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Understanding the biological basis for the differential response to HSP90 inhibition in NSCLC using proteomic technics.

Angela Marrugal[1] , Irene Ferrer[2] , Maria Dolores Pastor[3] , Amancio Carnero[4] , Luis Paz-Ares[5] , Sonia Molina-Pinelo[4]

1) Instituto de Investigación Hospital Doce de Octubre (i+12), Madrid, Spain. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain. 2) Instituto de Investigación Hospital Doce de Octubre (i+12), Madrid, Spain. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain. Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain. 3) Instituto de Biomedicina de Sevilla (IBIS) (HUVR, CSIC, Universidad de Sevilla), Sevilla,Spain. 4) Instituto de Biomedicina de Sevilla (IBIS) (HUVR, CSIC, Universidad de Sevilla), Sevilla,Spain. Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain. 5) Instituto de Investigación Hospital Doce de Octubre (i+12), Madrid, Spain. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain. Medical Oncology Department, Hospital Universitario Doce de Octubre, Madrid, Spain. Centro de Investigación Bio

BACKGROUND AND CONTEXT

HSP90 is the cancer chaperone given that stabilizes a lot of oncogenic proteins. Therefore, its overexpression has been associated to poor prognosis in some tumours types. This chaperone is very important in non-small cell lung cancer (NSCLC) since some of its proteins drivers depend on it. Thus, HSP90 inhibitors show great promise in NSCLC treatment and they could lead to better clinical outcome for this disease. However, supporting evidence of inhibition's efficacy will be essential for successful clinical improvement.

OBJECTIVES

- Evaluation of the efficacy of HSP90 inhibition in several molecular subgroups of NSCLC.
- *In vitro* research of a proteomic profile associated with the response to HSP90 inhibitors in NSCLC.

METHODS

Were used NSCLC cell lines carrying gene mutations, whose direct (EGFR mutated and EML4-ALK rearrangement) and indirect (KRAS mutated) relationship with HSP90 has been reported. In these cell lines, along with wild type cell lines as control, the activity of this chaperone was interrupted. For such purpose, pharmacological inhibition of HSP90 was achieved through geldanamycin and resorcinol derivatives. In addition, given that HSP70 complements HSP90 activity, concurrent treatment of HSP90 and HSP70 inhibitors was realised. The response to this inhibition was confirmed by western blot. Then proteins from each cell line, inhibited and untreated, were subjected to iTRAQ labelling. In order to find differentially expressed proteins that help us to understand the biological basis for the response based on HSP90 interactome.

RESULTS

In the NSCLC cell lines studied, the expression of the oncogenic proteins EGFR, EML4-ALK and CDK4, were decreased by the HSP90 inhibition. The EGFR positive cell lines and those that presented ALK rearrangement were the most sensitive cell lines to the inhibitors. This fact showed the strong dependence on HSP90 in the

oncoproteins drivers EGFR and EML4-ALK. A list of proteins that were differentially expressed, in treatments versus control, was obtained though iTRAQ. This allowed identify, using software tools, the oncogenic pathways associated with the inhibition. In addition, HSP70 overexpression compared to unprocessed cell lines confirmed HSP90 inhibition.

CONCLUSIONS

HSP70 induction in addition to oncogenic client proteins degradation, showed proof of treatment efficacy. Besides, through iTRAQ technology, we identified a list of differentially expressed proteins after inhibition which are associated with deregulated pathways involved in the tumorigenesis. Nowadays, we are carrying out different studies focuses on finding protein biomarkers of treatment response as well as the biological mechanisms under HSP90 inhibition in NSCLC.