Comparative transcriptomic/proteomic analysis in Hodgkin and non-Hodgkin lymphomas following Nutlin-3A-induced p53 stabilization and activation

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The p53 tumor suppressor gene, commonly mutated in human cancers, is mostly found as wild-type (wt) p53 in hematologic malignancies, representing an attractive target for novel, therapeutic strategies. HDM2, the main negative regulator of wt-p53, modulates its stability, subcellular distribution, and targets p53 protein for proteosome-mediated degradation. Nutlin-3A, a novel small molecule inhibitor of the p53-HDM2 module, activates and stabilizes the wt-p53 response. We have previously shown that Nutlin-3A induces p53-dependent cell cycle arrest and apoptosis in wt-p53 human lymphoma cells. This study investigates the differential transcript and protein expression in response to Nutlin-3A treatment, in 3 different lymphomas (Hodgkin’s and non-Hodgkin’s), using transcriptomics and proteomics approach. Within this frame, three human lymphoma cell lines (treated/non-treated) were used for stabilization and reactivation of p53. Microarray analysis was performed using Affymetrix GeneChips according to established protocols and stable-isotope labeling or label-free analysis using nLC-MS/MS for protein identification and quantitation. More than 600 transcripts and 3500 proteins could be relatively quantified, revealing significant information about the expression levels of p53 target molecules following Nutlin-3A treatment. The largest functional classes comprised proteins involved in metabolic processes, translation, gene expression, and apoptosis. However, differences in transcriptome/proteome profile and in the expression of the common proteins between each lymphoma subtype were also observed, reflecting their biological differences. Our findings provide a better understanding of the precise mode of action of Nutlin-3A, revealing significant information supporting the therapeutic concept of a functional p53 pathway in hematologic malignancies.

5. Drakos E et al. Leukemia, (2011); 25: 856–867