# The Role of Chaperones on Mutant p53 Aggregation

**Ferretti, G.D.S.[1,2], Kalume, D.[4], Rangel, L.P.[2,3], Silva, J.L.[1,2].**

[1]Instituto de Bioquímica Médica Leopoldo de Meis, Universidade Federal do Rio de Janeiro, [2]Instituto Nacional de Ciência e Tecnologia de Biologia Estrutural e Bioimagem, [3]Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, [4]Instituto Oswaldo Cruz, Fundação Oswaldo Cruz.

**Introduction and Objectives** Intracellular protein folding may require a complex machinery of molecular chaperones and metabolic energy, both necessary for the protein to adopt its functional native state. In spite of that, cellular environment may favor the aggregation of abnormal newly synthesized polypeptide chains, giving rise to potentially toxic species for the cell. The human p53 protein is a tumor suppressor that inhibits tumor growth and induces cell death, generally through apoptosis. When mutated, p53 acquires a less stable conformation with greater tendency to form intracellular aggregates, which contribute to the accumulation of p53 in tumors. Hsp90 has been shown to stabilize mutant p53 in cancer cells, leading to p53 accumulation. Prima-1 is a phase II drug tested in different cancer types which rescues unfolded p53 mutants into a wild-type-like conformation. In this work, we aim use this compound to evaluate the interaction between p53 and the chaperones HSP70 and HSP90 and their role in p53 aggregation. **Material and Methods:** Breast and ovarian cancer cells expressing wild-type (WT) or mutant p53 were treated or not with Prima-1 and analyzed by Western-blotting, immunoprecipitation with anti-olygomer antibody A11 and mass spectrometry. **Results and Discussion:** WTp53 cells show higher levels of HSP90 and HSP70 when compared to mutant p53 cells, both in soluble and pelleted insoluble fractions of cell extracts. MDAMB-231, a p53 mutant cell, when treated with Prima-1, lost interaction between mutant p53 and HSP90, which was demonstrated by western blotting and mass spectrometry of immunoprecipitates. However, no difference in protein levels was observed in total cell extracts. This effect was not observed for HSP70. **Conclusions:** Here, we demonstrate that Prima-1 has a positive effect in the erroneous interaction between mutant p53 and HSP90 in cancer cells. However, the mechanisms of p53 aggregation and its proteostasis need to be further elucidated to better understand cancer pathogenesis and improve cancer therapy.

**Key Words**: Chaperones, p53 Aggregation and Prima-1.

**Funding:** CNPq, FAPERJ and INCT.