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Preface: DNA damage, DNA repair, aging and age-related disease

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Aging is typically accepted as being a product of one's genetic composition and the cumulative effects of lifestyle practices and exposures. Humans reach a peak of growth and development around the time of their mid 20s. Starting at what is commonly referred to as "middle age", the operations of the body become more susceptible to wear and tear, and there is a general decline in physical and possibly mental performance. During the latter half of life, an individual is more prone to experiencing problems with a range of bodily functions and to developing various chronic or fatal diseases. The cardiovascular, digestive, excretory, nervous, reproductive and urinary systems are particularly vulnerable, and the most common age-related ailments include Alzheimer's, cancer, arthritis, diabetes, and heart disease. In several developed countries, the life expectancy, especially in females, is now into the 80s, with a maximal lifespan being reported of ~120 years. What dictates or regulates "why we age" and "why the aging body loses functional capacity" has been a matter of debate for centuries. It seems likely that several factors work together in the aging process, or that one particular factor is the primary culprit in a given individual.

Some important theories of aging, which in nearly all cases are not mutually exclusive, are listed in Table 1. Each of these theories is based on the premise that over the life span of an organism, alterations to cellular macromolecular integrity amass and ultimately lead to the progressive decline of the system and an increasing risk of death. In the collection of articles within this Special Issue – guest edited by Drs. David M. Wilson III and Peter J. McKinnon – several investigators have examined the contribution of DNA damage and the related repair/response systems to the aging process and age-related disease, such as cancer and neurodegeneration.

A link between DNA alterations and aging was put forth in 1959 by Dr. Szilárd, a Hungarian-American physicist who conceived the nuclear chain reaction and worked on the Manhattan Project. Recognizing the potentially devastating ramifications of atomic weapons, Dr. Szilárd changed research directions, and began considering factors that might influence the aging phenomenon. His "somatic mutation theory" proposed that "the elementary step in the process of aging is an 'aging hit,' which 'destroys' a chromosome of the somatic cell, in the sense that it renders all genes carried by that chromosome inactive." In other words, Dr. Szilárd theorized that genetic mutations within DNA would accumulate with time, ultimately resulting in "miscopying" and functional failure (Szilard 1959). Indeed, experimental studies using lymphocytes from humans or mice, or employing transgenic mouse models that harbor a

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defined reporter gene, demonstrate that mutations increase with age (Suh and Vijg 2006). And while the somatic mutation theory has evident vulnerabilities (see for instance the theoretical works of (Kirkwood and Proctor 2003)), the emerging picture that nearly 50% of the human genome is transcribed (with 1% representing protein coding sequences) suggests that only a few random spontaneous mutational events (i.e. point mutations, deletions/insertions, or chromosomal rearrangements) could have profound effects on the entire gene regulatory circuitry (Birney et al. 2007). As will be presented in greater detail in this Special Issue, the idea that DNA damage contributes to the aging process and particularly to age-related disease has growing support:

First, DNA is subject to continuous modification from both endogenous reactive chemicals, such as reactive oxygen species, and exogenous environmental factors, such as food agents, industrial genotoxins, and ultraviolet and ionizing radiation (Lindahl 1993). Moreover, DNA is intrinsically unstable, experiencing spontaneous base loss and deamination of uracil, to name a few, at high frequency. Despite the existence of an array of protective DNA repair systems (described within this Special Issue), there is evidence that several forms of DNA damage, such as strand breaks, alkali-labile sites (i.e. abasic lesions), base modifications (most notably, 8-oxo-2-deoxyguanosine) and cross-links (particularly protein-DNA), accumulate with age, although the findings depend on the measurement technique employed and the tissue or organ studied (Mullaart et al. 1990;Holmes et al. 1992;Bohr and Anson 1995). Such DNA damage, which is known to affect the efficiency and accuracy of DNA replication and RNA transcription, and to promote cell death responses (e.g. apoptosis) or malignant transformation, is most likely an underlying cause of the age-related dysfunctioning of cells (both dividing and non-dividing) and tissues (Gensler and Bernstein 1981). We note that nearly all eukaryotes have two separate genomes, the nuclear and the mitochondrial, and that DNA metabolism is clearly compartmentalized between them with little knowledge about potential crosstalk. Based on the consequences of defective DNA repair in the mitochondria and studies indicating age-associated accumulation of oxidative DNA base lesions, theories have speculated that modifications to the mitochondrial genome might be particularly important in the aging process (Wallace 2005).

Second, there is evidence that both antioxidant defense mechanisms and DNA repair responses decline with age, although again, the findings vary from study to study (Little 1976). The consequence of losing such protective systems is obvious, given the deleterious effects of unrepaired damage, and likely augments the age-dependent accumulation of DNA lesions discussed above.

Third, Hart and Setlow in their seminal paper reported that ultraviolet-induced excision repair by skin fibroblasts correlates well with the maximal life span of seven different mammalian species, supporting the idea that DNA repair capacity is important in determining longevity (Hart and Setlow 1974). This supposition was bolstered a few years later when it was discovered that mouse species displaying different life expectancies possessed a repair potential that correlated with maximal life span (Hart et al. 1979). However, when the organism's body size was taken into account, the correlation of DNA repair capacity with life expectancy disappeared (Promislow 1994). Nonetheless, other evidence suggests that intrinsic DNA repair levels associate with longevity. For instance, EBV-immortalized lymphoblastoid cell lines from centenarians possess higher than normal poly(ADP)ribose polymerase 1 (PARP1) activity, presumably reflective of an enhanced DNA strand break response (Muiras et al. 1998). On the other end, the rate of production of pro-oxidants, which are responsible for the majority of intracellular damage, has been found in several different species to inversely correlate with maximal life expectancy (Sohal and Orr 1992).

Fourth, studies that involve exogenous exposure of rodents to a DNA-damaging agent have revealed that such treatments result in reduced life span, yet, importantly, do not affect (i.e. accelerate) all aspects of normal aging (Bernstein and Bernstein 1991).

Fifth, and potentially most compelling, inherited disorders originating from defects in DNA damage response genes give rise to phenotypes that resemble the normal aging process. This connection is perhaps best exemplified by the human segmental progerias Werner syndrome and Cockayne syndrome (discussed in more detail herein). Finally, recent studies by Hoeijmakers and colleagues using genetically-defined DNA repair mutant mouse models suggest that "ageing and end-of-life fitness are determined both by stochastic damage, which is the cause of functional decline, and genetics, which determines the rates of damage accumulation and decline (Niedernhofer et al. 2006)."

In this Special Issue, Drs. Hans E. Krokan, Christi A. Walter and Susan P. LeDoux focus primarily on the role of endogenous (particularly oxidative) DNA damage – to both the nuclear and mitochondrial genomes – and processes related to base excision repair in aging and disease. Dr. Peggy Hsieh reviews the pathway of mismatch DNA repair and its prominent role in hereditary and sporadic cancers, as well as its potential involvement in the aging process. Dr. Laura Neidernhofer describes recent evidence implicating the pathway of nucleotide excision repair in protection against premature aging phenotypes. Dr. Paul Hasty focuses on the contribution of mechanisms responsible for resolving DNA double-strand breaks in both aging and age-related disease. The subsequent three articles, by Drs. Nathan A. Ellis, Tinna Stevnsner and Nicolas Levy, describe the molecular, cellular and clinical features of segmental progerias arising from defects in the RECQ helicase family (e.g. Werner and Bloom Syndrome), the Cockayne syndrome genes (i.e. CSA and CSB) or the Hutchinson-Gilford gene (i.e. Lamin A, LMNA), respectively. Dr. Eric Brown next discusses the role of ATR-dependent DNA damage responses in the maintenance of stem cell integrity and aging, and Dr. John M. Sedivy profiles the evidence indicating that cellular senescence is a contributing factor to aging and age-related pathology. The final two review articles, by Drs. Ella Englander and Peter J. McKinnon, summarize the role that DNA damage plays in the manifestation of neurodegenerative disease. The Special Issue concludes with commentaries from three leading scientists in the repair and aging community, Drs. James E. Cleaver, Jan Vijg and Philip Hanawalt. In total, the collection of reviews and commentaries herein provide a comprehensive, scholarly summary of topics related to "*the DNA damage and Repair Theory of Aging*".

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Table 1

Some Important Theories of Aging

It should be emphasized that these theories should not be seen as competing but as complementary.

Theory	Premise
"Wear and tear" theory	Dr. August Weismann, a German biologist, proposed in 1881 that the body and its cells are worn down by toxins in our diet and environment; by the excessive consumption of fat, sugar, caffeine, alcohol and nicotine; by the ultra-violet rays of the sun; and by the many other chemical, physical and emotional stresses to which we are routinely exposed (reviewed by (Kirkwood and Cremer 1982)). Moreover, with age, the body gradually loses its ability to repair associated damage, thus rendering older individuals more susceptible to disease. "The neuroendocrine theory", developed by Vladimir Dilman, Ph.D., elaborates on the "wear and tear" theory by focusing on the neuroendocrine system. It suggests that as we age, the body produces lower levels of hormones resulting in catastrophic effects on normal physiology, such as muscle atrophy and poor recovery from injury or illness (Dilman et al. 1986).
Hayflick limit (or "aging clock") theory	In 1961, Drs. Leonard Hayflick and Paul Moorhead discovered that human fibroblasts (from lung, skin, muscle, heart) can only divide a finite number of times in culture (Hayflick and Moorhead 1961). Dr. Hayflick also noted that, as these cells approached the end of their division limit, they acquired attributes commonly associated with old tissue, such as the destruction of their cellular structure, reduced capacity to produce energy or synthesize enzymes, and an intracellular buildup of waste materials. Dr. Hayflick concluded that these changes play a central role in the manifestation of aging, and result in the death of the individual well before all of its cells fail to divide. Arising from Hayflick's findings was the "waste accumulation theory", which postulated that cells produce more waste (e.g. toxins) than they can properly eliminate in the course of their life time, culminating in dysfunction and death. Many theories have been put forth to explain how Hayflick's limit (i.e. replicative senescence) is ultimately expressed in cells, and evidence clearly indicates a critical role for telomerase, a protein that maintains the caps of chromosome ends, in dictating replicative life span (i.e. the telomerase theory of aging) (Holt et al. 1996).
Genetic control theory	We are each born with a distinctive genetic code. i.e. our DNA blue-print. The "genetic control theory" proposes that each individual harbors a predetermined tendency to certain types of physical and mental functioning and that genetic inheritance plays a major role in determining how quickly we age and how long we live.
Error catastrophe theory	In 1963, Dr. Leslie Orgel wrote that because the "machinery for making protein in cells is so essential, an error in that machinery could be catastrophic (ORGEL 1963)." In particular, the production of proteins and the duplication of DNA are not always carried out with perfect accuracy. Since protective systems are occasionally "error-prone", the gradual accumulation of flawed molecules has been proposed to cause disease and other age-related changes. This theory differed slightly from the "somatic mutation theory" proposed by Dr. Leó Szilárd in 1959, in that it postulated an error in information transfer from sites other than just DNA (Szilard 1959).
Free-radical theory	One of the most popular theories of aging, first proposed by Dr. Denham Harman in 1956, is the "free radical theory of aging (Harman 1956)." This theory postulates that aging results from the gradual accumulation of cellular damage caused by reactions with highly reactive molecules known as "free radicals." Free radicals (or reactive oxygen or nitrogen species) are produced endogenously via normal metabolic processes or upon exposure to numerous exogenous agents, including ionizing radiation and cigarette smoke. Since mitochondria are responsible for manufacturing chemical energy and creating harmful free radicals, the constituents of this organelle (namely DNA) are the major sites for oxidative reactions. The "mitochondrial theory", developed by Dr. Harman in 1972, postulates that mitochondrial decay, in particular, results in impaired energy generation and dysfunctional cellular activity that gives rise to age-associated pathologies like skeletal muscular and neurological degeneration, heart failure, strokes, other diseases, and death (Harman 1972). Although not related to the "oxidative" theories above, the "cross-linkage theory" implicates another endogenous agent, i.e. crosslinking agents, in the formation of covalent bridges between macromolecules (e.g. proteins and nucleic acids) that effect cellular dysfunction and ultimately death.
Auto-immune theory	The autoimmune theory, proposed by Dr. Roy Walford in 1964, hypothesizes that two types of white blood cells of the immune system (i.e. B and T cells) weaken with age, and malfunction (Walford 1964). B cells lose their vigor in attacking bacteria, viruses, and cancer cells, and T cells lose their capacity to attack cells foreign to the body. These changes render the individual more prone to infections and tissue damage, which may ultimately cause death. Additionally, as the system breaks down, the body is more apt to have autoimmune reactions, in which the body's own cells are mistaken for foreign material and are destroyed or damaged by the immune system.