Inhibition of HSF1 as a Mechanism for Overcoming Hsp90 Treatment Resistance

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Hsp90 inhibitors have been attempted as a targeted therapy with poor results. Despite numerous clinical trials, there are currently no FDA approved Hsp90 inhibitors available. It is known that Hsp90 sequesters HSF1 in the cytoplasm to suppress HSF1 activity, an oncogenic transcription factor. We hypothesize that HSF1 activation in response to Hsp90 inhibition is a significant reason that previous Hsp90 inhibitors have failed. Once released, HSF1 enters the nucleus and drives expression of many processes that promote the initiation and progression of tumors. This hypothesis was tested by evaluating the response of cancer cells to Hsp90 inhibition with or without combined inhibition of HSF1, thereby removing HSF1 activity as a consequence of Hsp90 inhibition. We observed synergy between Hsp90 inhibition (17-DMAG) and HSF1 inhibition (KRIBB11) from calculation of combination index in ovarian cancer cells (OVCAR8) and breast cancer cells (BT474). This synergy observed in cell viability assays were further reinforced in spheroid formation and clonogenic growth assays where the combination of these inhibitors had a greater effect than either treatment alone. These results further support the hypothesis that Hsp90 inhibition efficacy is mitigated by increased HSF1 activity and that HSF1 inhibitors synergize with Hsp90 inhibitors to improve their efficacy.