Journal of Cancer Research & Therapy

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Anderson KM et al., J Cancer Res Ther 2015, 3(9):105-111
http://dx.doi.org/10.14312/2052-4994.2015-15

Review

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Contributions of stochastic events to biological evolution and cancer

Anderson KM[1,*], Rubenstein M[1], Guinan P[2,3] and Patel MK[3,4]

[1] Hektoen Research Institute, 627 S Wood Street, Chicago, IL 60612, USA
[2] Department of Urology, University of Illinois, Chicago, IL, 60612, USA
[3] College of Nursing, University of Illinois, Chicago, IL, 60612, USA
[4] Bel-Air College of Nursing, Panchgani, India

Abstract

Stochastic genetic and epigenetic events have been fundamental in contributing to the development of manifold life-forms, past and present. The development of malignant cell clones and the role of stochasticity as a driving force in cancer cell evolution complements, in a perverse way evidence for the role of chance in normal cellular development and evolution. Stochastic events at multiple levels of cellular control and implementation represent a primary driving force and an ultimate filter through which evolutionary innovation occurs. Stochasticity provides the opportunity for a random assortment of disparate genetic and epigenetic events, in some instances resulting in altered metabolic and developmental capabilities of sufficient stability and uniqueness to contribute to deterministic sequelae that promote the viability and procreation of cells under stress. Cellular evolution has so far resulted in a "survival of a (sic) fittest", often dependent mechanistically on and determined by stochastic events. The implications of this are mirrored in the evolution of malignant change, to some extent as a variant of "reverse engineering" of dedifferentiation. Efforts to reduce the incidence of malignant change will have to take in to account its random nature and further the understanding of this feature.

Keywords: stochastic events; biological evolution; cancer prime movers; epigenetic events; malignant cell clones

Introduction

In a recent report it was suggested that the risk of cancer affecting various tissues was a function of their number of stem cell divisions [1]. Basically it was a correlative study relating an estimated number of stem cell divisions in tissues of interest over a subjects' lifetime to the variation in incidence of cancer in these tissues. The authors concluded that excluding inherited and environmentally-induced cancers, the risk of experiencing DNA mutations conducive to malignant change in these cancers was related to the number of stem cell divisions over a lifetime.

A backlash of criticism of the paper and its' reporting was said to have resulted [2, 3]. Criticisms included, among others, over simplification and the omission of breast and prostate cancers, due however to insufficient data and the generation of undue pessimism regarding attempts to avoid cancer. Nevertheless, there is a great deal of evidence in support of the original thesis. For the generation of variant cells, especially those exhibiting major developmental, evolutionary or malignant change, stochastic (random) genetic and epigenetic mutations provide the major impetus for their creation [4-6]. Unless cells exposed to potentially lethal environmental or intrinsic genetic, metabolic or therapeutic stress circumvent them, their survival, individually and of the clone, or even the organism is at risk. Cells undergoing malignant change experience a series of mutations tending to ensure their continued proliferation and their increasing emancipation from normal cell- to- cell constraints.

Much of what follows is well known and has been championed by many [4-13]. Yet there seems to be a widespread reluctance to accept the role of chance at essentially every level of life, as all members of the biosphere experience it. For this, among other reasons, there can be some value in a brief overview of selected elements related to the proposed thesis [1]. We review some biological implications of "randomness", especially as it affects evolving cancer cells and its impact on cellular evolution, at least as far as we understand it. No extensive literature review is intended but a selection from the

***Corresponding author:** Dr. Ken Anderson, Hektoen Institute, 627 S Wood Street, Chicago, IL 60612, USA. Tel.: 1-312-996-7930; Email: Kanderso427@sbcglobal.net

Received 8 July 2015 *Revised* 11 September 2015 *Accepted* 21 September 2015 *Published* 29 September 2015

Citation: Anderson KM, Rubenstein M, Guinan P, Patel MK. Contributions of stochastic events to biological evolution and cancer. J Cancer Res Ther. 2015; 3(9):105-111. DOI:10.14312/2052-4994.2015-15

references available to us is provided. Table 1 presents an outline of the topics discussed. First, some comments about determinism and randomness.

Table 1 Topics considered in this paper.

1.	Are many if not a majority of cancers the result of stochastic events over which we have little, if any control?
2.	Determinism, stochasticity and randomness and their relation to extrinsic and intrinsic noise.
3.	The intersection of stochastic events and cellular elements; housekeeping, tactical and strategic levels of randomness.
4.	Stochasticity and the law of large numbers applied to biological events.
5.	Evidence for the role of random events in the developmental histories of non-malignant and malignant (cancer) cells and the "modern synthesis" of randomness in evolutionary theory of the 1940s.
6.	Summary, conclusions and comments.

Determinism, randomness and stochasticity

Deterministic programs and events are considered to be predictable provided sufficient understanding of their underlying mechanism is available. In contrast, stochastic events and processes do not have identified, mechanistic properties and are thought by many to be entirely random or "free" [14]. Some see a distinction between several forms of randomness, seemingly dependent upon context [15]. Randomness represents incomplete knowledge, inaccessible due to the inability to identify uncontrolled causes. A chaotic system (deterministic chaos) can have predictable properties although they can be difficult or even impossible to identify [15]. Stochastic circuits have been developed that produce fairly reproducible behavior [16]. The relative probability of an event need not be the absolute single defining feature, and rare events can be deterministic. A stochastic event may have some overall, but unknown probability, dependent upon the prior "state" of the system, contingent on its history. Certainly, "random" biologic events depend upon unknown features whose mechanisms have not been identified. However, as an approximation, and keeping exceptions in mind, it seems useful mentally to distribute most deterministic, stochastic, and random events along some sort of probability X-axis. Distinguishing deterministic events dependent upon potentially identifiable causes from multiple events due to a common cause is usually achieved by the use of controls.

Internal and external noise and stochasticity

In studies with E. coli [17] and subsequently by others with mammalian cells [18], extrinsic noise was defined as an event that identically affects two genes that include copies of the same promotor, one driving the expression of a cyan-fluorescent protein and the other yellow-fluorescence promotor [17]. Intrinsic noise due to randomness in transcription or translation was considered to affect only one of the promotors. Extrinsic noise was ascribed to variations in the numbers of polymerases, mRNAs or ribosomes affected and variability in rate constants related to these events. Both forms of noise were thought to be influenced by random thermal fluctuations.

A study of single cell RNA sequences in 430 cells from five primary glioblastomas demonstrated they varied in the expression of oncogenic signaling, proliferation, immune response and hypoxia [18]. There was a continuum of stemness-related expression states and glioblastoma subtypes were expressed across individual cells within a tumor, all evidence of intra-tumoral heterogeneity. In higher eukaryotes it was found that episodic protein and especially mRNA expression is a major contributor to cell to cell differences [19].

Chromatin modeling is a primary intrinsic contributor to individual cellular behavior [20, 21]. The distribution between eu and heterochromatin and the epigenomic transitions providing access to or suppression of genomic sites is under complex regulation. A technique that allows a form of single cell profiling with the use of a combinatorial cellular indexing applied to 15,000 cells demonstrated different coordinated chromatin in single cells between and among different cell type chromatin accessibility landscapes [22]. The ability to measure fluorescent protein synthesis, mRNA, exome and whole genome DNA and RNA sequences, eventually in single cells, has been instrumental in studies of cellular noise.

The relation between intrinsic or extrinsic noise and stochastic cellular events has been studied. Some authorities relate intrinsic and extrinsic noise with a potential occurrence of stochastic events [23]. Others identify "gene intrinsic noise" as molecular-level noise associated with gene expression [24]. Still others focus on the effect of noise on genes regulated at a system network level [25]. Multiple interactions between hierarchical (stem cell-related) and stochastic (somatic cell-related) noise are envisioned [26].

When 414 essential yeast genes were replaced by human orthologs, 47 percent of the human genes replaced their yeast orthologs [27]. Interestingly, initiation of DNA synthesis was not replaceable while sterol biosynthesis was. Similar gene modules tended to be replaceable and this did not require marked similarity in sequence.

Stochastic events without an identified "cause" and thus considered as "random", seem really to be conditionally random, associated with properties unique to the system considered. Their identification requires procedures to detect and distinguish them from deterministic noise. A stochastic event depending upon noise appears as a singular event(s) that presumably persists, coupled with and able to alter the metabolic, regulatory and developmental history of the affected cell and its' progeny. Presumably most random thermal noise does not achieve levels of intensity and persistence of stochastic noise able to alter the programming of differentiation, the metabolism, genotype and phenotype of the affected cells.

The intersection of stochastic events and cellular elements

A variety of factors have been implicated in the suppression [28] or accentuation of intrinsic noise [29]. Presumably these outcomes can vary from frequent minor incremental adjustments to less frequent, persistent alterations. Some may lead to changes in developmental history, including

very rare but fundamentally radical changes in cellular genotype and phenotype, with altered cell differentiation leading to basic changes in body plan and the creation of new species. Oncogenesis has been viewed as a re-ordering of cellular differentiation, either hierarchically via randomly aberrant stem cell development or stochastically with retrogression and adoption or reactivation by differentiated cells of evolutionarily much older functions embedded in the genome that may have been transiently active but have been suppressed.

It is tempting to suggest several gradations of stochastic events contributing to distinct if overlapping outcomes (Table 2). Stochastic Level I events could include effects on housekeeping events: reproduction, differentiation and cellular aging, according to well-established, ancient, previously implanted developmental programs. Level II random events could be viewed as having the effect of "Tactical" stochastic events that include responses to more complex stresses; Level III random events could be represented by very rare Strategic stochastic singularities involving genetic and epigenetic elements affecting fundamentally important metabolic or developmental networks and interactions. Those would result in major, even radical developmental modifications, presumably requiring persistent activation energies supporting more complex and extensive molecular interaction, many of them having been associated with very ancient evolutionary events. Their probability of occurrence was and is much less than events in the first two categories.

Table 2 Suggested distinction between hierarchical levels of randomness: Housekeeping, tactical and strategic levels.

Housekeeping (level 1) functions affected by random events. These might be considered random events that affect basic cell functions involved in the functioning of differentiated cells. A random up-regulation of an enzyme involved in drug efflux or others involved in DNA repair or replication could serve as representative examples. Individual enzymes or regulatory molecules and signal transduction or gene modules could represent interaction partners.
Tactical (level 2) random events viewed as responses affecting signal transduction, DNA synthesis and diverse regulatory pathways potentially responsive to stress. Mutations of oncogenes, suppressor and progressor genes, epigenetic modifications and components of cellular control and differentiation represent examples of entities exposed to unavoidable risks in living cells. Cell nodes and synthetic or regulatory modules represent higher order targets potentially exposed to stochastic modification.
Strategic (level 3) random events involving extensive reorganization of a genome due to widespread disruption of the then contemporary modes replication and differentiation. Examples could include speciation, the development of antero-posterior segmentation, dorsal ventral differentiation, bilaterality, formation of the head, etc. Some of these much more rare complex random developmental events may initially have only occurred once in the affected organism and subsequently evolved further.
These categories could blend to some extent, depending upon the combinatorial possibilities randomly presented by a form of stochastic optimization. Complex, higher order random events seem less probable than housekeeping and tactical stochastic events.

One can imagine an increasing complexity of response as the levels are ascended, culminating in major duplications in regions of, if not whole genomes [7, 8, 12, 13, 30]. This would provide an enormous increase in the potential genetic recombination and sites for further genetic change over geologic time. Duplicated genes in which one is free to diverge from the other, termed paralogues, are present in the HOX, globin and collagen gene families. Random events associated with malignant change would seem likely to affect more limited changes occurring in the first two proposed categories. Altering behavior of one or more of the 12 identified developmental signal transduction pathways [31], modifying the readout of RNA or protein elements associated with control of developmental programs, or inter-cellular interactions able to alter cellular behavior and promote cellular survival could be included among these more limited transitions.

These suggested categories need not be rigidly compartmentalized and important effects might originate in any of them, depending upon context. There is evidence that many, probably most stochastic events are usually null while others constitute "passenger" events without significant effects on cell viability or proliferation [32, 33]. Some would be deleterious [4–6]; certain inborn errors of metabolism or structure and fossil evidence of extinct species also inhabit that category. For an affected clone, oncologic dedifferentiation represents a release from the constraints of differentiation; for the host a potential threat to its survival.

An accumulation of prior stochastic events could include some that are activated in response to subsequent environmental or other stress. Some Level 1 events might only involve an increase in the activity of an enzyme, for example concerned with extruding a chemotherapeutic agent from the cell. Level II responses to more serious stress might involve development of additional controlling, implementing or suppressive events, modifying or supplementing resident deterministic capabilities. Finally, the probability of rare Level III events involved in more widespread genomic reorganization may be restricted by more stringent thermal energy requirements or a requirement for the development of new metabolic and developmental pathways, among other factors.

Duplication and mutation of HOX and other genes with the gradual institution (over evolutionary time) of bi-laterality, antero-posterior segmentation, dorsal-ventral differentiation and formation of the head [5, 7, 8, 12, 13, 30] are striking examples of what are considered to have been fundamentally random evolutionary events related to extensive gene duplication and subsequent widespread genomic modification. These should characterize the more complex and extensive changes in Level 3. As judged from fossil evidence [34], many ultimately unsuccessful attempts by multicellular organisms and their stressed cells to promote cell, clonal and organismal survival have occurred. Lack of effective deterministic and stochastic responses to cellular stresses or activation of deleterious responses should consign stressed cells and organisms unable to circumvent environmental or other challenges to extinction. It has been demonstrated that actively replicating cells [35] experience more random mutations than quiescent cells. Random events of this sort presumably were related to extensive gene duplications

in the past, leading to development of HOX and other duplicated genes [7, 8, 12, 30]. The susceptibility to "errors" occurring during DNA synthesis and cellular replication is well established [36].

These errors represent the physical basis for random changes in the genome and its expression. The more widespread the changes, the greater the probability of an underlying extensive genetic and consequent phenotypic result. In the case of HOX gene duplication, the argument is that at some time in the distant past, extensive duplications of regions of an ancient genome gave rise to phenotypic changes including body segmentation, this in part due to mutation over time of paralogues [7, 8, 12, 30].

The argument that stochasticism is an ultimate driving force of cellular evolution, operating for some by a Monte Carlo random assortive combination of genetic and epigenetic events has been advanced by many with interest in this area [5, 10, 11, 13, 39-43]. The modern synthesis of developmental biology which developed during the 1940s grounded the diversity of a population in the random appearance of mutations [7]. Major developmental events involve more radical alterations in the genome, for this discussion designated level 3 strategic modifications through which major future evolutionary developments have to pass (Table 2). Lesser genetic and epigenetic adjustments (levels 1 and 2), perhaps more likely implicated in the more restricted developmental responses of malignant cells, may not possess sufficiently complex combinatorial options to underwrite radical departures in developmental programming. As the level of random events and their complexity increases it seems likely that a greater number of other molecular partners may be required for their implementation. These considerations also seem relevant for stochastic events in non-malignant cells. In all these situations, a stochastic trial and error, a form of "stochastic optimization" [44] provides the arbitration of chance as it operates in a biological environment to promote, leave unaffected or impair the survival and reproductive "fitness" of the subject organism under stress. Paradoxically, the successful outcome of stochastic alterations on the genome ultimately depends upon the deterministic implementation of those events. Combinations and re-assortments that contribute to a survival of a fittest endure; the other outcomes consign stressed cells either to stasis or oblivion.

As regards random events potentially affecting nascent cancer cells, stochastic alterations including increase, decrease or absence of function of potential targets could include participants from among the 120-plus identified oncogenes, suppressor genes gene/ enzyme/ protein/ protein/ DNA/ RNA (mRNA, sRNA and untranslated micro and other RNAs), lipid moieties, operators, repressors, co-repressors, enhancers and related entities, signal transduction processes as they may comingle in various configurations [31], the nodes, modules and cassettes contributing to the hubs and kernels of networks central to programming of cellular replication, differentiation, quiescence and death.

Stochasticity and the law of large numbers applied to biological events

It may seem odd that random genomic events can lead to populations of cells exhibiting deterministic outcomes affecting their survival. If affected cells initially are few in number, stochastic effects can be disproportionately influential. Although the final composition of a small population of replicating cells is uncertain due to genetic drift, the change in the frequency of a gene variant in a population due to random sampling [37], were proliferation of one clone sufficiently robust to outgrow their unaffected companions, it could eventually become the dominant clonal representative.

The "law of large numbers", essentially the addition of small Gaussian uncertainties [15], is often invoked to reduce the effect of aberrant cells on a population's subsequent composition. Individual variations, some related to noise, are summed, in bulk, in a kind of mass-action averaging, the outcome however appearing as deterministic due to the large number of cells expressing behaviors close to some broad average. To employ a previous analogy [38], individual molecules of H_2O in a wave are distinctive in many ways, perhaps even somewhat chaotic, yet the wave eventually reaches the shore, a deterministic outcome. It does so due to an overall structure related to the relationships between the much larger numbers of more average molecules of water, a structure sufficient to dilute out effects of the lesser number of outliers, unless their effect or numbers were sufficiently disruptive to disturb the forces maintaining the behaviors of the much more numerous average molecules.

Evidence from the developmental histories of non-malignant and malignantly transformed cells

Many studies concerning stochastic gene expression during the development of hematopoietic stem cells, individual olfactory cells responding to specific olfactory stimuli, photoreceptors in drosophila, pleuripotent cephalic neural crest cells, immune cell differentiation and pleuripotent stem cells from many different organs undergoing apparently "random" selection of developmental decisions are reviewed by J-J Kupiec [13]. Mono-allelic expression in single cells of mouse preimplantation embryos of from 12 to 24 percent were observed that occurred randomly, and were dynamic in that they differed from cell to cell [45]. Cellular p53 regulation has been described with deterministic and stochastic modelling [46-48]. These and other examples strongly support the thesis that cell differentiation is influenced by stochastic processes subject to natural selection. A "deus ex machina" argument is not needed to account for biological evolution. However, complex subtleties can affect the topic, such as an appropriate definition of fitness [49].

A current view is that relatively stable developmental programs have evolved to generate similar, deeply embedded and generally reliable deterministic outcomes. In one comparison of epigenetic profiling of human, rhesus macaque and mouse CNS corticogenesis, promotors and enhancers were enriched in modules associated with human neuronal proliferation, migration and organization

[50]. These correlated programs were consistent with common regulatory mechanisms. The ability of HOX genes to regulate the number of digits in a mouse limb, described with a Turing reaction-diffusion mechanism, by progressively reducing Hoxa13 and Hoxd11-Hoxd13 genes from Gli-null background mice led to progressively more extensive polydactyly [51]. Other studies indicate a progressive central to peripheral development of the extremities, indicative of the deterministic progression of an evolutionarily successful "program" of development [52]. Deeply "embedded", evolutionarily ancient, conserved "programs" may be less subjected to random variation. Had they been transiently active but became functionally silent in heterochromatin, they still might be reactivated by an epigenetic mechanism.

In studies of differentiation, stochastic interventions do not seem to have characteristically intruded on basic housekeeping cell functions to distinguish the newly endowed cell clone from dissimilar ones. The overall consistency of successful human embryological development, estimated at about 70 percent of fertilized ova, does not speak for a common occurrence of major phenotypic intrusions by stochastic events in successful live births. These usually successful outcomes are highly deterministic, at least at the level of the phenotype, yet significant genomic differences between identical twins have been reported. While major programmatic themes of human development usually proceed along what appear to be phenotypically deterministic venues, excluding the occurrence of spontaneous abortions and various inborn or acquired developmental "errors", the extent to which such development is modified by stochastic events, normally with apparently limited overall effects on development, is less apparent. Disruptions in development due to activation of oncogenes or inaction of suppressor genes provide a window into which an estimate of a frequency with which deleterious effects of stochasticism on the host can occur [6, 53]. In a study of single SW480 cancer cells, single nucleotide and copy number variations especially affecting purine to pyrimidine exchanges in the former were observed [53]. From this it was possible to measure mutation rates of 44 candidate genes of this cancer cell line.

Literature concerning the development of cancer cells, whether via stem cells (a forward development stem cell theory) or retrogression of differentiated cells based on mutations of somatic cells, termed by some the "stochastic" theory, provides further evidence for the role of random genetic and epigenetic change in the dysdifferentiation of malignant cancer cells.

Individual cancers typically contain a number of genetically distinct clones related to the parental strain [54]. A recent study of potential somatic mutations in sunlight exposed eyelid epidermis demonstrates from two to six somatic mutations per megabase per cell with positively selected mutations in 18 to 32 percent of normal skin cells with about 140 driver mutations per square cm of skin [6]. Multiregion sequencing of primary renal carcinomas and their metastases found from 63 to 69 percent of all somatic mutations were not detected across every tumor region sampled [55]. In a study of primary and metastatic pancreatic cancer, somatic mutations were separated into founder and progressor mutations. The percentages detected within the tumors and between metastases to the liver and lung differed [56]. These developmental events were considered to have occurred over a period of up to 10 years. Blood cell proliferation was demonstrated to be affected randomly by stochastic events occurring during proliferation [57].

Many of the reported studies correlate the behavior of cancers studied with mathematical analyses consistent with the intrusion of random (unidentified) events. Metastatic human colon cancer is reported to contain clonally derived cancer cells which, when injected into mice initiated tumors resembling the original cancer [43]. Unique (stochastic) and clonal (hierarchical) chromosomal changes were present. Lung cancer metastases have been modelled using human autopsy data analyzed with a Makov chain Monte Carlo- based program yielding results consistent with a multidirectional stochastic process [58]. Mouse melanoma cells either develop melanin or not according to a stochastically derived program [59]. Based on such information, representative of many additional studies, the conclusion is that cancer cell development, while depending upon a strong component of retained determinism, is subject to the driver mutations of proto-oncogenes, proto-suppressor genes and progressor mutations, as may be randomly activated or suppressed, depending upon context. The argument that stochastic interventions are the ultimate permissive driving force of normal and pathologic (oncogenic) cellular evolution, operating by a sort of Monte Carlo random assortive, stochastic optimization, re- combination of genetic and epigenetic events has been advanced by many with interest in this subject [39-44]. A form of deterministic and stochastic back- and- forth, trial and error, subject to the arbitration of chance, to either promote or impair the survival and reproductive fitness of the subject organism is proposed. Only those combinations and re-assortments promoting these dual outcomes, facilitate survival of the (really a) fittest; other outcomes either consigned stressed cells to oblivion or to stasis. Efforts to identify the outcome of stochastic variation as it may interact within potential genetic partners in *C. elegans* have been presented [60]. But whether affected cells are related to deviant stem cells or derived from somatic cells by a form of dedifferentiation [61], a major role for chance is envisioned.

Summary and comments

To return to the original question: are many and possibly even a majority of cancers due to random developmental and differentiation-related errors, rendering them difficult if not impossible to circumvent? In the original formulation, the development of many cancers is believed due to the occurrence over a lifetime of random mutations in replicating stem cells [1]. In essence, M (total somatic mutations) = u (mutation rate) x D (# cell divisions). In a recent modification, $M = (u + u_e)$ (epigenetic changes) x D [62]. Since it is not clear how D, the number of cell divisions of a actively proliferating organ such as the colorectal system, can be manipulated, genetic and epigenetic

mutation rates significantly dependent upon stochastic events are the factors potentially available for attempts at modification.

The considerable evidence, some of which was alluded to, for the random occurrence genetic and epigenetic cell "events" underlying malignant change, associated especially with cellular replication in aging individuals, provides a strong argument for this formulation. Because stochastic events are believed to occur more often in actively proliferating cells, various leukemias would seem prime candidates to be more prevalent at all ages, due to the enormous generation of hematopoietic cells over a lifetime, more in accord with colorectal adenocarcinoma, but this does not seem to be the case. Perhaps these cells are an exception proving the rule, and hematopoietic cells, having undergone unique routes to their respective cellular fates somehow suppress the occurrence of many random events during proliferation.

The elements of the argument apply to mechanisms underlying biological evolution, as exemplified by the afore-mentioned modern synthesis in the developmental biology of the 1940s in which random mutations were considered to account for diversity in populations [7]. Chance evolutionary and developmental events occur at many levels, as in one example, determination of cell types in which a stochastic event in *C. elegans* causes increased production of one type of cell rather than another [7]. Major evolutionary events such as speciation seem to have required major genomic reorganization dependent upon extensive initial and subsequent stochastic interventions. Through a mechanism of sequential genetic refinement via what seems to be a form of stochastic optimization [44], members of the biosphere have developed to the extent we find them and ourselves. Applying this general argument to the to the evolution and mal-differentiation of malignant cells does not seem an unreasonable stretch; cells evolve successfully or not, associated with and at times because of stochastic interventions as they allow affected cells to respond to environmental and other stresses.

Presently we understand that DNA synthesis and cytokinesis are inherently more error-prone and as people age, increase the probability of malignant change with increasing cumulative numbers of cells that have proliferated. It does not appear that increased random mutation occurs in all actively metabolizing cells, at least as exemplified by hepatic and other active secretory cells with unexceptional rates of cancer and low rates of proliferation. An important first question is whether mechanisms to correct replicative errors are less error-prone in cells from younger, compared with those from more elderly individuals. This determination requires assays for estimating the numbers of apparently random genetic events in proliferating cells. If DNA repair processes do degrade with age, are there means of maintaining or augmenting the repair mechanisms of cells in both young and older individuals? Any significant reduction in cumulative mutation rate over a number of years might extend the time a clinically important cancer would have developed by sufficient additional years, ideally well after an individual died from natural causes. This represents a different set of questions for research, possibly eventually involving some form of genome-related attempt to reduce the rate of cellular aging, stabilize repetitive DNA, maintain the integrity of telomeres, reduce cellular oxidative stress and otherwise maintain or restore the internal environment of aging cells to that of an earlier state.

A review of available comparative studies of worldwide cancer incidence in diverse national and ethnic groups and of the subsequent cancer histories of immigrant groups to North America and Europe should provide insight into potentially beneficial dietary and other life-style practices, especially when correlated with assays for random mutations associated with cellular proliferation of target organs. Studies of parabiosed young and older animals suggests a role for growth differentiation factor 11, which declines with age, in reducing cardiac hypertrophy in the older animals [63], although this result has been challenged. Modifying the function of sirtuins [64] by resveratrol [65] or other agents and evidence of deterioration of heterochromatin with aging [66, 67] represent collateral studies related to the effects of aging that might have implications for the frequency of stochastic events in proliferating cells.

Conclusions

Benign stochastic responses in stressed cells have promoted clonal and species evolution to the present state. To be at risk from the possibility of malignant randomness, as all potentially are, need not necessarily mandate extreme pessimism.

Funding

We are funded by private donations.

Conflict of interest

The authors declare no conflict of interest

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