Increased resistance to drugs and longer life cycle by the administration of exogenous agents to normal human cells

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Introduction

Recent studies have shown that the phenomenon of oncological resistance to chemotherapy and radiotherapy is related at the molecular level to some mechanisms involved in the cellular aging process. Increased resistance and increased longevity have been observed in normal cells exposed to stressors through adaptive mechanisms. However, it is not known whether these common molecular mechanisms between both phenomena can be artificially inducible through the administration of external agents to normal human cells, whether they are biological compounds or recombinant metabolites.

Objectives

The aim of this work is to study the increment to drug resistance and the life cycle of normal cells after administration of exogenous agents.

Methods

A PubMed search was carried out using the keywords “ageing, resistance, HSP, drug, normal cell”. Articles related to the administration of exogenous agent, biologicals and recombinant, to human normal cells were analyzed.

Results

It has been reported that the administration of ascites fluid containing an activator of HSP72 to human fibroblasts to study whether resistance to stress and cell survival is increased, after exposure to a thermal stress of 43°C. HSP72 is involved in protein folding, transport, and degradation, as well as in repairs of stress-induced protein damage. It also participates in cell apoptosis, in such a way that an increase in its production prevents apoptosis induced by factors that damage DNA. This effect is produced by the inhibition of the JNK protein kinase that initiates the apoptosis pathway. By blocking apoptosis, the cell can repair the induced damage providing increased resistance to stress. Mild stress confers resistance against subsequent exposure to severe stress. The results reported show an increase in the resistance to stress and an increase in the cellular longevity. Moreover, the addition of glycerol to human fibroblasts produces an improvement in cellular anti-ageing functions (related to increase thermal and oxidative resistance) when these cells are subjected to an external factor. Acute exposure to 200–400 mM glycerol was found to be sufficient to induce refolding of denatured proteins, as well as to improve cell resistance to heat and oxidative stress without compromising cell viability. Furthermore, treatment of human fibroblasts with glycerol helped to maintain cell proliferation in the presence of levels of H_2O_2 (oxidative stress) that induce senescence. On the other hand, glycerol increased the activity of the proteasome and decreased the function of p53 (which is involved in cell division). These observed activities could result not only from the direct activity of glycerol, but also from a beneficial induction of the proteasome and heat shock chaperones. Another approximation reports that the HSP22 protein present in *Drosophila* was cloned in a retrovirus vector to be inoculated in human fibroblasts. Previously, it was observed that HSP22 in flies was positively regulated during ageing leading to greater longevity, since it increased resistance to thermal and oxidative stress. It was found that fibroblasts possessing HSP22 showed a younger morphology and continued dividing (without entering senescence, compared to controls). On the other hand, lower levels of beta-galactosidase were found leading to a longer lifespan and slowing of the ageing rate. The administration of a recombinant human HSP70 protein to retinal pigment cells was studied to assay the resistance increase to oxidative stress. In this way, the cells were subjected to hydrogen peroxide concentrations of 1.25 mM and a 37 % decrease in IL6. An increase in cell viability of 32 % and a decrease in cell lysis of 43 % was observed. Moreover, HSP70 was administered together with a fragment of an antibody (Fv-HSP70) and subsequently subjected to oxidative stress (H_2O_2), leading to a decrease in cell death and an increase in survival.

CELL TYPE	INOCULATED SUBSTANCE	STRESSOR	EFFECT
Human fibroblasts	HSP72 activator	Heat (43°C)	-Less apoptosis -Improved cell survival
Human fibroblasts	Glycerol	Heat (37°C; 45°C) and oxidative (H_2O_2) stress	-Improved cell survival -Greater resistance to thermal and oxidative stress -Increases proteasome activity -Decreases p53 activity
Human fibroblasts	HSP22 cloned into retrovirus vector	Heat (37°C)	-Younger morphology -They continue to divide -Longer lifespan -Slowering of the aging speed
Pigment cells of the retina	Recombinant HSP70	H_2O_2	-Decreases cell lysis by 43% -Decreases IL6 by 37% -Increases cell viability by 32% -Less age-related macular degeneration
Human alveolar cells	Fv-HSP70	H_2O_2	-Decrease cell death -Greater survival

Conclusions

These results suggest that exogenous HSP70 provides protection against oxidative stress and that it could be a good therapeutic strategy to treat age-related macular degeneration. On the other hand, externally inoculating a heat shock protein to human alveolar cells makes them more resistant to stressors. The inoculation or stimulation of HSP in healthy human cells, not previously present, is beneficial to induce an increase in cellular resistance to oxidative stress and an increase in cell longevity.