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Review

Gene expression and DNA repair in progeroid syndromes and human aging

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Abstract

Human progeroid syndromes are caused by mutations in single genes accelerating some but not all features of normal aging. Most progeroid disorders are linked to defects in genome maintenance, and while it remains unknown if similar processes underlie normal and premature aging, they provide useful models for the study of aging. Altered transcription is speculated to play a causative role in aging, and is involved in the pathology of most if not all progeroid syndromes. Previous studies demonstrate that there is a similar pattern of gene expression changes in primary cells from old and Werner syndrome compared to young suggesting a presence of common cellular aging mechanisms in old and progeria. Here we review the role of transcription in progeroid syndromes and discuss the implications of similar transcription aberrations in normal and premature aging.
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Keywords: Gene expression; Progeroid syndromes; DNA repair; Human aging; Werner syndrome

1. Progeroid syndromes as a model for human aging

Human segmental progeroid syndromes are monogenic diseases accelerating some, but not all of the features found in normal aging (Martin, 1978) (Table 1). Aging is a complex multifactorial process, and progeroid syndromes provide useful models for aging research. Causative genes can be studied, identifying processes potentially relevant to the mechanisms of aging. The classic example is Werner syndrome (WS), caused by a

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Table 1
Some segmental progeroid disorders

	Gene defect	Cellular processes affected	Mean life-span	Phenotype	References
Werner syndrome	Loss of function mutations in WRN, DNA helicase	Transcription, DNA repair (DSBR (HR and NHEJ), SSBR/BER), DNA recombination, DNA replication, chromosomal aberrations, telomere metabolism, apoptosis	~48 years	Graying of hair, skin atrophy, atherosclerosis, malignancies, diabetes mellitus, disorder of lipid metabolism, hypogonadism, autoimmunity, degenerative vascular disease, osteoporosis, cataracts, regional fibrosis	Nakura et al. (2000), Kipling et al. (2004), Hasty et al. (2003), Opresko et al. (2003), Blank et al. (2004), Poot et al. (2001), Cheng et al. (2004), Pichierri et al. (2000)
Cockayne syndrome	Loss of function mutations in CSA and CSB, putative DNA helicase.	Transcription, apoptosis, DNA repair: NER (TCR), BER of some types of oxidative damage	~20 years	Neurodegeneration, atherosclerosis, diabetes mellitus, disorder of lipid metabolism, hypogonadism, hypertension, osteoporosis, cataracts, regional fibrosis, deafness, thin hair, poor growth	Nakura et al. (2000), Kipling et al. (2004), Hasty et al. (2003), Licht et al. (2003), Selzer et al. (2002)
Hutchinson–Gilford progeria syndrome	*LMNA* gene (Lamin A), Nuclear envelope	Nuclear stability and transcription	~12 years	Atherosclerosis, sarcopenia, alopecia, sclerosis, osteolysis, reduced adipose tissue	Kipling et al. (2004), Hasty et al. (2003)
Bloom syndrome	DNA helicase	Transcription, DNA replication, DNA repair, DNA recombination, apoptosis, chromosomal aberrations	~28 years	Cancer predisposition, hypogonadism, regional fibrosis, growth deficiency, diabetes mellitus predisposotion, cataracts	Nakura et al. (2000)
Rothmund–Thompsons syndrome	DNA helicase	Recombination	~Normal	Alopecia, malignancies, poikiloderma, cataracts, osteoporosis, graying of hair, hypogonadism	Hasty et al. (2003)