of transposons, resulting in an efficient repair of germ line damage [22]. Therefore, extracellular microRNAs (miRNAs) are involved in this epigenetic inheritance in mammals [23]. With regards to the role of PIWIs in germ line immortality, there is a balance between transposon action (which inhibits germ line cell differentiation) and PIWI action which silences the expression of genetic elements, maintaining an optimal function of the germ cell [24]. MicroRNAs are regulated by other non-coding RNAs such as the intergenic RNA. An imbalance of this regulation can lead to disease and dysfunction [25]. This helps us examine and understand better the overall function and value of microRNAs.

As mentioned above, it increasingly appears more likely that non-coding RNAs may mediate transfer of information from somatic cells to germ cells. Further evidence suggests that exosomal microRNAs and exosomal proteins may also mediate information transfer from soma to germ line [23]. This is important because it suggests that environmental factors can induce epigenetic alterations and alter the information transfer from soma to germ line, with results which can be experienced not only in individual organisms but can also be felt through generations. Siblings produced from young or ageing parents have similar lifespans, and this further highlights the fact that germ line cells are

resistant to age-related degeneration. Of course, there are many other factors that afford fidelity of information transfer in germ cells.

Apart from microRNAs there are certain other mechanisms involved in soma to germ line cross-talk. Certain interventions which downgrade reproduction may also cause a lifespan extension. Ablation of germ cells in C. elegans leads to an increased lifespans which shows that signals from the germ line have a direct impact upon somatic cell survival, and this may be due to an increased resistance of somatic cells to stress [11]. One mechanism involves the FOXO-family transcription factors (such as Daf-16) in somatic tissues, which are up-regulated following signals from damaged germ line cells [26]. Daf-16 then regulates downstream genes which are involved in somatic life-span extension. Additional loss of germ line cells, increases further the already long lifespan of somatic cells [26].

Intracellular clearance systems are also up-regulated following signals from the germ line [27]. This is significant because it indicates that germ cells have direct control over the health and longevity of somatic cells. In addition to this, protein homoeostasis in somatic cells is well-maintained when germ cells are damaged and it is significantly downgraded when germ cell function increases [28]. There exist mechanisms in germ cells which may induce somatic cell reprogramming and somatic stem cell pluripotency [29, 30]. Kim et al. [31] have shown that when male sticklebacks experience a benign and safe environment:

> "*…subsequently reduced their investment in carotenoid-based sexual signals early in the breeding season, and consequently* ***senesced at a slower rate*** *later in the season, compared to those that had developed under harsher conditions. This plasticity of ageing was genetically determined. Both antagonistic pleiotropy and genetic variation in the rate of senescence were evident only in the individuals raised in the harsher environment"* (emphasis mine).

This confirms that a benign environment delays ageing and reproduction, along the r-K selection model. The more safe and benign (but still positively challenging) the environment is, the more likely it is that ageing need not take place, as resources are no longer preferentially diverted to the germ line - there is no need, as the organism has reduced chances of early death. This and many other examples show that mechanisms for soma-to-germ line reallocation of resources exist in nature, are likely to be widespread (in insects, higher animals etc.), and can be made to operate by manipulating the environment to make it less dangerous albeit still mildly challenging.

To put it simply, these findings suggest once more that, on the whole, when germ cells are healthy, somatic repair decreases, and when germ cells are stressed, somatic repair improves (Figure 2). This process depends on clues and factors from the environment, which reflect how likely it is that the individual organism will survive in that specific environment. Dangerous environments shift the emphasis of resource allocation to the germ line, whereas safe environments reverse this trend to allow for better somatic repair, and thus increased longevity. The process is made possible by the existence of cross-talk pathways and mechanisms between the two parties involved, a process reminiscent of the importance of having dialogue channels open in the political realm when there is the possibility of conflict [32].

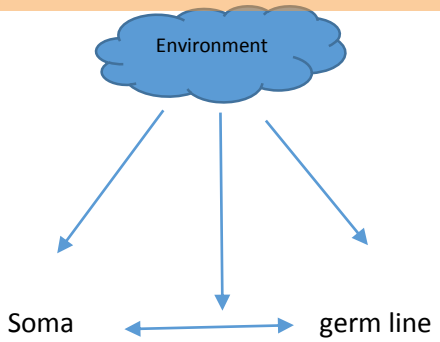

Figure 2. A simplified diagram showing the impact of environmental challenges. In this diagram there is cross-talk between soma and germline which, at present favours the germline with increased repair resources, but can, conceivably, be reversed.

The 'Indispensable Soma Hypothesis'

As mentioned above, evidence is gathering, suggesting that that the disposable soma theory of ageing is not unidirectional and the soma may not, after all, be always 'disposable' [10]. Under certain conditions of evolutionary necessities there could be increased somatic maintenance at the expense of germ cells. This, translated into clinical terms, may mean that the soma (as defined in Box 1) experiences continual repair and lives without any significant age-related chronic degeneration. I have suggested [33] that some of these evolutionary pressures could be dependent upon how well one makes themselves 'indispensable' within the global techno-cultural environment, through intense (but hormetic) sharing of information, which has an impact on somatic neurons which, then, diminish the evolutionary importance of germ line cells (Figure 3).

Figure 3. Challenging information results in damaged germ line cells. Environmental high-quality information which creates a tendency for action, up-regulates human neurons, which generate IRE-1 (among many others) which results in cell line cell apoptosis, an event which subsequently releases signals to upgrade the repair of somatic cells.

Ermolaeva et al. [34] present research which seems to support this view. Their report raises the possibility that DNA damage in germ cells may protect somatic cells. They suggested that DNA damage in **germ cells** can up-regulate stress resistance pathways in **somatic cells** and improve stress

response to heat or oxidation. This is profoundly important because it shows that, in principle, when germ cells are damaged, they initiate a cascade of events and produce agents which can then protect somatic cells against systemic stress. It can be deducted that this can be a possible mechanism for the phase transition discussed in other chapters, because it provides the conceptual basis for the altered biological mechanisms. One somatic stress protection mechanism originating from germ cells is mediated through the MAP (mitogen activated protein)-kinase homologue MPK-1 in germ cells. This triggers other agents which are hitherto poorly described, to up regulate elements of the Ubiquitin-Proteasome system in somatic cells. As a result, there is increase resistance to stress in somatic tissues. This mechanism may reflect an innate tendency to reverse the trade-off between germ cell and somatic cell repair: when the germ cells are compromised, there is delay in offspring production matched by an increased repair of somatic cells [34].

Another possible biological mechanism involved in immortalisation has been described by De Vaux et al. [35]. They confirm that the Mi2 protein (a nucleosome-remodelling protein) causes repression of transcription and is involved in the repair of germ line DNA. They also suggest that a Mi2 homolog in C.elegans called LET-418/Mi2 is one main factor which drives development and reproduction in early life and then causes dysfunction in later life. Inactivation of LET-418/Mi2 can result in increased resistance to stress and enhanced longevity, therefore it can regulate lifespan. The authors suggest that this agent is involved in germ cell apoptosis. This provides a biological basis for a possible mechanism which could be potentially subjected to modulation, in order to produce life-span prolongation. It also confirms the general concept that germ line dysfunction results in somatic lifespan extension as a counter effect.

In summary then, and in simple terms:

1. Healthy germ cells tend to divert resources away from somatic tissues, in order to improve their own survival

2. Challenged or 'positively-stressed' somatic neurons initiate injury and apoptosis in germ cells

3. Damaged germ cells may produce agents which protect somatic tissues.

This makes perfect evolutionary sense: If germ line cells are damaged (and thus the survival of the species is at risk), then an effective alternative would be to achieve survival through a longer and more efficient somatic repair. From the point of view of evolution, if the species cannot survive, then at least the individual bodies should. In fact, this is the original plan embedded in natural laws. Research in this area is slowly unravelling the different mechanisms involved. Overall, it seems plausible, though speculative, that by acting in a way that increases one's value in the global landscape (and this may be achieved via continual, hormetic exposure to information and challenges), one is subjected to biological and evolutionary mechanisms which increase one's survival. This is the **'indispensable soma hypothesis'**: a soma which makes itself indispensable by acting positively within the general process of successful adaptation, may experience a reversal of the effects that govern the disposable soma theory, and thus live longer. In reality, the most likely agent able to achieve such a scenario is the human neuron and its supporting tissues, i.e. entire non-reproducing techno-culturally aligned humans [36].

The role of transposable elements in soma to germ line communication

Let me examine some further details regarding the possible operation of these mechanisms. One fruitful and promising area of research in this respect, is the study of transposable elements.

Transposable elements, or transposons, are DNA sequences which may migrate and take new positions within the genome. This may result in new functions or new malfunctions, for example due to the creation of mutations or due to reversal of the effects of existing mutations (Figure 4)

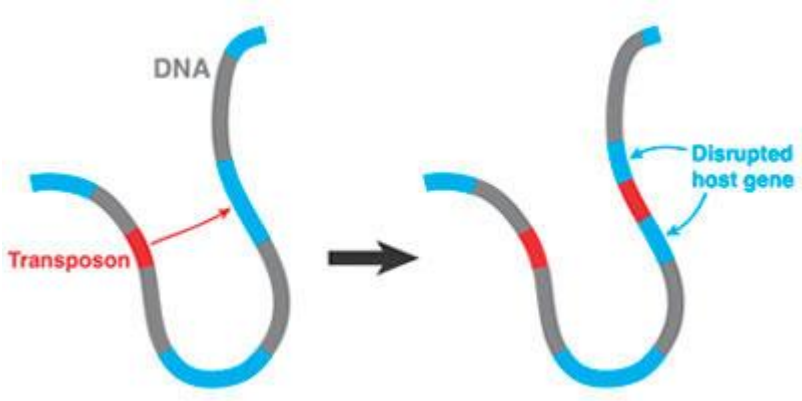

Figure 4. The transposition of a genetic element within the genome. Transposons can replicate and then insert themselves randomly throughout the genome. This can cause mutations which can be negative, neutral or positive, depending of the function being studied (Illustration by Phillip Dumesic, UCSF. https://www.ucsf.edu/news/2013/02/13535/gene-invaders-are-stymied-cells-genome-defense)

Regarding one possible epigenetically-based mechanism of immortalisation, Smelick and Ahmed [7] quote:

> *"Maintenance of epigenetic silencing of repetitive elements such as transposons is another critical feature of the programming process that is essential for genome stability. Carefully co-ordinated epigenetic silencing and reprogramming could, therefore, constitute a chromatin maintenance mechanism that contributes to germline immortality"*

This implies that is such a mechanism exists it could in principle be applied on somatic cells if it is required by evolutionary necessities. The role of transposons in germ line immortality has been examined by Fontana who introduced the concept of Epigenetic Tracking as mentioned above [15]. This is an evolutionary method of generating complexity. He suggests that transposition in somatic cells drive cellular differentiation and development, and transposition in germ cells facilitates evolution. This implies that regulation of transposons both in soma and germ line may result in effective damage repair and improvement of function. I posit that positive regulation in somatic transposons may be achieved through the mechanisms that regulate the assimilation of novel information by the cell. We know that transposon expression is responsive to challenging ambient stimulants, and that cells undergoing hormetic stress may trigger transposon activity. Transposons act both locally and globally through microRNAs, and in this way behave as regulators of the stress response [37]. It is also known that genetic manipulation using transposons, such as the sleeping beauty (SB) transposon [38] is a useful approach in the study of mutagenesis and genetic behaviour,

both in the soma and in the germ line. It is possible, though speculative, that fractions of ancient genomes that accumulated specific mutations, (but that were able to repair somatic damage) exhibited the phenomenon of 'stochastic loss' whereby active transposons may have completely disappeared from the genome. However, this loss has no significance in the germ line because horizontal transfer is capable of rescuing any active transposons which start exhibiting stochastic loss. As a result, the genome of somatic cells became progressively less stable, whereas the genome of germ line cells remained active and fully functioning. This is a useful concept which indicates, once again, a clear genomic dichotomy between soma and germ line, a dichotomy which lends itself to manipulation and possible reversal. As the SB transposon forms part of the Tc1/mariner superfamily [39], members of which are very widespread in nature, there is no reason to believe that its actions are rare or bear no significance in the case we are examining (i.e. in human somatic maintenance). Therefore, transposons including the well-studied SB transposon may be a fruitful area of research which can elucidate senescence-reversing mechanisms. According to Ivics et al. [38]:

> *Protecting the genome from transposable element (TE) mobilization is critical for germline development. In Drosophila, Piwi proteins and their bound small RNAs (piRNAs) provide a potent defense against TE activity. TE targeting piRNAs are processed from TE-dense heterochromatic loci termed piRNA clusters. Although piRNA biogenesis from cluster precursors is beginning to be understood, little is known about piRNA cluster transcriptional regulation. Here, we show that deposition of histone 3 lysine 9 by the methyltransferase dSETDB1 (egg) is required for piRNA cluster transcription. In the absence of dSETDB1, cluster precursor transcription collapses in germline and somatic gonadal cells and TEs are activated, resulting in germline loss and a block in germline stem cell differentiation. We propose that heterochromatin protects the germline by activating the piRNA pathway.*

This highlights some further details regarding the role of transposons and microRNAs in germ line-somatic cross-talk. Suppressing transposon activity hinders germ line development and this may then incite germ cells to produce somatic-protecting factors as discussed above. Karnaukhov and Karnaukhova [40] have examined two processes leading to germ line immortality, through correction of genomic errors. They quote:

> *In 2009 we proposed a solution for the problem of "escaping germ line from aging" within the framework of a wide range of hypotheses based on the aging notion as a process of accumulation of genomic errors…. It has been found that the mechanism providing "correction" of genomic errors in germ line cells involves two elements which are well known and common practically for all eukaryotic organisms: Gene recombination (crossing over)* …(and gamete selection*). It is well known that as a result of gene recombination (crossing over) in cells of germ line the haploid daughter cells-precursors are replicated. These haploid daughter cells (gametes) contain 1/2 of the genetic information of next generation organism. Need to note here, that the density of gamete's genomic errors differ from the density of genomic errors in germ line cells of maternal organism. Indeed, the stochastic nature of the location of genomic errors and the stochastic nature of gene recombination (crossover) leads to the random distribution of errors between gamete's genomes. And it is important that the density of the genomic errors in some of them is lower than in the cells of germ line of maternal organism…. The given mechanism of "correction" of the genomic errors is the process of selection of precursor cells (gametes) with minimal error density. This becomes possible of an excessive number of gametes. Moreover, the haploidy of such cells raises the efficiency selection inasmuch as it elevates the specific contribution of every error into the overall reduction of gamete functionality. Although each element of this mechanism (gene*

recombination + gamete selection) was in itself well known and studied, the conclusion that the reduction of the density of genomic errors comes out from their joint action, was an priority of our previous works. This solution of the paradox of the "not aging germ line " rehabilitates a wide range of aging hypotheses united by the idea of degradation of the genetic information by aging.

Their comment is a useful reminder of some mechanisms of genomic error correction in the germ line. In this case, the correction of errors is due to a combined action of gene recombination and gamete selection, both of which could also be made to operate in somatic cells. Of course, the element of speculation here is considerable, although not impossible. We know (or, at least, we can infer) that such mechanisms may be subjected to exaptation which can produce functions that were not present originally [for example 41]. Exaptation (the shift in the function of a trait during evolution, when a trait is co-opted for a different function than the original) may underlie some mechanisms which are involved in homoeostasis but it may also operate within the scenario presented in this book, which is the re-allocation of resources from germ line to soma. Those mechanisms originally developed in order to facilitate resource flow from soma to germ line (such as gene recombination and gamete selection), may (under certain circumstances, such as those discussed above) be exapted and operate in the opposite way: shift the balance of repair from germ line to soma [42]. This may not be a very long process, as it operates through epigenetic mechanisms some of which involve fast microRNA regulation [43].

Conclusion

This discussion builds on the previous analysis of the effects of hormesis and environmental enrichment, as it concentrates specifically upon the genetic effects of such stimulation. We may now be able to better appreciate that:

a. there is a bidirectional cross-talk between soma and germ line, and

b. factors and mechanisms which mediate (or can modify) the dynamics of this cross-talk are being increasingly elucidated.

Environmental factors may directly or indirectly influence epigenetic networks and ultimately influence chromatin and histone modifications resulting in altered protein expression. This research helps us conceive a facilitating mechanism where environmental information (via appropriate challenges) may affect germ line function, and provides a medium whereby we could potentially intervene and influence this function (ultimately aiming to redirect repair resources from germ line to soma). I reiterate here that the term 'somatic cell' referred to in this discussion is more likely to be primarily a neuron, and secondarily all cells that support the neuron's survival (i.e. essentially, a human organism surrounding a human brain). Although the mechanisms involved in this hypothesis need further elucidation, and the speculative inferences need further grounding, it may be possible to commence suggesting biologically-founded mechanisms which may underpin our earlier speculations: that the environment via epigenetic factors such as microRNA and transposons, can influence the balance between somatic vs germ cell immortalisation, resulting in improved somatic repair, a reduction of age-related degeneration, and thus increased human lifespan.

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