**Hsp90 Inhibitor Treatment for Cushing Syndrome and Other Diseases**

**Key Words:**

Heat shock protein 90, corticotroph, adenoma, novobiocin, silibinin, glucocorticoid receptor

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**Heat shock protein 90 is a chaperone protein commonly involved with the proper folding of cellular protein products into mature proteins. The chaperone is under investigation for its role in abnormal cell propagation, particularly in cancerous cells. In Cushing syndrome, Hsp90 will tightly bind the glucocorticoid receptor protein and cause a decrease in receptor sensitivity. The inactivity of the receptor protein leads to corticotroph adenomas and the main symptoms of Cushing syndrome. Since Cushing syndrome is caused by both steroid treatment side effects and genetic predisposition, finding an effective treatment for the disease rather than just its symptoms is crucial. Three Hsp90 inhibitors were tested in corticotroph adenomas in the treatment of Cushing syndrome symptoms. It was found that silibinin, a recently discovered Hsp90 inhibitor, upregulated the sensitivity of the glucocorticoid receptor and led to alleviation of symptoms in mice models. These results imply that Hsp90 inhibitors may be a viable answer to diseases beyond cancer.**

**Introduction**

Heat shock protein 90 (Hsp90) has been rapidly gaining the attention of the scientific research community. Hsp90 is a cellular protein that acts as a molecular chaperone; that is, it binds to other cellular proteins and assists in proper protein folding. It also helps stabilize its target proteins to avoid cell stress factors like heat or destruction. Hsp90 is most notably studied today for its involvement in disease, particularly in the proliferation of cancerous cells. Under normal circumstances, a cancer cell would be targeted by the host’s immune system for destruction and destroyed, preventing further proliferation of the cell. However, Hsp90 acts to stabilize the cell and resist the immune system attack and other stressful environmental factors. One known way Hsp90 helps with cell proliferation is by stabilizing signaling molecules on the cell such as growth factor receptors. Furthermore, Hsp90 acts as a catalyst to allow greater protein production thanks to its chaperone capabilities, allowing the cancer cell to rapidly grow and divide. It also acts to stabilize otherwise unstable proteins produced by the cell in a cancerous state; certain oncogenes can survive to completion and allow the cell to continue its abnormal cycle. Because of its prominence in the stabilization and proliferation of cancer cells, researchers have recently been targeting Hsp90 to determine ways to safely inhibit its function and potentially treat cancer in humans. However, Hsp90 inhibition may be another viable treatment option for diseases outside of cancer.

**Recent Progress**

Thanks to recent research, many inhibitors of Hsp90 have been discovered. Most of them act by binding to a terminal end of Hsp90 outside of the protein’s binding site and change the conformation of Hsp90, causing it to release its target protein and preventing it from further chaperoning other proteins. This mechanism of Hsp90 inhibition prevents the abnormal cell from successful proliferation and can result in cell death. In corticotroph cells, glucocorticoid receptor proteins (GRs) require direct interaction with Hsp90 to fold and produce mature GRs. One function of GR in the cell is to suppress the transcription of proopiomelanocortin (POMC), which is a precursor to adrenocorticotropin (ACTH), a corticotroph stress hormone (1).

Lack of functional GR allows excessive secretion of ACTH, leading to hypercortisolism characterized in Cushing syndrome. Other symptoms of Cushing syndrome include fat deposits on the upper back, shoulders, and face, pink or purple stretch marks, easily bruised skin, and slow healing of wounds (2). In humans, Cushing syndrome is mainly seen in complications associated with certain steroid use; these steroids are often prescribed for asthma, lupus, arthritis, or for post-surgery treatment. However, it can also appear as a hereditary disease due to hormone imbalance. Finding ways to effectively treat Cushing syndrome, whether it stems from medication side effects or from family genes, is an essential step in preventing a possibly fatal disease.

In a research study done by Riebold et al, Hsp90 inhibition was utilized to determine their effects on corticotroph adenomas commonly seen in Cushing syndrome. These adenomas overexpress Hsp90 compared to normal, noncancerous cells. In Cushing syndrome, it was found that when Hsp90 bound to GR for protein folding, the chaperone remained bound past maturation, causing a glucocorticoid resistance in the corticotroph adenomas. When an inhibitor binds to Hsp90, it forces the chaperone into another conformation that results in the release of its target protein; this mechanism could allow normal functioning of GRs and, in turn, alleviate the symptoms of Cushing syndrome. The researchers used three Hsp90 inhibitors in their experiments: 17-AAG, which binds to Hsp90’s N-terminal end, novobiocin, which binds to Hsp90’s C-terminal end, and silibinin, a recently discovered Hsp90 inhibitor whose mechanism was uncertain.

Their initial hypothesis was that since silibinin was pharmacologically similar to novobiocin, it would have a similar mechanism to the known inhibitor. Normally, inhibitors like 17-AAG bind to Hsp90 and force the release of an immature GR, resulting in degradation of the unfinished protein. The researchers found that treatment with silibinin actually increased the concentration of GR sites in the adenoma cells, meaning the GR released from Hsp90 was mature and the mechanism of inhibition was novel compared to other Hsp90 inhibitors. The research team then investigated the Hsp90 inhibitors’ effects on GR transcriptional activity. While 17-AAG suppressed GR transcription, novobiocin and silibinin enhanced transcription. It was also discovered that GR mutation that altered the GR and Hsp90 interactions interfered with silibinin, indicating that silibinin’s activity is reliant on Hsp90. The researchers then tested the inhibitors’ effects on the inhibition of POMC transcription and ACTH production. It was found that silibinin repressed transcription of POMC. Interestingly, silibinin did not repress ACTH production in normal cells, but it did suppress ACTH production in corticotroph adenomas, which indicated that silibinin’s main activity was in restoring GR sensitivity. The last experiment performed focused on silibinin treatment in mice with an allograft model of Cushing syndrome. During treatment, the researchers found that oral administration of silibinin expressed lower tumor growth rates, lower ACTH and corticosterone levels, and reduction of abnormal fat accumulations in treated mice than in vehicle mice. It was ultimately concluded that Hsp90 inhibitors, especially silibinin, were a potentially viable and effective method for treating Cushing syndrome via restoration of GR activity.

**Discussion**

While Cushing syndrome is a relatively uncommon disease in the United States, it can lead to more severe complications than implied by the trademark abnormal fat deposits. Cushing syndrome can contribute to heightened blood pressure, diabetes, depression, bone loss, and, as stated previously, cancer (2). However, treatment options are somewhat limited to reducing corticosteroid intake, surgery, or medications targeting symptoms of Cushing syndrome. Providing an alternative to invasive or potentially ineffective treatment is a very promising aspect of this study. Hsp90 inhibitors are being extensively studied primarily for cancer treatments, and while Cushing syndrome can lead to cancer, many symptoms of the disease are alleviated by Hsp90 inhibitor treatment, particularly by silibinin. Since Hsp90 may play a role in the persistence of many different kinds of abnormal cell function, it is possible that inhibitors of the chaperone can be used to treat a wide variety of diseases. For example, certain neurodegenerative diseases, such as Parkinson’s disease, Huntington’s disease, and Alzheimer’s disease, stem from deregulation of critical cell protein folding guided by Hsp90; control or inhibition of Hsp90 may alleviate the symptoms of these diseases (3). As more functions and critical roles of Hsp90 are discovered, more possible treatment options for previously untreatable diseases may be uncovered. Further research may want to pursue not only finding more mechanisms involving Hsp90 but also investigating other protein counterparts working in tangent with Hsp90, such as Hsp70.

**References**

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