

Chaperone Protein Hsp90 a Possible Key in Treating Fungal Infections Caused by *Candida albicans*

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With fungal infections on the rise, a clear and decisive treatment is a must. Focusing on *Candida albicans* and its chaperone protein Hsp90 there are potential researches that would have special focus in targeting the protein and discovering its functions in order to cease infections and death. Hsp90 proteins are known to be effective in targeting antifungal treatments; however, its direct functions relating to *C. albicans* are unknown. Scientists have discovered that inhibition of Hsp90 will increase the efficacy of important antifungal drugs, including azoles and echinocandins. *C. albicans* has many virulence traits including, but not limited to, biofilms and morphogenesis. These factors increase the pathogen's ability to adapt and become resistant to drugs. Hsp90 shares a large part in making this possible. With experiments involving model mice and model yeast, *Saccharomyces cerevisiae*, there is hope in creating a new therapeutic target for Hsp90 and *C. albicans*.

Introduction

Infections caused by fungi have been on the rise, increasing fatalities anywhere from 30% to 90% in humans. In the recent two years, the frequency of these infections has increased 200%. The leading cause of fungal infections belongs to *Candida albicans*. Out of all hospital-acquired fungal infections, *C. albicans* is responsible for 88% and is the fourth highest cause in all hospital-acquired infections. Nearly 50% of infected patients perish from the pathogen. Living within oral cavities or gastrointestinal tracts of healthy hosts, *C. albicans* causes superficial infections of oral and vaginal epithelial cells. For immunocompromised patients, such as those with HIV or cancer, the disease is fatal when spreading throughout the bloodstream and invading organs.

Recent Progress

Pathogenic *C. albicans* has a virulence factor that is influenced by many different aspects. These traits include adhesins on the surface of cells that help in adhering

epithelial cells, secretion of proteases that harm the host's cells, an ability to create biofilms, and by being able to alter between yeasts and filaments. Morphogenesis is another trait contributing to the pathogenicity of *C. albicans*. Morphogenesis plays a big role in biofilms. Genes that oversee morphogenesis are also associated with genes that code for other virulence traits such as adhesins and proteases.

Fungal infections are typically difficult to treat; an issue that can possibly be related to evolutionary similarities between fungi and humans. The antifungal drug of choice is usually azoles. Azoles target the major sterol of fungal membranes, ergosterol, and inhibits its synthesis by blocking lanosterol 14 α -demethylase, encoded by *ERG11* in *C. albicans*. This means the targeting of Erg11 results in a buildup of ergosterol, thus inducing a high amount of stress on the cell membrane. Over time, cells have built up resistance to this treatment on the cell as a whole via efflux pumps or changing the target, Erg11. The cells also resist toxicity by changing the ergosterol biosynthesis

pathway. A new antifungal treatment has emerged. It uses echinocandins that inhibit (1,3)- β -D-glucan synthase which also creates stress on the cell. Hsp90 (heat shock protein 90), a molecular chaperone, is one of the most prolific proteins in cells. It is also the target in immune responses to several infections, including fungal. Combining with co-chaperones, Hsp90 has a crucial part in proteins' folding, activation and stability. As previously stated, fungal infections are a leading cause in infections and deaths of humans, but with Hsp90, it is possible to gather information that will lead to a therapeutic target for antifungal drugs.

In regards to *C. albicans*, inhibiting Hsp90 results in several alterations. First it can transform yeast to filaments by way of a temperature-dependent morphogenetic reaction. Another is that the blockage of Hsp90 creates depletion in the resistance to azoles and improves azole performance. Along with having a negative effect on the resistance to azoles, inhibiting Hsp90 also prevents the resistance to echinocandins. The drug can now be considered fungicidal. These two drugs are the leading medications used to treat antifungal infections. As of current time, these are also the only two Hsp90 interactors located in a fungal pathogen. Provided that Hsp90 is compromised in *C. albicans*, the drugs can work to their full extent and hopefully treat the infection.

Candidal Hsp90 is part of an immunodominant antigen found in *C. albicans*. This sub-fragment can be identified in the serum of patients diagnosed with candidiasis. In survivors of candidiasis, human recombinant antibodies of the subfragment can be found. In cases of fatalities, the antibodies are always missing. What scientists want to know is why this occurs and what importance it plays in overcoming infection.

Discussion

Co-chaperones of Hsp90 can be identified in organisms, such as plants, animals and model fungi. In mammals we know that Hsp90 is vital in the role of certain processes and the final step in major proteins concerning signal transduction. However, Hsp90 co-chaperones have not been identified in *C. albicans*. We know that Hsp90 has a part in candidal infections through morphogenesis and virulence, but its true functions in *Candida* are yet to be determined. It is also unknown as to how those subfragments found in surviving patients' serum are developed. Further research of Hsp90 could reveal much more about *C. albicans* and in return give scientists more information about treating its pathogenicity. In experiments involving *Saccharomyces cerevisiae*, the Hsp90 chaperone can show its functions in the yeast. This can be useful in showing how the Hsp90 subfragment could be associated with its functions in *C. albicans*.

Because Hsp90 has heavy involvement with the resistance mechanisms of *C. albicans*, it provides a good outlet for experiments and research to find a suitable antifungal treatment for the pathogen and others like it which also rely on Hsp90 for protein function.

Cells from both *C. albicans* and *S. cerevisiae* give the same Hsp90 fragments that deteriorate partially the same protein initially found in *C. albicans*. When *S. cerevisiae* undergoes respiratory growth, another breakdown of Hsp90 appears. For these reasons, we can hope to use *S. cerevisiae* to better understand Hsp90's function in candidal infections and how the fragments are discovered in patients' serum. In model mouse experiments, inhibiting Hsp90 shows toxicity when aimed toward fungal infections. This is motivation to continue research with Hsp90 in hopes of finding a way to inhibit the chaperone and treat fungal infections caused by *C. albicans* ultimately and effectively.

References

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