

[No] Need for Speed: Late-Onset Diseases as Evolution's Power Brakes

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Abstract

Degenerative disease and cancer are the top causes of death in middle and advanced age and it seems that this trend will continue, at least in the near future. Modern medicine has an impressive arsenal of methods and tools to detect monitor and control a wide variety of diseases and conditions, including diseases with onset in middle and advanced age. Nevertheless, they are very rarely completely cured. Why, despite all the efforts of research and healthcare, we still keep failing in our efforts to cure late-onset diseases? It might be that we are trying to fight against laws of Nature that were purposely put in place so that evolution may go on but could not advance before its time. Relatively recently, we proposed the hypothesis that 'death of old age' and cancer may be viewed as Nature-made mechanisms or larger-scale checkpoints that keep the rate of evolution in check and preserve the population and the species at the expense of individuals. At this point in our development, we cannot change the rules of Nature. It is within our power, however, to anticipate, prevent and modify the outcomes of late-onset disease. Thus, we ought to keep on with research and development aimed at management of late-onset disease and improving the quality of life for the patients.

Keywords: DNA repair; Aging; Cancer; Late-onset disease; Evolution

Introduction

One may fall but he falls by himself: Kipling R, The Winners (1888)

Modern people may have longer lifespan than their predecessors, but longer life does not necessarily mean a healthier life. On the contrary, the prevalence of common diseases with onset late in life (degenerative disease such as cardiovascular disease, neurodegenerative disease, joint disease and cancer) has significantly increased in the last decades. Like Tithonus, who was given eternal life but not eternal youth, humans pay the price for living longer by spending larger parts of their lives in late age and experiencing the slow decline in health and fitness associated with advancing age. Is it possible to live a long life free of disease? Indeed, there are many among the 'oldest old' that may confidently say that they are and have always been generally healthy (in fact, this 'disease escaper' phenotype is quite common among centenarians) [1,2]. Nevertheless, in the end, everyone dies. Degenerative disease and cancer are the top causes of death in middle and advanced age. It seems that this trend will continue, at least in the near future, as modern medicine has made remarkable successes in the field of delaying course of late-onset disease and preventing complications, but has not managed to invent a complete cure. Why, despite all the efforts of research and healthcare, we keep failing in our efforts to cure late-onset diseases? It might be that we are trying to fight against laws of Nature that were specifically put in place so that evolution could go on but would not advance before its time. In this commentary we will try to summarize the main points in our hypothesis that aging and cancer may be Nature-made mechanisms that were developed in order to prevent undesired acceleration of the evolutionary process or 'genome integrity checkpoints' preserving the population and the species at the expense of individuals [1].

Everything is for the Best. But is it?

The capacity to evolve is one of the defining characteristics of living matter, along with metabolism, growth, capacity to maintain homeostasis and reproduction. Theoretically, life could exist without evolution, but for a short term only and/or in unchangeable environmental conditions. As the latter is impossible even within the sheltered environment of a petri dish, as long as there is life, there is evolution.

Upon being asked about the definition of evolution, the average person usually replies with 'survival of the fittest', which is, in fact, an abridged version of Charles Darwin's definition of natural selection. Indeed, evolution seems to work in an orderly fashion, producing whatever adaptations are needed so that living organisms could inhabit a wide variety of environments and removing (or, rather, letting waste away) what is no longer useful or may have become detrimental to survival. After all, evolution gave the living matter the capacity to change its size, shape and metabolism to the requirements of the environment. It produced the lungs of the first air breathing creatures, allowed the primitive humans to free their front paws from the function of walking so that they could dedicate their use to manipulating tools and created the human brain. It may seem, indeed, that evolution works entirely for the benefit of its subjects. But evolution does not plan for the future. Rather, it works for the here and now, that is, the natural selection is carried out according to what may provide adaptive advantages in the present environment.

The molecular basis of evolution is the random, hit-and-miss process of mutagenesis. It is presently known that the likelihood for occurrence of mutations at different sites within a complex genome is subject to bias (e.g. cytosines in CpG dinucleotides and C:G nucleotide pairs are more likely to be subject to mutation than other nucleotides, the mutation frequency is higher in males than in females, etc.) [3]. Nevertheless, considering the size and the complexity of the genomes of higher eukaryotes, the chances that a mutation event would affect a particular site are, overall, roughly equal. It is only after a mutation event has occurred that natural selection begins its work, driving evolutionary forces in a direction that may produce organisms with fitness superior to the fitness of their ancestors when a particular environment is concerned.

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The term 'evolution' is normally used in an abstract manner, as a concept of something that has happened long ago or is going to happen in the future. In fact, evolution has gone on since the beginning of life and is presently at work. However, we normally notice only drastic changes in the phenotype or obvious errors of the evolutionary process such as *de novo* occurring genetic disease. How come that we are not normally aware that evolution affects every living creature on Earth, every cell in our bodies and makes use of every one of us in real time? The answer is simple. Every cell of presently living creatures on Earth (and possibly, many of those that lived before us) possesses a well-developed and (normally) very efficient early warning and intervention system that scans for, detects and obliterates changes at DNA level that may, potentially, have deleterious effects.

Those effects may generally be divided into two groups:

-Effects that cause deviations from the default cell programme (differentiate, perform specific function, age and die) that is, potentially carcinogenic damage;

-Effects that interfere with the designated function of the cell (production of specialized progeny, or, in specialized cells synthesis of specific proteins or other substances, transmission of impulses, transfer of molecules and particles, other specific functions) that is, DNA damage that may result in substandard performance of the cell.

You shall not Pass. G1/S Checkpoints and the Fate of the Cell that does not Comply with Requirements

It is presently believed that there are two distinct cell cycle checkpoints for each of the two types of change listed above. Each of these checkpoints must be passed before a non-transformed cell is allowed to progress from G1 to the S phase of the cell cycle [4]. Failure to comply with the requirements of each checkpoint results in cell cycle arrest and potentially, grave consequences for the cell. Typically, cells that have sustained DNA changes that have been assessed as potentially carcinogenic are routed to the pathway of programmed cell death. Cells with DNA alterations that may result in adverse effects on their normal functioning are subjected to check-up and repair of damage. In case the damage is assessed as irreparable, permanent replicative arrest (replicative senescence or cell aging) may be imposed. Thus, the G1/S checkpoint (and possibly, the other checkpoints throughout the cell cycle) serve the purpose to screen out for those cells that are on the brink of becoming possibly dangerous to the integrity of specific tissues or the organism as a whole.

The mechanisms of DNA damage detection and repair have developed early in the beginning of life on Earth and have subsequently evolved from bacteria to higher vertebrates and man as much as any other process or function. These mechanisms normally work with remarkable efficiency so that in genomes of higher eukaryotes (about 10⁹ bp) every cell division would result in only about a dozen mutations [5]. Since the majority of the eukaryotic genome is non-coding DNA, it is likely that these mutations would have no significant effect on the phenotype of the carrier cells. Of course, considering that cell division occurs about 50 times in the life cycle of the average human cell, it is likely that some of these covert mutations may actually result in phenotype modification and that the effects of mutations that have occurred in a single cell may have a cumulative effect. In order to reduce the deleterious potential of the cumulative effect, evolution has developed a higher-level checkpoint that is, essentially, an expanded version of the G1/S cell cycle checkpoint that activates permanent replicative arrest. This higher-level checkpoint is what we commonly call aging slow but

progressive decline in the capacity to renew cell populations in the body resulting from accumulation of potentially deleterious DNA changes.

Degenerative Disease or Cancer? Make your Choice

Aging is part of life. It occurs in different tissues at a different pace and may last several decades, eventually resulting in the death of the individual. In many modern societies, aging is not viewed as a normal process, but, rather, as a consequence of 'unhealthy living'. However, aging and 'death of old age' may actually be the 'correct (that is, pre-programmed by Nature) way of ending a life for virtually all multicellular organisms living today. In the end, everything and everyone dies. Exceptions of the rule are several members of the phylum Cnidaria that defy the aging process by reverting from adult stage back to immature stage [6].

Thus, too little genetic change is generally a good thing on a cellular level. Some types of cells such as stem cells employ additional mechanisms in order to maintain their genome unchanged and preserve their capacity for proliferation and differentiation [7]. On organism level, high capacity to maintain genomic integrity may also be a good thing. It is believed that individuals with higher-than-average capacity for detection and repair of genomic damage may be at decreased risk for many of the common adult-onset diseases and may have increased reproductive fitness [8,9]. On a population and species level, however, groups of individuals that maintain very strictly the integrity of their genome may eventually doom themselves to genetic stagnation. The above mentioned Cnidarians have not changed significantly for nearly 600 million years. They may be able to live practically forever without aging (and cancer, for that matter, unless predators of injury end their life), but they have forfeited their capacity for evolution.

On the level of single eukaryotic cells, too much genetic change normally results in decline in proliferation capacity and/or death. On organism level, the effects are roughly the same. Individuals that cannot promptly repair their DNA but have sustained their capacity to kill cells carrying persistent genomic damage exhibit the severe, early-onset phenotypes of 'defective repair syndromes' such as xeroderma pigmentosum, Cockayne syndrome, ataxia-telangiectasia and others. Individuals with subtle defects in their capacity to repair DNA (or individuals suffering from diseases and conditions associated with increased levels of genomic damage, such as diabetes) and normal capacity to induce programmed cell death of damaged cells may be at increased risk for a variety of degenerative diseases [9,10]. As was already mentioned, most degenerative diseases may be diagnosed early and treated so that the course of the disease is slowed down and the development of complications delayed, but they cannot, at the present moment, be cured. Thus, cells and individuals that have become abnormally prone to genetic change are effectively removed from the common genetic pool.

What happens to cells that are prone to persistent genetic damage and have managed to dispose of their inherent ability to respond to death signals? They embark on the way of cancerous transformation. Cancer cells accelerate the normal process of evolution by increasing the mutation rate in their genomes by orders of magnitude and selecting for alterations that enhance their survival. Over several months or years they may lose virtually all properties of the original cell, may develop other properties, may expand their bulk massively or may travel and colonize distant tissues and organs. Indeed, in an environment that readily provides nutrients and space to grow, cells that are capable of practically unlimited proliferation and have managed to overcome the strict control over genomic integrity may meet with little resistance.

Nevertheless, the micro-evolution of cancer has, like evolution in general, a major drawback. It adapts the living unit to a particular environment or, as Richard Dawkins once put it, it has no long-term goals [11]. Adaptations that work very well in one environment may become a disadvantage when the conditions change. Eventually, the presence of cancer cells in the multicellular organism will disrupt its integrative functioning and the organism will cease to exist, depriving the cancer cells of their comfortable environment. The death of the body affected with cancer will unavoidably lead to the death of the cancer itself. Indeed, if the smaller checkpoints such as replicative senescence (aging) and programmed cell death ('death of old age') may be ignored or switched off, the final checkpoint of cancer is not avoidable. In this case, no alternative but death exists as there are no more mechanisms and pathways to overcome or shortcut. The potential genetic danger to the population, to the species and to life itself is thus truly eliminated. Thus, cancer may be viewed as a Nature-made mechanism, a final checkpoint that is triggered by accumulation of alterations that may endanger the genetic pool of the population and the species [2,10]. It works by elimination of the source of the threat at population level and effectively returns the rate of evolution back to normal.

Change of Plan. Could We hope to be able to Cure Late-Onset Disease?

Modern medicine has an impressive arsenal of methods and tools to detect, monitor and control a wide variety of diseases and conditions, including diseases with onset in middle and advanced age. Nevertheless, they are very rarely completely cured. Almost every one of us knows someone that has lost the battle with late-onset disease and many of us may have to do that battle at some point. It may appear heartless to accept late-onset diseases as a legitimate evolutionary tool. Let us not forget, however, that Nature is neither caring nor heartless. It works to preserve life in general and may not tolerate extremes that lead to genetic stagnation or, in contrast, to increased changeability, as both may mean extinction of life. At this point in our development, we cannot change the rules of Nature. It is within our power, however, to anticipate, prevent and modify the outcomes. Perhaps now it is the time for us to acknowledge that there is but little hope for a universal and complete cure for late-onset diseases but there is enormous opportunity for development of individualised treatments.

Do we still have hope that cancer may one day be prevented or cured? The answer is yes and no. Many types of cancer may apparently be prevented, as successful screening programmes for several type of cancer readily demonstrate. For many types of cancer, the progression to later stages may be prevented or slowed down significantly when diagnosed early. Survival rates of individuals with several types of metastatic cancer have increased significantly with modern antitumor therapy.

Is it possible to eradicate late-onset disease (cardiovascular disease, neurodegenerative disease, cancer and others) completely? In the view that aging and cancer are Nature-made checkpoints that obliterate

errors that had happened at the level of the previous checkpoints, the answer is no. It is more likely that with the achievements of modern research and clinical medicine, the life expectancy of individuals with late-onset disease that were diagnosed and treated early may become similar to the life expectancy of those that died 'of old age'. There is also significant advancement in research of genotype-phenotype correlations of aging phenotypes and late-onset disease and a number of genetic and phenotypic markers have been developed that may aid in the prognostication of age of onset and potential course of disease [9,12,13]. Thus, we may need to re-evaluate and restructure the goals of modern research and clinical care, concentrating more effort at development of treatment and management strategies that may significantly improve survival and quality of life for the patients with common late-onset diseases.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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