HEAT SHOCK PROTEINS OVEREXPRESSED IN TUMOUR CELLS AND THEIR RELATIONSHIP WITH AGEING AND CELLULAR RESISTANCE TO TREATMENT

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Introduction

Heat shock factor 1 (HSF1) is an important regulator of protein quality control by inducing HSP proteins. HSF1 is considered a potential target for cancer therapy because it is overexpressed in several tumour types and its increased expression has been associated with a poor prognosis, because it modifies carcinogenesis by improving cell proliferation and survival in response to oncogenic stimuli. Some authors indicate that HSP proteins and the HSF1 factor are involved in the etiology of breast cancer. However, very little is known about the role of HSP proteins overexpression in the response to radiotherapy and chemotherapy treatment. In addition, a relationship with cellular ageing mechanisms has been suggested, the approach of which could improve treatments.

Objectives

The aim of this work is to study the expression of heat shock proteins in tumour cells and their relationship with the ageing phenomenon and the resistance to the radiotherapy and chemotherapy treatment.

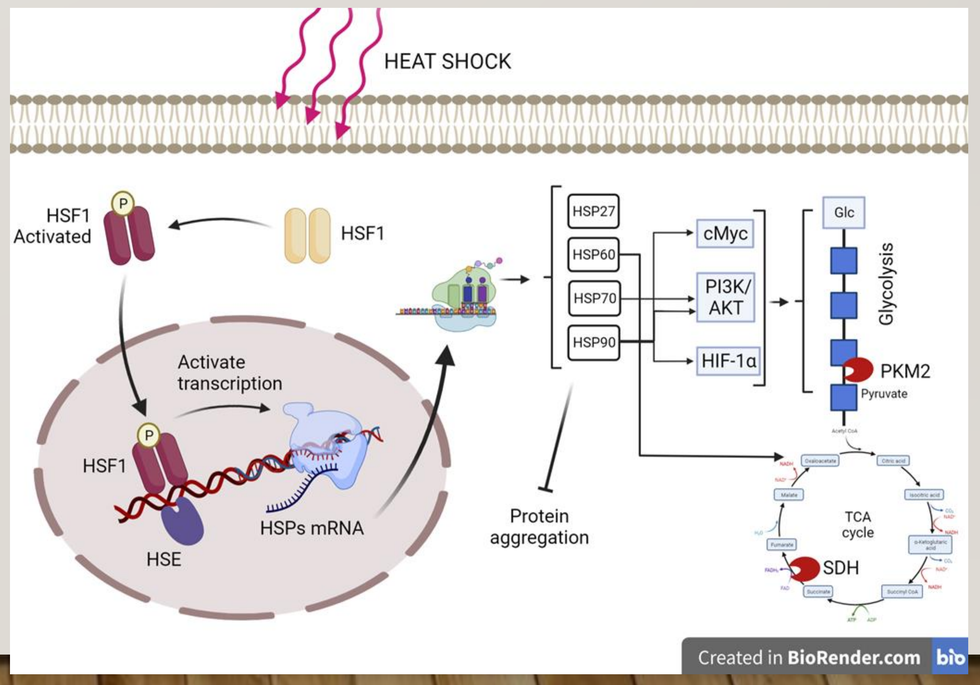
Methods

A broad search in several medical databases (pubmed, scopus, wos) was made looking for articles reporting the expression of heat shock proteins in tumour cells. Only articles describing results of chemotherapy and radiotherapy treatment, and ageing were taken into account. Search keywords: tumour, HSP, chemotherapy, radiotherapy, ageing.

Results

The HSP27 and HSP70 proteins increase in concentration during the transformation of healthy mammary cells into tumour cells, leading to a decrease in apoptosis and senescence. On the other hand, the HSP90 protein plays an important role in facilitating cell transformation, stabilizing the mutated and overexpressed oncoproteins found in breast tumours. This allows the activation of transformation pathways and growth stimulation in the absence of growth factors, as well as an increase in resistance to tumour treatment. HSF1 plays a role as a transformation facilitator in breast cancer. The results obtained are also reflected in a study where women with breast cancer were selected and followed for about 25 years to study how their disease progressed based on the levels of HSF1 in the cells. Thus, it was observed that women with high levels of HSF1 had greater tumour progression and lower survival. On the other hand, the HSP22 present in *Drosophila* was cloned in a retrovirus vector, which was inoculated in human cancer cells. These cancer cells were transferred to mice to study how they evolved in the presence of a stressor and compared to a control group that did not express HSP22. Breast cancer, lung cancer, and osteosarcoma cells showed increased migration, independent growth, the formation of more tumours, and increased resistance to treatment. The overexpression of mortalin (which is a type of HSP70) in breast tumour cells was significantly correlated with the histological grade (tendency to ductal subtype), the clinical stage (greater stage III) and lymph node metastasis in relation to those breast cancers that did not express mortalin. In addition, to further assess the progression of breast cancer where mortalin levels were greatly increased, the disease-free survival and overall survival rate in 155 cases of women with breast cancer were studied. Thus, the patients who overexpressed mortalin had a lower disease-free survival and overall survival than those who had low expression of it. Recently, it has been reported the different HSP that are overexpressed in ovarian cancer and their implication in its development. HSP90 levels are shown to be elevated causing an increase in tumour progression, as well as the ability to metastasize. On the other hand, the overexpression of HSP70 induces an increase in tumour growth and HSP60 a decrease in the overall survival. All of these HSP previously discussed produce an increase in resistance to the treatment. Finally, note that HSF1 levels are also high, implying an unfavorable prognosis for the patient. On the other hand, the levels of HSP expressed in lung adenocarcinoma cells were studied, where an increase in HSP90 was evidenced. These tumours have a worse prognosis in patients where HSP levels are higher, as well as an increase in resistance to treatment and an increase in cell growth.

CELL TYPE	OVER-EXPRESSED HSP	EFFECT
Breast cancer cells	HSP70, HSP27, HSP90 and HSF1	-Decrease apoptosis and senescence -Stabilization of oncoproteins -Increased cell growth -Increased drug resistance
Breast cancer cells, osteosarcoma and lung cancer	HSP22 cloned in retroviral vector and inoculated	-Increase in migration -Independent growth -Formation of more tumors -Increased resistance to treatment
Breast cancer cells	HSF1	-Increased cell growth -Decreased cell survival -Increase in drug resistance
Breast tumor cells	Mortalin (HSP70)	-Increased cell growth -Decreased survival -Increased drug resistance -Increased metastasis -Major tumor stage
Breast tumor cells	HSP70, HSP27, HSP90, HSP40 and HSF1	-Decrease apoptosis and senescence -Increased tumor progression -Increased drug resistance
Ovarian cancer cells	HSP90, HSP70, HSP40 and HSF1	-Increased tumor progression -Increased metastasis -Decreased survival -Increased tumor growth
Lung adeno-carcinoma cells	HSP90	-Increased cell growth -Decreased survival -Increased drug resistance



Conclusions

As it has been reported, the increase in the concentration of HSP in tumour cells produces an increase in the capacity for replication, migration, and drug resistance. HSP and HSF1 factor are involved in the etiology of breast cancer. The overexpression of HSP27, HSP40, HSP70, HSP90 and HSF1 in breast cancer leads to increased multidrug resistance, inhibition of apoptotic cell death, and acceleration of tumour progression. Furthermore, the presence of very high levels of HSP90 resulted in a ductal type carcinoma.