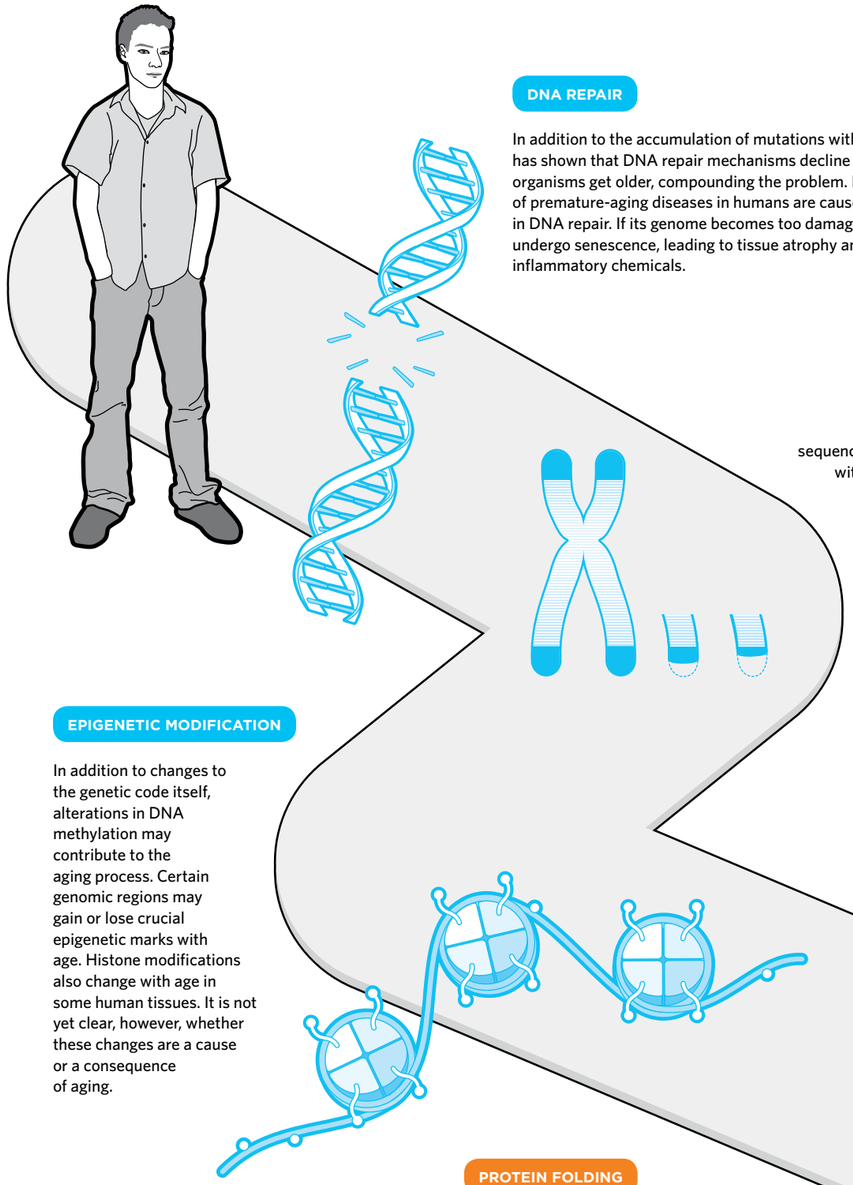
GENOME CELL ORGANISM

AS TIME GOES BY

Aging is the outcome of diverse and complex changes in normal biological functions, from the accumulation of DNA damage to dysfunction of proteins and altered communication both within cells and among distant tissues in the body. Researchers are beginning to piece together how we age at the level of our genomes, our cells, and our whole bodies, in hopes of identifying strategies for slowing decline and extending healthy life span.



DNA REPAIR

In addition to the accumulation of mutations with age, research has shown that DNA repair mechanisms decline as cells and organisms get older, compounding the problem. Indeed, a number of premature-aging diseases in humans are caused by defects in DNA repair. If its genome becomes too damaged, a cell will undergo senescence, leading to tissue atrophy and release of pro-inflammatory chemicals.

TELOMERES

In most cells, telomeres, the repetitive sequences at the ends of chromosomes, shorten with age, eventually triggering apoptosis or senescence. Moreover, telomeres are particularly sensitive to stress-induced DNA damage, and studies have linked shortened or damaged telomeres to decreased life span in mice and to age-related ills such as organ dysfunction and elevated cancer risk in humans.

EPIGENETIC MODIFICATION

In addition to changes to the genetic code itself, alterations in DNA methylation may contribute to the aging process. Certain genomic regions may gain or lose crucial epigenetic marks with age. Histone modifications also change with age in some human tissues. It is not yet clear, however, whether these changes are a cause or a consequence of aging.

PROTEIN FOLDING

Beyond the level of the genome, numerous other cellular components can influence aging. Proteins, for example, whose function is dependent on a specific conformation, are more likely to be misfolded in older cells than younger ones, though it is still unclear whether these changes lead to aging processes or are merely a consequence of them. Aging also seems related to declines in the production of molecular chaperones that help fold proteins and in the functioning of pathways that clear misfolded proteins.

MITOCHONDRIAL FUNCTION

Reactive oxygen species (ROS) wreak havoc on a cell and have been proposed as one of the many drivers of aging. As primary producers of ROS, mitochondria have long been presumed to contribute to age-related damage. But growing evidence that some level of ROS signaling is critical for normal physiology has researchers restructuring their view of the organelle's role in aging.

CELLULAR COMMUNICATION

Cellular crosstalk mediated by circulating regulatory molecules can also affect aging. For example, blood from young mice has been shown to restore some lost function in the hearts, brains, and skeletal muscles of older mice. Decreases in secreted growth differentiation factor 11 (GDF11) and overactivation of the transcription factor NF-κB may be two important drivers of aging.

STEM CELLS

As they age, stem cells become less able to divide and replenish the various cell types of the body. While the mechanism responsible for this cellular decline is still unknown, quiescent stem cells remain vulnerable to DNA damage, and often have weakened DNA repair pathways. Age-related shifts in stem cells' epigenetic marks and in their cellular niches may also contribute to aging.