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Venue: Central 5-41 2F (Meeting Room #42)
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Title: Computational and experimental insights to the response of p53 mutant cancer cells to Ashwagandha-derived withanolides

Tumor suppressor p53 protein is found be mutated in more than 50% cancer cases. These mutations induce local or global changes in protein structure thereby affecting its binding to DNA. The structural differences between the wild type and mutant p53 thus provide an opportunity to selectively target mutated p53 harboring cancer cells. Restoration of wild type p53 activity in mutants using small molecules is one such option for cancer therapeutics. In this study, we first used molecular modeling approaches to investigate the structural changes between the wild type and various mutant p53 proteins ($p53^{V143A}$, $p53^{R249S}$, $p53^{R273H}$ and $p53^{Y220C}$) and explored the therapeutic potential of Withaferin-A and Withanone for restoration of wild type p53 function in cancer cells. $p53^{V143A}$ mutation did not show any significant structural changes and was also refractory to the binding of withanolides. $p53^{R249S}$ mutation on the other hand disturbed the hydrogen bond network, thereby affecting its binding to DNA. However, in this case withanolides were not selective to the mutant p53. $p53^{R273H}$ also did not show any selective binding with the withanolides. $p53^{Y220C}$ mutation created a cavity near the site of mutation with local loss of hydrophobicity and water network. Here, the mutated structure could accommodate withanolides with much more affinity, suggesting their conformational selectivity to target $p53^{Y220C}$ mutant. These computational predictions were then validated in cancer cells harboring the specific mutant p53 proteins using various molecular assays. We demonstrated that Withaferin A, Withanone and the extract rich in these withanolides caused restoration of wild type p53 function in mutant $p53^{Y220C}$ cells. This was attributed to the induction of p21WAF-1-mediated growth arrest/apoptosis.