Chetomin as a Potent Hsp90 Inhibitor

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INTRODUCTION

Molecular chaperones are essential for life. In the crowded microenvironment of the cell, molecular chaperones are known to serve crucial roles in elongation during translation, post-translational protein modification, cellular signaling, proteolysis, and sub-nuclear trafficking [1]. Based on these functions, molecular chaperones, namely the Hsp90 machine, have been linked to the development of cancers, obesity, neurodegenerative and cardiovascular diseases. There have been several Hsp90 inhibitors in clinical trials to date yet none have been approved by the FDA as a cancer therapy agent in part, due to their induction of anti-apoptotic mechanisms in cancer cells [2]. Therefore, there is an urgent need to develop alternative therapeutic agents without these detrimental effects. In this spirit, we have developed a unique cell-free high-throughput screen (HTS) platform based on the progesterone receptor (PR), an established physiological protein of Hsp90 (1). This assay closely captures most of the steps of PR chaperoning and measures the recovery of its hormone-binding activities after mild heat treatment. It also allows for the identification of inhibitors of the core components of the Hsp90 machine (i.e. Hsp90, Hsp70, Hsp40, Hop and P23). During our initial screening of 175 natural products from North African medicinal plants, we discovered that Chetomin is a highly potent inhibitor of the Hsp90 chaperoning machine. Chetomin was originally identified as a HIF pathway inhibitor [3,4]. Interestingly however, HIF1-α is also an established client of Hsp90. We propose that the true target of Chetomin is the Hsp90 machine, which would open new potential for developing this compound into a promising anti-cancer therapeutic agent.

RESULTS

Impact of IM3 on human cancer cell lines. Cell were treated for 48h with the indicated IM3 concentrations.

DISCUSSION

Chetomin is a highly potent compound with the ability to kill entire cancer cell cultures at nanomolar concentrations. In our studies conducted at normoxic conditions when the amount of HIF-1α in the cells is low, cancer cell death rates are sustained, and evidence shows degradation of several known client proteins of Hsp90 which are crucial to carcinogenesis. This is indicative of Chetomin having a different target than what was initially proposed as HIF1-α. Along with the degradation of known Hsp90 clients, it was observed that Chetomin did not induce and or slightly induced expression of anti-apoptotic proteins characteristic of pro-survival mechanisms triggered by previous generations of Hsp90 inhibitors. The most promising data thus far has come from the EMT-6 cell line. Therefore, more research may be done to understand why the compound is much more efficacious in triple negative mammary carcinomas than in other cell lines tested.

CONCLUSIONS

- Chetomin is a highly potent Hsp90 inhibitor.
- Chetomin is highly effective in killing cancer cells at as low as nanomolar concentrations without overexpressing proteins associated with pro-survival mechanisms of previous Hsp90 inhibitors.
- Chetomin is particularly effective in triple negative murine mammary carcinomas.

Future Directions

- Determine which part of the Hsp90 machine Chetomin interacts with via an intrinsic fluorescence docking study.
- Perform cell culture experiments with Chetomin in Hypoxia to understand how it kills tumor cells in a setting similar to that of the tumor microenvironment.
- Determine what portion of the compound is responsible for its high cytotoxicity.

References


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