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**Heat Shock Proteins as Possible Biomarkers for Diagnosing Various Stages of Cancer.**

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**Word Key:** (HSPs) or (HSP)-Heat shock protein(s)

**Abstract**

**Heat shock proteins (HSPs) are a type of molecular chaperone that is mainly known to only be active during times of extreme cell duress. Heat shock proteins aid in refolding damaged proteins as well as helping to ensure that proteins are correctly folded. Although heat shock proteins appear to contribute positively during times of extreme environmental duress evidence has also indicated that they contribute to the rapid growth of tumor cells as well as not allowing proper cell death as means of controlling cell development. Over expression of these proteins has often times been associated with a number of cancers in humans as well as a strong resistance to known treatments. Exciting results indicate that there is a possibility of identifying and diagnosing early stage human cancers (specifically liver cancer) by testing for the overexpression of heat shock proteins, and using them as a biomarker indicator of cancer cells.**

**Introduction:**

Heat shock proteins (HSPs) were first discovered when they were found present in cells under extreme heat conditions. They are now known for being present during cell stress in general, such as conditions of extreme cold and UV light. HSPs are also present during the processes of protein assembly and folding, as well as secretion and are only induced whenever certain stress signals are triggered. There are multiple types of HSPs, which are all categorized by their size, with HSP27 being the smallest and HSP90 being the largest known. These proteins are critical for cellular life due to the fact that they play a pivotal role in protective mechanisms especially the refolding of damaged proteins. HSP27 can mainly be found in the cytosol of the cell and is involved in cell growth, tumor progression, and differentiation (1). HSP 90 is mainly an anti apoptotic protein that must work together with other smaller HSPs such

as HSP40 and 70 in order to maintain its normal functions. HSP 90 has appeared to be the most prominent type of HSP due to its abundant presence in malignant tumors (2). The following study looks at utilizing various HSPs as possible biomarkers in identifying cancer during early stages of development (specifically liver cancer in this case). A biomarker is defined by the National Cancer Institute as “A biological molecule found in blood, body fluid, or tissues that is a sign of a normal or abnormal process, or of a condition of a disease”(3). With such a heavy presence of Heat shock proteins in cancers, research is beginning to indicate that these proteins can be used as specific biomarkers in identifying and diagnosing human cancer.

**Recent Progress:**

AFP (alpha-fetoprotein) was once a commonly used biomarker for diagnosis of liver cancer but was later discovered to have an extremely low sensitivity for diagnosis, it was eventually considered to no longer be a suitable biomarker for this specific disease, due to its evidence of such low sensitivity and accuracy (2). In a recent study a quantitative measurement of the specific HSP 90 alpha in plasma was observed as a possible new biomarker for liver cancer. It was chosen due to the fact that it had been found to move to the surface of the cell as well as secrete into the extracellular space of cancer cells (2). The study was performed by taking 1647 patients who were either at risk, or already in the varying stages of liver cancer, and testing the levels of HSP 90 alpha found in their plasma (2). These results were then compared to a controlled group of individuals who were not at risk of liver cancer. The studies results seemed to indicate that concentrations of HSP 90 alpha in the plasma of late stage liver cancer patients was far higher than those in the lower stages of liver cancer (2). In order to test the possibility of diagnosis in early stages of liver cancer, the patients that were considered to be in the early stages of liver cancer had their HSP alpha 90 levels tested and compared to the control group of HSP alpha 90 results. The data for individuals in the early stages of liver cancer was found to have significantly higher concentrations of HSP alpha 90 in their plasma than those observed in the control group of non-risk patients (2). This form of measurement for the diagnosis of liver cancer showed large sensitivities in finding early stage cancer patients with small tumors (<3cm) from patients that are not at risk of liver cancer at all (2). Once the HSP alpha 90 data had shown to support the hypothesis that it was a viable biomarker for identifying liver cancer its results were compared to the previously used biomarker of AFP. In comparison to the AFP the plasma HSP alpha 90 had a sensitivity rate of 93.3 percent vs AFP, which had a sensitivity rate of identifying liver cancer at only 61.1 percent (2). The same research group did a large-scale study analyzing the data of a possible new biomarker currently being studied that involves using microRNA to detect the presence of liver cancer. The microRNA results were then compared to the results of the plasma HSP alpha 90 (2). When compared it was found that the reported findings for the microRNA sensitivity in diagnosis as only having a sensitivity diagnosis of 69.1-71.3 percent, which was far less than the indicated results of 93.3 percent sensitivity by the plasma HSP alpha 90 (2). A different study has also begun to

contribute to the idea that heat shock proteins could be used as biomarkers for not only liver cancer, but nearly all human cancers (1). Instead of just looking at HSP alpha 90 as the main biomarkers, the smaller sized heat shock proteins are being studied with evidence suggesting that each one contributes to certain types of cancer such as HSP27 with prostate cancer, HSP60 with

cervical cancer, and HSP90 with brain tumors all expressing raised levels of concentration when tumor cells are present for these specific cancers (1).

**Discussion:**

Although this research is a strong step forward in helping doctors to identify cancer from a very early stage, it is not by any means a cure. This study is simply showing that HSPs specifically, are a very useful and accurate biomarker in identifying cancers during the early stages of development, especially when compared to the previously used biomarker of AFP as indicated in the study results above. It would make sense that heat shock proteins would be considered a quality biomarker. This is due to the fact when it comes to cancers the main function of the HSPs is to respond during times of extreme cell duress. When a cell is cancerous and constantly regenerating without any system of killing the old cells of the organism to be replaced with new, this causes tumors. Tumors are defined by the national cancer institute as “ an abnormal mass of tissue that results when cells divide more than they should, or do not die when they should” (4).Since heat shock proteins’ main function is to attempt to refold damaged proteins as well as help with the correct folding of proteins, it would be reasonable to believe that the heat shock proteins would be overexpressed in cancerous cells due to their need to assist the damaged cellular processes. The study mentioned above seems to pretty strongly indicate that heat shock proteins are possibly the future of being able to identify early stages of cancer to within a relatively accurate degree when controlled to known non-risk individuals. The next step in the field of this study is to begin to look at possibly creating inhibitors specifically designed for which ever heat shock protein is being over expressed in order to slow down and suppress the growth of tumors by blocking the available metabolic pathways of heat shock proteins associated with specific types of cancer (1). Although we are a long way from fully understanding the existence and growth of cancer, it is important that steps be taken to properly identify cancers from a very early stage in order to treat the disease in a timely fashion. With the findings found above this could be the first steps to identifying cancer more efficiently and timely than ever.

**References:**

1. Lianos, Georgios D. “The Role of Heat Shock Proteins in Cancer.” *Cancer Letters*,

Elsevier, 23 Feb. 2015,[www.sciencedirect.com/science/article/pii/S0304383515001305](http://www.sciencedirect.com/science/article/pii/S0304383515001305).

(2) Fu, Yan. “Plasma Heat Shock Protein 90alpha as a Biomarker for the Diagnosis of Liver

 Cancer: An Official, Large-Scale and Multicenter Clinical Trial.” *EBioMedicine*, vol.

 24, 12 Sept. 2017, pp. 56–63. *ScienceDirect*

 (3) “NCI Dictionary of Cancer Terms.” *National Cancer Institute*,

 www.cancer.gov/publications/dictionaries/cancer-terms/def/biomarker.

 (4) “NCI Dictionary of Cancer Terms.” *National Cancer Institute*,

 www.cancer.gov/publications/dictionaries/cancer-terms/def/tumor.