Response of normal human cells to stress-causing agents and their relationship with ageing and cellular resistance

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Introduction

It has recently been published that there is an important relationship, from the biological and therapeutic point of view, between aging and resistance to agents that cause cell damage. Some authors have described molecular mechanisms involved in both phenomena. The study of these mechanisms and the response of normal human cells would help to understand the relationship between the phenomenon of resistance and ageing in order to prevent the adverse effects of radiotherapy and chemotherapy on healthy tissues.

Objectives

The aim of this work is to study the response of normal cells to stress causing agents and their relationship with ageing and cellular resistance.

Methods

A PubMed search was carried out using the keywords "cell ageing, resistance, HSP, stressor". Articles between 1999 and 2021 related to human normal cells were analyzed.

Results

Exposed human fibroblasts to 41°C during their useful life showed a 3-fold increase in the levels of HSC70, 7-fold increase of HSP70 level and 4-fold increase in HSP27. On the other hand, an 80 % decrease in HSP90 level was observed. Aged human fibroblasts showed increased basal levels of HSC70, HSP70 and HSP27, which caused an alteration in the maintenance of adequate structural and functional capacity. This stressor (thermal factor) activated HSF1, which is a chaperone transcription factor, thus increasing their number. Therefore, a beneficial cellular anti-ageing effect was observed. The results showed a maintenance of juvenile morphology, a reduced accumulation of damaged proteins, increased levels of various HSP, increased antioxidants and a greater resistance to ethanol, hydrogen peroxide and ultraviolet A (UVA) irradiation, as well as increased activity of the proteasome. Other authors found that in young fibroblasts the levels of HSP70 increased by 96 % when applying the stressful dose at a low level in the first hour, 189 % in 2 h and 237 % after 20 h. Low doses of heat shock in keratinocytes showed hormonal and biochemical anti-ageing effects with a maintenance of cell morphology and vigor. It is important to indicate that an improved replicative lifespan (increased by 26 %), an increase in proteasome activity (increased by 60 %) and an increase of almost 2-fold HSP level were observed. In addition, the activity of the Na–K ATPase pump increased by 90 %, producing an increase in the cellular metabolic rate. Oxidative stress refers to progressive cellular damage caused by reactive oxygen species (ROS) and contributes to protein misfolding, accumulation of HSP proteins, and functional abnormalities of retinal pigment epithelial cells during cellular senescence and age-related macular degeneration pathology. The inhibitors of the HSP90 protein, geldanamycin and radicicol, produce beneficial effects in response to oxidative stress and cytotoxicity in retinal pigment cells. The concentration of HSP70 protein increased considerably during all exposure times (6 to 48 h) (3000 % increase in relation to control). Both geldanamycin and radicicol caused a marked accumulation of HSP27 proteins (about 50 % more). Similar results have been described recently in exposed human colon cells and monocytes, showing an increase in HSF1, HSPA6, HSP70 and HSP72 genes.

Conclusions

As indicated, by applying low doses of a stressor, normal cells increase the number of HSP leading to increased survival. This phenomenon is considered a cellular adaptive response. The results show that treatment with low doses of a stressor improve the functional capacity of human cells in terms of greater resistance to stress, increased proteasome activity, and reduced lipofuscin accumulation. There is evidence of oxidative modification of a specific transcription factor in aged cells. In this sense, ageing affects the function, distribution and modification that HSP proteins undergo. Previous induction by heat at low doses is beneficial for the expression of HSP70 and the subsequent increase in cellular resistance to hypoxic and oxidative stress factors. The fact that normal human cells are subjected to low doses of a stressor could be beneficial in vitro, since it increases the concentration of HSP70, HSC70, HSP27 and decreases the level of HSP90. These alterations increase cell resistance in vitro to oxidative, hypoxic and thermal factors, as well as increase proteasome activity, improve cell morphology and vigor, and favor a longer cell life cycle.

CELL TYPE	STRESSOR	HSP LEVEL	EFFECT
Human fibroblasts	Heat (41°C), 1hour, 2 times a week	-HSC70: 3-fold increase -HSP70: 7-fold increase -HSP27: 4-fold increase -HSP90: 80% decrease	-Increased cell survival -Increase cellular resistance to stress -Higher proteasome activity -Lower lipofuscin accumulation
Human fibroblasts	Heat (41°C), 1 hour, 2 times a week	-Increased HSC70, HSP70 and HSP27 -HSP90 decrease	-Increased cell survival -Increase cellular resistance to stress
Human T-cells	Heat (42°C), 30 minutes	-66% reduction in HSP70 transcription rates -HSF1 and SP1 DNA-binding reduced with age	-Altered molecular response to stress with age
Human fibroblasts	-Conditioning: heat (41°C), 1 hour -Resting 1h, 2h and 20h. -Hypoxic stress (carbonyl-cyanide-m-chlorophenylhydrazone) and oxidative stress (hydrogen peroxide)	-1h: HSP70 increases 96% -2h: HSP70 increases 189% -20h: HSP70 increases 237%	-Increased cell survival -Increase cellular resistance to hypoxic and oxidative stress
Human keratinocytes	-Control group: 37°C -Group 1: heat (41°C), 1 hour, 2 times a week -Group 2: heat (43°C), 1 hour, 2 times a week	-Group 1: HSP: 2-fold Increase -Group 2: No alterations	Group 1: -Replicative lifespan increased 26% -60% increase in proteasome activity -Increased cellular metabolic rate -90% increase in Na/K pump activity -Maintenance of youth -Maintenance of cell morphology Group 2: -No anti-aging differences compared to controls
Retinal pigment cells	-Geldanamycin -Radicicol	-HSP70: increases 3000% -HSP27: increases 50% -Does not modify HSP90 or HSC70	-Less progression to age-related macular degeneration
Human fibroblasts	Heat (42°C), 1-2 hours	-Decrease in induction of the hsp70-reporter gene activity -Attenuated activation of HSF1 DNA-binding activity	-Oxidative modification of specific transcription factors in aged cells -Altered function and distribution of proteins with age
Human monocytes	Exercise 60 minutes with heat at 40°C	HSP72: 58 +/- 27% increase	-Greater tolerance against thermal factors -Improved cell survival
Colon cells	-Heat 39.5°C -Hypoxemia	Heat: -HSPA6: 10% increase induced HSP70 increase Hypoxemia: -HSPA6: 12% increase induced HSP70 increase	-Higher tolerance to stress -Improvement in the regulation of glucose metabolism
Lung fibroblasts	Heat at 42°C for 1 hour	HSP40: 25000% increase HSP70: 100% increase	-Improved cell survival -Binding of misfolded proteins -Protection against stress
Colon cells	-Heat 40°C and 42°C -Hypoxia	HSP70 -40 ° C heat only: 25% increase -Only heat at 42°: increase of 75% -Heat at 40 ° C + hypoxia: increase of 35% -Heat at 42 ° C + hypoxia: increase of 100% HSF1 -40 ° C heat only: 25% increase -Only heat at 42°: increase of 35%	-Improved cell survival -Improvement in the recovery and integrity of the intestinal barrier -Higher resistance to stressors
Lung fibroblasts	Silicon (5-40 µg / ml) for 9 weeks	HSP60: -6 weeks: 25% increase -7 week: 100% increase HSP70: -6 weeks: 20% increase -7 weeks: increase 50% HSP90: -8 and 9 weeks: 20% increase	-Increased cell survival -Increased resistance to stress