Abstract:

Amongst the numerous genetic alterations that occur in cancer cells, is overexpression of DNA repair proteins (DNA-RP) in a disease-stage associated manner which has also been correlated to chemo/radiotherapy (CRT) resistance and poor overall prognosis. DNA-RP overexpression has been reported to involve post-translational protein stabilization mediated by the molecular chaperone Heat shock protein 90(HSP90), thereby preventing proteasome-dependent degradation of these HSP90 “client” proteins. Hence, HSP90 inhibitors (HSP90i) have been heralded as co-therapy agents for cancer patients that have developed resistance to first-line treatments such as temozolomide (TMZ). Under conditions in which its function is blocked by HSP90i, HSP90 client proteins rapidly become (poly)ubiquinated and undergo degradation resulting in improved sensitization of cancer cells to CRT. We observed that HSP90i promote the proteasome-dependent (i.e. blocked by inhibitors PS-341 and MG-132) degradation of a range of DNA-repair client proteins. We have also identified H-2Kb/Db-presented peptide epitopes derived from these DNA-RPs that may be recognized by Type-1 CD8+ T cells after specific vaccination. We are currently investigating the capacity of HSP90i to conditionally sensitize melanoma cells to the tumoricidal action of CRT as well as CD8+ T cells reactive against overexpressed DNA-RP that constitute HSP90 client proteins.