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The double life of DNA

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Abstract

This issue of *Current Opinions* focuses on the dual role of DNA in life and death. In ancient Roman religion and myth, Janus is the god who looks both to the past and to the future. He guides the beginnings of life, its progression from one condition to another, and he foresees distant events. The analogy to DNA could not be stronger. Closely interacting with the environment, our basic genetics provides the origin of life, guides the quality of health with age, predicts disease, and ultimately foresees our end. A shared and deep interest in the origin of life has long prompted our desire to define aging, and, ultimately, to understand whether it can be reversed. In this special issue, the authors collectively review concepts of normative aging, DNA instability, DNA repair, the genetic contribution of age and diet to disease, and how the basic molecular transactions of DNA give it a double life that guides health and survival, as well as the transitions to death.

Perhaps the most intuitive interest in aging stems from our fascination with eternal life and the potential for a “fountain of youth”. Amazing advances in genetic analysis provide surprising promise that artificial life extension may someday be possible. Rapid advances in sequencing technology have promoted enormous strides in assessing the molecular genetics of aging. Articles by Suh and Vijg, highlight the power of whole genome approaches, with ever-advancing bioinformatics analysis helping us to understand those specific features of gene actions that support exceptionally long life spans, like those seen in *Homo sapiens*. An exciting development, reviewed by Rando and colleagues, is the role of stem cell niches during aging as a key to the limitation of regenerative capacity. Indeed, personalized interventions in aging are foreseeable since, as discussed by Hicks and Vijg, genetic profiles of aging and disease, and the individual contributions of genes, can now be obtained at the single cell level.

Not surprisingly, whole genome analysis of aging humans pinpoints the importance of more esoteric aspects of the genome. Non-coding regions within introns and between genes code for regulatory species of RNA, that guide global access and regulate the decision to express a gene. Additionally, microsatellite DNA often serve as hot spots for recombination and sites for random integration. For some time, microsatellites were thought to be genetic signatures with no attributed function. Recent evidence, however, suggests that chromatin organization, replication and regulation of transcription may all be transactions that are affected by simple repetitive sequences. Indeed, DNA is often added or subtracted at microsatellites, which can lead to stable inherited changes that influence gene function. In

comparison to other genomic sequences, repetitive loci exhibit relatively high rates of instability, and have naturally evolved in humans to be longer than in other species. These alterations in simple repetitive sequences lie at the center of DNA evolution and sequence diversity, which drives adaptation.

On the other hand, as discussed by McMurray and Ranum, changes in repetitive sequences such as trinucleotide repeat (TNR) expansion can also signal rapid evolution, with potentially deleterious effects on RNA, protein expression, and gene function. Age-dependent somatic changes in triplet repeat expansion influences the onset of disease pathology in a group of neurodegenerative diseases such as Huntington's disease. McMurray reviews recent models that account for the tipping point at which the length of the TNR initiates somatic instability and its toxic effects. Although many mechanisms contribute, a proposed toxic oxidation cycle is at least one major pathway by which the removal of oxidized bases initiates a DNA oxidation-break-excision cycle that leads to the accumulation of somatic mutation. An oxidative model for age-related mutation is attractive in that it links somatic instability with mitochondrial and inflammation mechanisms of aging. New particularly RNA-based mechanisms may influence the threshold at which the lesion load results in expansion. At the protein level, Ranum reviews Repeat Associated Non-ATG translation (RAN-translation). RAN-translation due to expanded repetitive regions occurs in all reading frames in the absence of a starting ATG site. At CAG tracts, for example, age-dependent translation of somatically expanded CAG, AGC, and GCA produces increasingly toxic homopolymeric proteins of polyglutamine, polyserine, and polyalanine tracts, respectively.

It is important to emphasize that unusual phenotypes, such as those typified by trinucleotide expansion disease, are appropriate models for the study of aging, as they embrace one of the major evolutionary theories of why we age, *i.e.*, the "mutation accumulation" theory. As discussed by Erickson, the idiosyncratic sets of mutations accumulating in the germ line do not reach a phenotypic level of expression until those phenotypes escape the force of natural selection, which in human subjects is well underway by early middle age. Indeed, Hickson reports links among microsatellites, aging, and our cells' ability to deal with bumps and breaks at telomeres, whose length varies greatly between species, from approximately 300 base pairs in yeast, to many kilobases in humans. Telomeric repeats keep chromosome ends from fraying and sticking to each other, yet, each time a cell divides, the telomeres get shorter. When they get too short, the cell can no longer divide and either becomes inactive (senescent) or dies. At least in cells capable of dividing, Hickson discovered DNA bridges that appear to be residual "string-like" connections between two separated daughter cells. Since they are present after mitosis, these GC-rich repetitive sequences are models for telomere breaks and/or general processing pathways of "difficult to replicate" sequences. The direct link of telomeric "end of replication" processing, DNA repair, and aging is exciting, although poorly understood.

d'Adda di Fagagna discusses an interesting counterpoint to the story. When telomeres become critically short, they are sensed as damaged. which triggers a DNA damage response (DDR)-initiated cellular senescence. Despite the fact that chromosomes bear ends that resemble a DNA double strand break (DSB), telomeres are generally not recognized as

DSBs. There may be different types of cellular senescence, and/or the role of telomeres in DNA repair may not be restricted to their shortening. These mechanisms are important since it is becoming apparent that reversing telomere shortening through temporary activation of telomerase may be a potent means to slow aging.

Our most practical interest in aging, however, remains our everyday experience that disease manifests more frequently at older ages. The phenomenon is unlikely to be simply a wider window with increasing statistical probability that an aberrant phenotype will emerge. Rather, aging appears to contribute to disease in ways that remain unclear. Arguably the most clinically significant disorders of aging are dementias of the Alzheimer type. Indeed, developed societies of the world have been undergoing unprecedented increases in their elderly populations. This trend is continuing and will inevitably lead to vast increases in a wide array of degenerative and proliferative disorders of aging. Among these, cancer and neurodegenerative diseases are perhaps the most devastating in terms of their functional, emotional and economic effects. Efforts to prevent or ameliorate these disorders will require emerging and strengthened interactions among communities with interests in basic research on mechanisms of aging, disease, and basic research on the molecular biology of nucleic acids.

Why might DNA transactions be of special significance to our understanding of aging and diseases? First, there is the obvious fact of the centrality of processes like DNA replication, transcription, repair and recombination to all biological phenomena. In the past, DNA modifications have taken center stage as mechanisms for age-dependent genetic disease, and, until recently, relatively little attention was given to RNA. However, as highlighted by Bjoras and by Klungland, modification of RNA and RNA editing may, in fact, ultimately provide the most direct impact on the accumulation of somatic mutations in aging humans. Second, the genomic instability observed in progeroid syndromes provide direct insight into the molecular genetics of aging, and how gene alterations promote earlier ages of onset and accelerated rates of phenotypic development. These changes are surprisingly complex, as Zhou points out in discussing the striking overlap of the most important of the abnormal phenotypes with what is observed in “usual” or “normative” aging. While there is ample evidence of genomic instability in the classic progeroid syndromes, the Werner syndrome and Hutchinson-Gilford syndromes, much more research is required concerning the potential direct impacts of the primary gene mutations upon the central nervous system (CNS).

Suffice it to say that molecular mechanisms of DNA replication and repair can teach us a great deal about aging, and only recently have we given sufficient attention to those connections. Indeed, there has been a surge of interest in the role of epigenetic events in the biology and pathobiology of aging. Studies of human twin pairs, for example, have shown striking “epigenetic drifts” in gene expression as a function of age. Skinner takes this one step further with his remarkable finding that the response to environmental exposures has heritable consequences on male fertility, in the absence of sequence changes in DNA. It is now clear that three-dimensional packaging of DNA exerts previously unimagined regulation of the organism by controlling processes such as development, sex determination, the DNA damage response, and cancer. Although old in concept, chromatin is perhaps the newest frontier of genome research. We include in this issue two reviews by Workman and

Kurdistani, who cover the effects of histone modifications and transcriptional mechanisms on age-related neurodegeneration. New concepts, however, raise issues as to whether histone modifications have additional functions that gauge cellular acetate flux, which integrates control of metabolism with gene expression.

Metabolism has proven to be an endless source of intricate and unexpected mechanisms that the cell uses to coordinate DNA dynamics, to stave off disease and to extend healthy life span. In this regard, an important family of genes linking metabolism to the DNA damage response is the sirtuin class, consisting of proteins with mono-ADP-ribosyltransferase or deacetylase activity. Indeed, circadian rhythms are generated by an intrinsic cellular mechanism that controls a large array of physiological and metabolic processes, and erosion of these patterns is associated with aging-related features. As expertly described by Sassone Corsi and Mostoslavsky, several of these proteins have been associated with both anti-aging and anti-disease activity, in some cases by regulating DNA repair capacity. Nutrient sensing pathways are logical “master regulators” as they integrate mitochondrial damage, chromatin, DNA repair, and aging. Pothof points out, however, that not all DNA damage is equal, implying that there must be methods to “fine-tune” repair detection and control.

Owing to the far-reaching character of beginnings and transitions, DNA supports both ubiquitous and discrete function. Much of the interest recently has focused upon mitochondrial DNA rather than nuclear DNA. Moreover, recent findings support an additional mechanism for control of cellular and tissue function by mitochondria through complex mitochondrial-nuclear communication mechanisms, and potentially through extracellular release of mitochondrial components that can act as signaling molecules. Current, exciting studies by Cuervo provide evidence that dying mitochondria up-regulate cytoprotective activities to promote healthy aging. Mitophagy, autophagy, mitochondrial number, fission and fusion events, and the mitochondrial unfolded protein response require mitochondrial-nuclear communication for the transcriptional activation of nuclear genes. The induction of these signaling pathways is a shared feature in long-lived organisms spanning from yeast to mice.

The enthusiasm for understanding the biology of aging in the context of DNA repair and genomic instability is evident by its increasing presence at national and international meetings. Although clearly recognized as key factors in disease, discussions of these topics have been heavily weighted towards cancer. We designed this issue to expand our thinking towards broader concepts, the molecular genetics of a range of human diseases, and the context of normative aging. Many of these topics have been overlooked entirely, or often embedded within the larger scope of cell cycle regulation. We hope that this issue of *Current Opinions* helps to fill the gap.

Cynthia and Jan