

Drugs: Cell Ageing

Therapeutics

Atherosclerosis

Stress

Senescence

p38 MAPK in rapid Werner syndrome cell ageing

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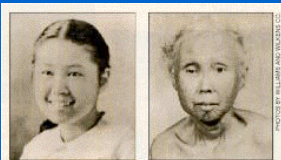
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The Investigation

Objectives

Werner is a syndrome that has numerous features that resemble rapid ageing, including premature hair greying, cataracts and skin ageing, and is associated with early onset of diseases associated with elderly individuals, such as atherosclerosis and type II diabetes. WS is widely used as a model for certain aspects of normal human ageing.

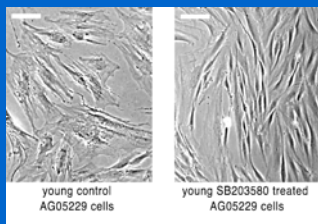
Individual with WS



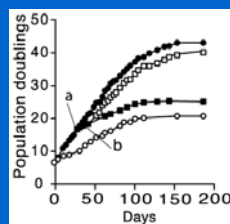
Taking its toll. As a teenager (left) this Japanese American looked normal, but by age 48, the effects of Werner's syndrome were readily apparent. [Image credit: William and Wilkens Publishing Inc.]

The disease seems mainly to affect certain organs that have dividing cell populations in the body. This is reflected in culture as WS fibroblasts have a much reduced lifespan compared to normal fibroblasts. This rapid ageing of WS cells is thought to underlie many of the accelerated ageing features of WS individuals. We have found a drug (SB203580) that prevents this accelerated ageing of WS cells.

Stressed cells in WS



Correction of cell stress and increase in lifespan by SB203580 treatment



However, the actual target of SB203580 is not clear and the objective of this work is to further elucidate the drug target.

Potential Benefits

For older people

Individuals with WS show early onset of atherosclerosis, osteoporosis and type II diabetes. In addition, they have high circulating plasma levels of inflammatory cytokines such as TNF α . This is suggestive of high inflammatory levels. The prime candidate for our drug target is p38 MAP kinase that plays a pivotal role in inflammatory processes. If, as our data suggests, p38 is involved in the rapid senescence of WS cells, then it is possible that anti-inflammatory drugs such as SB203580 (or derivatives) may form the basis of therapeutics for WS. If inhibition of p38 *in vivo* can reduce the levels of TNF α , these may reduce the probability of developing coronary heart disease and may result in a longer life for WS individuals. In addition, if aspects of WS ageing such as skin atrophy result from p38 activity, then drugs such as SB203580 may alleviate this.

For society

Atherosclerosis and other inflammatory diseases are a major public health problem, and it is possible that studies into WS may shed some insight into the underlying causes. Thus, therapeutics developed for WS may find use in normal individuals, to reduce the burden of inflammatory disease in the general population. The diseases are more prevalent as individuals age. Indeed, pharmaceutical companies have in class III trials several other drugs of this class to combat inflammatory disease.



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