ACQUISITION RESISTANCE TO BLEOMYCIN DEREGULATES HSP77 AND HSP60 PROTEINS IN RESPONSE TO STRESS

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Introduction

Heat shock proteins (HSPs) belong to a group of proteins that help protect cells from stress caused by certain elements (heat, cold, and low amounts of oxygen or glucose). Also, they may be present in high concentrations in cancer cells. HSP90 is the most implicated in tumor cell resistance. Several preclinical studies demonstrated an antitumor effect of some HSP90 inhibitors, provoking apoptosis, necrosis and decreased tumor proliferation. Furthermore, other HSPs, such as HSP70 and gp96, are being studied in vaccines to treat cancer. It is essential to perform more studies to verify the exact role of these proteins in response to stressors.

Objectives

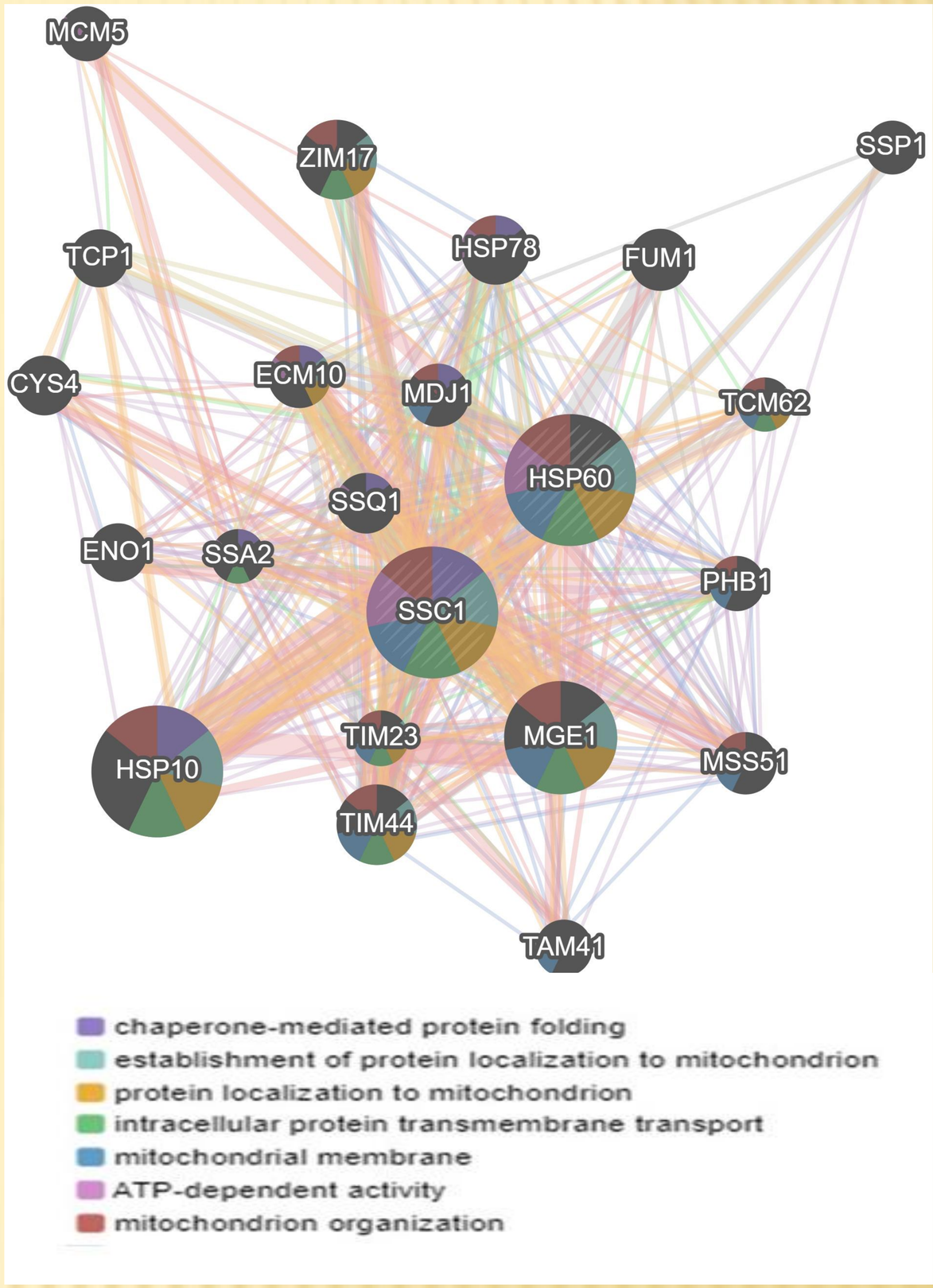
The goal of this work is to study the role of HSP proteins in response to an acquired bleomycin resistance.

Methods

By continuous exposure of a wild type strain of *Saccharomyces cerevisiae* to bleomycin acquired resistance was get. For studying protein expression the value of emPAI (exponentially modified protein abundance index) was used. Further analysis was made by metabolic analysis software.

Results

HSP77 (SSC1 gene) is a constituent of the import motor component of the Translocase of the Inner Mitochondrial membrane (TIM23 complex); also, it is involved in protein translocation and folding. The transport of proteins into the mitochondria requires the participation of 4 protein complexes intercalated in the membrane: called TOM, TIM22, TIM23 and SAM. HSP60 (HSP60 gene) is a tetradecameric mitochondrial chaperonin. It is required for ATP-dependent folding of precursor polypeptides and complex assembly. It prevents aggregation and mediates protein refolding after heat shock. Also has a role in mtDNA transmission. Bleomycin-resistant strain, compared to the wild type strain, showed an increased expression of 2,9 and 2,7 times more, respectively. Thus, this overexpression suggests that these proteins may be involved in the metabolic pathways that lead to bleomycin resistance. After the cytotoxic bleomycin effect, molecular and cellular mechanisms to synthesise proteins for the purpose of resisting the drug and survive are incremented by cells. Therefore, the folding of the synthesized proteins could be improved by the increase of HSP77 and HSP60. Furthermore, thermal stress or the presence of toxic agents produce the overexpression of this protein family coding genes. Thus, these proteins may represent new biomarkers of resistance. The homologous genes in humans are ATP2C1 and HSPD1, respectively.



Functions and interactions between genes that encode proteins with ΔemPAI > 2.5 in bleomycin-resistant strain.

Conclusions

The HSP77 and HSP60 protein overexpression is implicated in bleomycin resistance. The resistant adquisition to antineoplastic drugs deregulate proteins involved in response to stress factors.

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