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Targeting oncoprotein stability: HSP90 Inhibitors as potential chemotherapeutics to overcome cancer drug resistance

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Identification of mutated tyrosine kinases as underlying genetic events in the pathogenesis of several cancer types led to the development of chemotherapeutics that target their activity. The successful use of imatinib (Gleevec or Glivec) in the treatment of chronic myeloid leukemica (CML) has revolutionized the field of targeted cancer therapy. However, the emergence of secondary drug resistance upon targeted treatment has posed significant clinical challenge in multiple cancer types. For example, point mutations in the kinase domain that abrogate inhibitor binding were reported in EGFR (non-small cell lung cancer, NSCLC), ERBB2 (breast cancer), ALK (neuroblastoma), c-KIT (gastroinstesinal stromal tumors, GIST) and FLT3 (acute myeloid leukemia, AML) kinases. Thus, there is an urgent need to identify alternate treatment strategies to effectively treat cancer as well as to prevent the emergence to secondary drug resistance. It is important to note that several oncoproteins, especially mutated kinases were shown to be HSP90 clients i.e., these non-native versions of the protein bind to and are stabilized by the HSP90 chaperone. It has been shown previously that the inhibition of HSP90 activity by specific inhibitors lead to the destabilization and as a consequence degradation of the HSP90 client oncoproteins. However, since many house-keeping proteins inside the cell are also stabilized by the HSP90 chaperone, it is uncertain if selective toxicity against cancer cells versus healthy cells can be achieved. To test this hypothesis, we established a panel of isogenic cell lines that stably express FLT3-ITD mutation with wild-type or drug-resistant mutant kinase domain. Biochemical analysis revealed that all the FLT3 mutants tested bind to HSP90 and were degraded upon HSP90 inhibitor treatment. Importantly, HSP90 inhibitors induced dose-dependent toxicity selectively in cells that were transformed by FLT3 mutants. Even though HSP90 inhibitors showed non-specific toxic effects on non-transformed (wild-type) cells, a significant therapeutic window was achieved at certain inhibitor concentrations. Interestingly, a combination of FLT3 kinase inhibitor and HSP90 inhibitor abrogated the emergence of secondary drug resistance in a cell-based screening assay. Thus, these pre-clinical results indicate towards the possibility of the usage of HSP90 inhibitors to target FLT3-mutant AML either alone or in combination with kinase inhibitors. Furthermore, these results encourage for the development of novel HSP90 inhibitors with enhanced efficacy to selectively target cancer cells.

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