AGING CHANGES IN SPECIFIC TISSUES THAT PREDISPOSE TO DISEASE

Aging changes in some tissues increase susceptibility to age-related disease as a secondary or downstream phenomenon (Fig. 94e-3). In humans, this includes, but is not limited to, the immune system (leading to increased infections and autoimmunity), hepatic detoxification (leading to increased exposure to disease-inducing endobiotics and xenobiotics), the endocrine system (leading to hypogonadism and bone disease), and the vascular system (leading to segmental or global ischemic changes in many tissues).

Inflammaging and Immunosenescence Old age is associated with increased background levels of inflammation including blood measurements of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α). This has been termed *inflammaging*. T cells (particularly naïve T cells) are less numerous because of age-related atrophy of the thymus, whereas B cells overproduce autoantibodies, leading to the age-related increase in autoimmune diseases and gammopathies. Thus older people are generally considered to be immunocompromised and have reduced responses to infection (fever, leukocytosis) with increased mortality.

Detoxification and the Liver Old age is associated with impaired detoxification of various disease-causing endobiotics (e.g., lipoproteins) and xenobiotics (e.g., neurotoxins, carcinogens), leading to increased systemic exposure. In humans, the liver is the major organ for the clearance of such toxins. Hepatic clearance of many substrates is reduced in old age as a consequence of reduced hepatic blood flow, impaired hepatic microcirculation, and in some cases, reduced expression of xenobiotic metabolizing enzymes. These changes in hepatic detoxification also increase the likelihood of increased blood levels of, and adverse reactions to, medications.

Endocrine System Hormonal changes with aging have been a focus of aging research for over a century, partly because of the erroneous belief that supplementation with sex hormones will delay aging and rejuvenate older people. There are age-related reductions in sex steroids secondary to hypogonadism and, in females, menopause. Age-related declines in growth hormone and dehydroepiandrosterone (DHEA) are well established, as is the increase in insulin levels and associated insulin resistance. These hormonal changes contribute to some features of aging such as sarcopenia and osteoporosis, which may be delayed by hormonal supplementation. However, adverse effects of long-term hormonal supplementation outweigh any potential beneficial effects on lifespan.

Vascular Changes There is a continuum from vascular aging through to atherosclerotic disease, present in many, but not all, older people. Vascular aging changes overlap with the early stages of hypertension and atherosclerosis, with increasing arterial stiffness and vascular resistance. This contributes to myocardial ischemia and strokes but also appears to be associated with geriatric conditions such as dementia, sarcopenia, and osteoporosis. In these conditions, impaired exchange between blood and tissues is a common pathogenic factor. For example, the risk of Alzheimer's disease and dementia is increased in patients with risk factors for vascular disease, and there is pathologic evidence for microvascular changes in postmortem studies of brains of people with established Alzheimer's disease. Similarly, strong epidemiologic links have been found between osteoporosis and standard vascular risk factors, whereas there are significant age-associated changes in the microcirculation of osteoporotic bone. Sarcopenia might also be related to the effects of age on the muscle vasculature, which is altered in old age. The sinusoidal microcirculation of the liver becomes markedly altered during aging (pseudocapillarization), which influences hepatic uptake of lipoproteins and other substrates. In fact, it has often been overlooked that in his original exposition of the free radical theory of aging, Harman proposed that the primary target of oxidative stress was the vasculature and that many aging changes were secondary to impaired exchange across the damaged blood vessels.

GENETIC INFLUENCES ON AGING

There is variability in aging and lifespan in populations of genetically identical species such as mice that are housed in the same environment. Moreover, the heritability of lifespan in human twin studies is estimated to be only 25% (although there is stronger hereditary contribution to extreme longevity). These two observations indicate that the cause of aging is unlikely to lie only within the DNA code. On the other hand, genetic studies initially undertaken in the nematode worm *C. elegans* and, more recently, in models from yeast to mice have shown that manipulating genes can have profound effects on the rate of aging. Perhaps surprisingly, this can often be generated by variability in *single* genes, and for some genetic mechanisms, there is very strong evolutionary conservation.

Genetic Progeroid Syndromes There are a few very rare, genetic premature aging conditions that are called progeroid syndromes. These conditions recapitulate some, but not all, age-related diseases and senescent phenotypes. They are mostly caused by impairment of genome and nuclear maintenance. These syndromes include the following:

- *Werner's syndrome.* This is an autosomal recessive condition caused by a mutation in the *WRN* gene. This gene codes for a RecQ helicase, which unwinds DNA for both repair and replication. It is typically diagnosed in teen years, and there is premature onset of atherosclerosis, osteoporosis, cancers, and diabetes, with death by age of 50 years.
- *Hutchinson-Gilford progeria syndrome (HGPS).* This usually occurs as a de novo, noninherited mutation in the lamin A gene (*LMNA*), leading to an abnormal protein called progerin. LMNA is required for the nuclear lamina, which provides structural support to the nucleus. There are marked development changes obvious in infancy with subsequent onset of atherosclerosis, kidney failure, and scleroderma-like features and death during the teen years.
- *Cockayne syndrome.* This includes a number of autosomal recessive disorders with features such as impaired neurologic growth, photosensitivity (xeroderma pigmentosa), and death during childhood years. These disorders are caused by mutations in the genes for DNA excision repair proteins, *ERCC-6* and *ERCC-8*.

Gene Studies in Long-Lived Humans The main genes that have been consistently associated with increased longevity in human candidate gene studies are *APOE* and *FOXO3A*. ApoE is an apoprotein found in chylomicrons, whereas the ApoE4 isoform is a risk factor for Alzheimer's disease and cardiovascular disease, which might explain its association with reduced lifespan. FOXO3A is a transcription factor involved in the insulin/IGF-I pathway, and its homolog in *C. elegans*, daf16, has a substantial impact on aging in these nematodes. Genome-wide association studies (GWAS) of centenarians have confirmed the association of longevity with *APOE*. GWAS have been used to identify a range of other single nucleotide polymorphisms (SNPs) that might be associated with longevity including SNPs in the sirtuin genes and the progeroid syndrome genes, *LMNA* and *WRN*. Gene set analysis of GWAS studies has shown that both the insulin/IGF-I signaling pathway and the telomere maintenance pathway are associated with longevity.

Of particular interest are people with Laron-type dwarfism. These people have mutations in the growth hormone receptor, which causes severe growth hormone resistance. In mice, similar knockout of the growth hormone receptor (GHRKO mice, Methuselah mice) is associated with extremely long life. Therefore, subjects with Laron's syndrome have been carefully studied, and it was found that they have very low rates of cancer and diabetes mellitus and, possibly, longer lives.

Nutrient-Sensing Pathways Many living things have evolved to respond to periods of nutritional shortage and famine by increasing cellular resilience and delaying reproduction until food supply becomes abundant once again. This increases the chances of reproductive success and survival of offspring. Lifelong food shortage, often termed *caloric*