EXPOSURE OF CANCER CELLS TO HEAT SHOCK PROTEIN INHIBITORS INDUCES DECREASED TUMOUR SURVIVAL

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Introduction

The observation of an increase in resistance to drugs used in cancer chemotherapy has led to more in-depth studies on the relationship between exposure to HSP inhibitor drugs and induction of resistance. The HSP90 protein is essential to ensure the survival of some tumour cells, so its inhibition is an important target for some drugs. It has been identified that the inhibition of HSF1, highly expressed in hepatocellular carcinoma, induces an inhibition of HSP90; which leads to laying the foundations for possible combined treatments. HSP90 is necessary for the folding and stability of proteins, which are essential for cell growth, differentiation and survival. Due to this characteristic and the fact that HSP90 is expressed at higher levels in cancerous tissues, inhibition of HSP90 can overcome cell growth signals and drug resistance in many cancers such as osteosarcoma, pancreatic, glioblastoma, and mesothelioma.

Objectives

The aim of this work is to study the effect of heat shock proteins inhibitors in the survival and proliferation of different cancer cells in vivo and in vitro.

Methods

A search in pubmed and scopus was made looking for articles related to heat shock proteins inhibition in different tumour cells in vivo and in vitro. The keywords used were “heat shock proteins, tumour cells, cancer, inhibition, survival”. Publications from the year 2009 were considered.

Results

The application of imetelstat twice a week for 14 to 36 weeks on three osteosarcoma cell lines in combination with the HSP90 inhibitor, alvespimycin, showed a 50 % telomerase inhibition and a reduction in cell growth, as well as a decrease in the formation of osteosarcoma colonies. On the other hand, when imetelstat was applied in combination with alvespimycin, it was observed that telomerase inhibition was 13 % greater than when imetelstat was administered alone, accelerating telomere shortening. In this case, cell growth arrest was produced. The combination of anticancer agents that are used as a treatment in pancreatic cancer in combination with drugs that inhibit HSP90 (such as ICPD47 and ICPD62) have been studied. The combination of HSP90 inhibitors and anticancer agents have a synergistic anticancer effect in pancreatic cell lines, with the most potent combinations being ICP47 with GEM and ICP47 with 5FU. On the other hand, mild hyperthermia has shown an increase in the effect of ICP47 in several lines of pancreatic cancer. Similar results were found in melanoma cells co-exposed to hyperthermia and geldanamycin, showing a 1.8-fold increase in the activity of HSP90 inhibitor. Other authors reported in pancreatic tumour cells using ganetespib, as an HSP90 inhibitor, a reduction in tumour proliferation and survival when combined with the chemotherapy 5FU and radiation. A reduction in HSF1 was also observed. Some authors investigated the resistance of glioblastoma to treatment with temozolamide by adding a small interfering RNA to produce a decrease in BIS (cell death suppressor gene). This study evaluated the response of glioblastoma cells subjected to this interfering RNA that resulted in BIS depletion and, together with temozolamide, resulted in lower resistance to treatment and lower cell survival. As a consequence of the depletion or decrease of BIS, a decrease in HSF1 and an alteration in cell resistance are produced, thereby decreasing tumour survival. Other authors studied the response of chemoresistant malignant mesothelioma cells by adding an HSP90 inhibitor, such as ganetespib, alone and in combination with the usual treatment (pemetrexed+cisplatin). These authors observed that when administering ganetespib alone a chemosensitization of tumour cells was produced. In addition, when adding this drug together with pemetrexed+cisplatin, the cellular senescence was produced (70 % more than when administering ganetespib alone), thereby reducing resistance to the first-line treatment. DCZ5248 compound induced the inhibition of both HSP90 and autophagy at late stage, leading to cell cycle arrest and apoptosis. This fact makes this substance to have a powerful antitumoural activity.

CELL TYPE	STRESSOR	INHIBITION	EFFECT
Melanoma cells	-Low heat dose at 43°C + geldanamycin (HSP90 inhibitor)	HSP90	-Increased effect of geldanamycin in combination with low doses of heat (1.8 times)
Osteosarcoma cells	-Imetelstat -Imetelstat + alvespimycin	-Imetelstat: telomerase -Alvespimycin: HSP90	Imetelstat: -Telomerase inhibition (50% compared to control) -Reduction of cell growth -Decrease formation of osteosarcoma colonies -Not complete growth arrest. Imetelstat + alvespimycin: -Higher inhibition of telomerase (13%) -Complete arrest of cell growth
Glioblastoma stem cells	-Temozolamide + BIS inhibitor (small interfering RNA)	HSF1	-Lower expression of HSF1 -Decrease resistance to treatment
Malignant pleural mesothelioma cells	-Ganetespib -Ganetespib + pemetrexed + cisplatin	HSP90	-Cell sensitization -Increased senescence (70% higher when the three drugs are combined) -Drug resistance decrease
Pancreatic tumor cells	-GEM and 5FU (common anticancer) in combination with ICPD47 and ICPD62 (HSP90 inhibitors) -Heat at low doses	HSP90	DRUGS: -Anticancer synergistic effect. Lower resistance to treatment DRUGS + LOW DOSE HEAT: -Increase the effect of ICP47
Pancreatic tumor cells	Ganetespib + 5FU + external irradiation	HSP90	-Reduces tumor proliferation -Decreases tumor survival -Lower treatment resistance
Colon cancer cells	DCZ5248	HSP90	-Inhibition of both HSP90 and late stage autophagy that leads to cell cycle arrest and apoptosis -Potent antitumor activity -Induces degradation of HSP90 client proteins (CDK4, CDK6, AKT, and RAF1) -Induces vacuole formation, LC3 II conversion and p62 upregulation

Conclusions

All tumour studied show an increase in resistance to treatment and an increase in cell survival. This response is related to an increase in the heat shock protein HSP90, since it participates in the assembly of telomerase, causing telomeres not to be shortened and leading to a longer cell life. When an HSP90 inhibitor is administered together with the usual treatment of this type of tumours, a decrease in cell survival and resistance to the antineoplastic treatment was observed. Recent scientific and clinical data show that HSP90 inhibitors strongly affect the survival of cancer cells and their use in combination with anticancer agents makes it possible to postpone cellular resistance to chemotherapy.

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