Evaluating the role of p38 MAP kinase in the accelerated ageing of WS fibroblasts

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What is Werner Syndrome?

1- physiology

- Werner syndrome is an autosomal recessive disorder that belongs to a category of diseases called premature ageing disorders
- WS individuals display the premature onset of many age-related phenotypes:
  - juvenile bilateral cataracts
  - tight skin and skin atrophy
  - premature hair-greying and hair loss
  - symptoms of age-related diseases such as type II diabetes mellitus, osteoporosis, and premature atherosclerosis
- Age of diagnosis in the late thirties
- Major cause of death is myocardial infarction at a median age of 47
- Widely used a model for some aspects of normal ageing

What is Werner Syndrome?

2- cell biology

- WS fibroblasts have much reduced growth rate
- WS fibroblasts have much reduced replicative capacity
- WS fibroblasts look senescent even when young

*These features may be causal to the accelerated ageing in this disease (Kipling, et al., Science 305, 1426-1431; 2004)*

WS fibroblasts resemble cells that have undergone stress-induced premature senescence

young AG0529 cells

phase contrast x10; phalloidin x20

Stress responses are transduced by p38 mitogen-activated protein kinase

stress

Stress Load

MKK3/6

p38α MAPK

p21

p53

MK2/3

HSP27

pHSP27

Growth arrest

F-actin stress
SB203580 abrogates the p38 stress response

SB203580
Inhibits the α and β forms of p38 MAPK
No effect on the γ and δ forms

4-(5-(fluorophenyl)-2-(4-methylsulfonyl)phenyl)-1H-imidazol-4-yl)pyridine

Effect of SB203580 on cell morphology

Effect of SB203580 on WS cell growth (AG05229C cells)

Immunoblot analysis of p38 activity

However!?

SB203580 also inhibits other kinases that may affect cellular growth

Therefore--

• Use a p38 that is resistant to SB203580, express in WS cells and test effects of drug
• Use siRNA knockdown of RIP kinase and test effects of Drug
• Use drugs with selectivities for the other possible targets, e.g., for JNK

• By these means get a clearer understanding of the mechanism of action of SB203580 in WS cells.
Future--

Once the actual mechanisms of action of SB203580 are elucidated, it is hoped that drugs of this class may be used as therapeutics for WS, e.g., in the Werner mouse model initially.

If stress mechanisms are prevalent to normal ageing, then perhaps p38 therapeutics may be relevant to normal ageing.

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