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Review Article

A Review on Role of HSP70 in Treatment of Cancer

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ABSTRACT

HSP 70 (Heat shock proteins) are an old defense mechanism found in all species. By facilitating the correct folding and refolding of misfolded proteins and aiding in the removal of aged and damaged cells, these proteins function as molecular chaperons Hsp100, Hsp90, Hsp70, Hsp40 and tiny heat shock proteins are example of heat shock proteins. Heat shock protein 70 interact with a broad range of molecules, including unfolded, natively folded, and aggregated proteins, through its substrate binding domains and offers cytoprotection against a variety of cellular stressors. High levels of Hsp70 expression enable cells to endure fatal wounds under pathological circumstances. Increased Hsp70 inhibits apoptosis by interfering with many apoptotic signaling pathways.

INTRODUCTION

Hsp70 is a crucial protein for the cell to retain its proteins and is quite similar to those found in other animals. This protein performs the role of a molecular chaperon, assisting in the correct folding of proteins, preventing their aggregation, and facilitating the proteasomes breakdown of the proteins. Hsp70 has a significant role in signaling, programmed cell death, and protein transport across membranes; disorders like cancer have also been linked to imbalances in the latter.

Membranes of the HSP70 family function as molecular chaperone. Intracellular hsp70s facilitate the construction of poly protein complexes, the folding and transport of proteins and newly generated peptides, and the defense of cells against fatally stress -induced damage. Additionally, Hsp70 can dissolve damaged or aberrant proteins, aid in the folding of developing proteins, and stabilize proteins from denaturation. It may also have a variety of functions. According to some research, the up regulation of Hsp70 in cancer cells protected the survival of malignant cells by acting as an inhibitor of tumor cell

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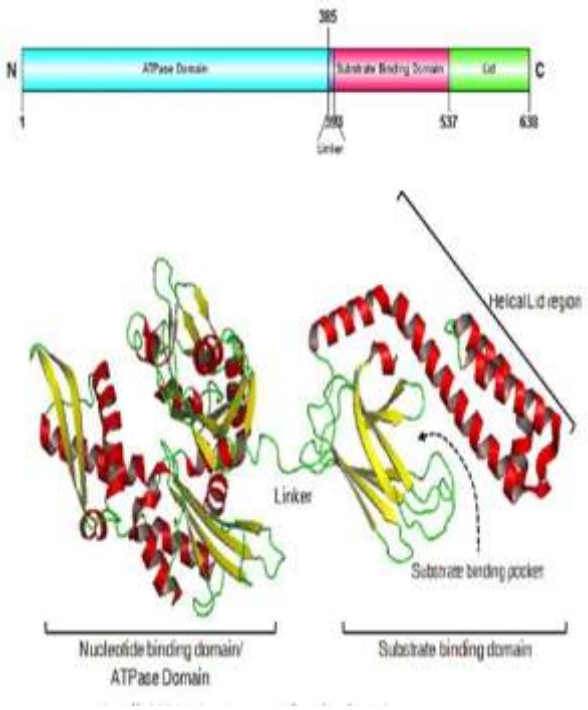
apoptosis and the anti-cancer immune response in both intrinsic and extrinsic pathways.[1]

STRUCTURE OF HEAT SHOCK PROTEIN

Heat shock proteins are critical in the cell in terms of refolding misfolded proteins and in numerous housekeeping functions that enable the cell to survive in a stressed environment. Hsp70 is a 70 kDa protein with a nucleotide binding domain and substrate binding domain Linked together with a short inter domain linker the majority of structural and functional information regarding this protein is derived from the bacterial homolog Dnak.[2][3]

MECHANISM OF HEAT SHOCK PROTEIN



Heat shock proteins a cells protective mechanism that function as molecular chaperons as they ensure the proper folding of the newly synthesized proteins, recondition damaged proteins, and mark misfolded proteins for degradation, this keeping cellular proteostasis. The heat shock response is induced by a variety of stimuli which also include heat and is largely mediated through heat shock factors that bring about rapid synthesis of Hsp's before the cell returns to regular functioning; about the same time that the stress is alleviated.

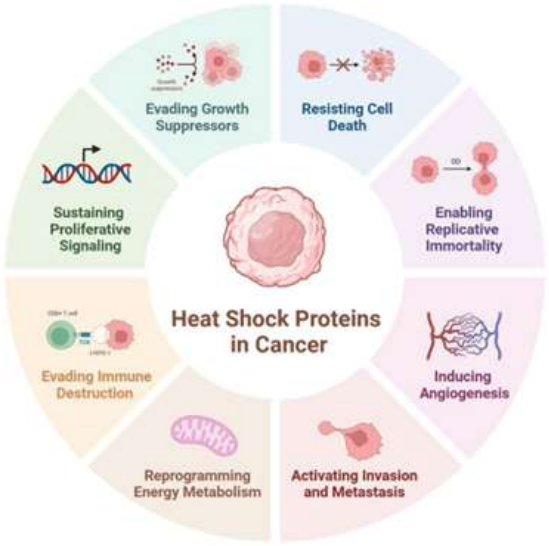
1. Stress Activation
2. Chaperone activity
3. cellular recovery dropping [4]

ROLE OF HSP70 IN CANCER

Cancer cells are perpetually under both external and internal pressure. The tumors are undergoing cytokine onslaught, suffering from a lack of oxygen due to a restricted blood supply, being exposed to an increasing number of free radicals that are produced due to their high metabolic rate and accumulating misfolded proteins because of their decreased genetic stability. In endometrial cancer, Hsp70 is linked to poor differentiation. In uterine cervix cancer, the amount of Hsp70 in cancer tissue is related to the size of the tumor and proliferation. In oral cancer, Hsp70 rising levels are connected to carcinogenesis in poorly differentiated squamous cell carcinoma. In liver

cancer, HSP70 is an early hepatocellular carcinoma marker. Hsp70 has been found in the blastemal and epithelial components of nephro blastomas in the cancer of the urinary system and there are higher levels after chemotherapy. The inhibition of Hsp70, Hsp90, is lethal to tumor cells ,in contrast to normal cells.

Decreasing the Hsp70 expression level specifically kills cancer cells in cell culture and in xenograft tumor models in mice. Most of the cancer cells, lacking Hsp70, die through the lysosomal death pathway. hsp70 obstructs the mitochondrial apoptosis pathway by inhibiting Apaf-1 mediated activation of caspases -9 and -3 as well as by dominating the function of caspase-3. Loss of Hsp70 causes very quick premature senescence in several cancer cells lines that can be activated by cell cycle inhibitors p 16 and p 21.[5][6][7][8]



DRUGS TARGETING HSP70 FOR CANCER TREATMENT

The majority of drugs that target HSP70 for the treatment of cancer are small molecules inhibitors, like PES(2-phenylethyne sulfonamide), VER-155008which attach to the ATP- binding domain and prevents HSP70 . Additional examples include substances like Apoptozole and naturally occuring flavonoids like EGCG and myricetin these inhibitors function by causing apoptosis, or the death of cancer cells more sensitive to other therapies, such as radiation.

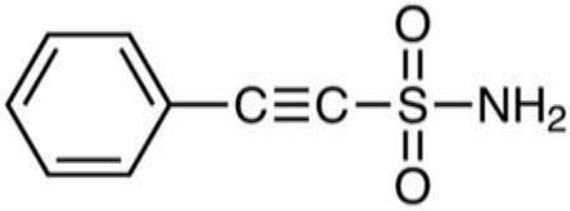
MECHANISM OF ACTION OF GIVEN DRUGS

1. **DRUG NAME:** 2-Phenylethyne sulfonamide (PES)

MOA OF PES

The moa of 2-phenylethyne sulfonamide on HSP70 involves Covalent targeting of certain cysteine residues that are located in the substrate binding domain (SBD) of the protein. This covalent change interrupts the ability of Hsp70 to execute its chaperone functions, of a result of this, a lot of misfolded proteins are formed. autophagy is impaired, and the process of cell death is initiated.

STRUCTURE



2-Phenylethyne sulfonamide (PES)

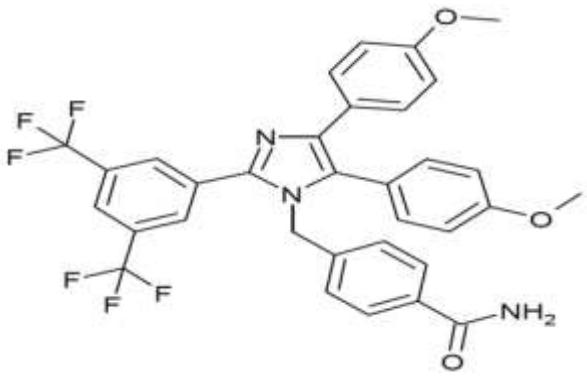
2. **DRUG NAME:** Apoptozole

MOA OF APOPTOZOLE

Apoptozole hinders Hsp70 action by binding to its ATPase domain this disrupting the ATPase activity. Consequently, the influx of Hsp70 into the lysosomes of cancer cells, occurs lysosomal membrane permeabilization is induced, and hence caspase dependent apoptosis is triggered. this process, through blockade of lysosomal function,

leads to impairment of cancer cells autophagy which along with the death of cells further facilitates by the disruption of lysosomal function.

STRUCTURE



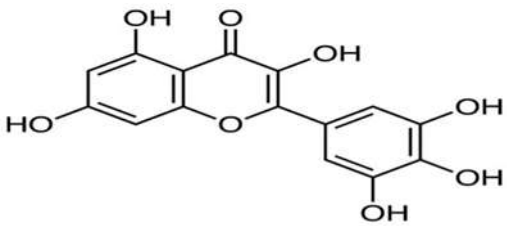
Apoptozole

3. DRUG NAME: Myricetin

MOA OF MYRICETIN

Myricetin as a single agent does not intentionally inhibit the Hsp70 protein family directly, however it indirectly induced Hsp70 expression via Protective pathway against cellular stress (i.e. Heat stress). According to one of the studies, Myricetin may interfere the Dnaj regulation of Dnak (Hsp70) by binding at an allosteric site. [9][10]

STRUCTURE



Myricetin

RESULTS

Drugs that specifically target HSP70 appear to be potent in pre-clinical cancer research. Such drugs have been reported to slow down tumor cell proliferation, sensitive the irradiated tumors, and also activate the tumor cells death pathway. Besides, the inhibitors like PES and Apoptozole interfere with HSP70 engagement with co chaperons or its ATPase function, thus inhibiting the cancer derived signaling pathways. However, authors of these studies clearly state that there are no drugs targeting Hsp70 that have been approved for clinical use as of now, and they are still at different stages of preclinical and clinical trials.

CONCLUSION

Possible New Ways: the scientific community must still consider working on Hsp70 inhibitors more selective in killing cancer cells and able to take advantage of its double nature to fight against cancer as the next step of their research.

Therapeutic Opportunity: Hsp70 blockage by inhibitors is a promising strategy to facilitate the application of standard therapies as well as to evoke anti-tumor immunity.

Dual Edged Sword: Hsp70 is a multifaceted protein in cancer biology mainly supporting tumor progression and treatment resistance. however, it still remains a potential source of immunotherapeutic benefits.

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