DNA repair dysfunctionality in lung cancer

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DNA repair dysfunctionality is related to genomic instability, an important hallmark of cancer cells. The study of DNA repair mechanisms (regulation, efficiency, and associated biomarkers…) in lung cancer will allow a better comprehension and prediction of the clinical evolution of this disease. Differential degrees of DNA repair dysfunctionality between patients might explain why some DNA-damaging anticancer agents yield highly heterogeneous therapeutic responses. We previously showed that long-term survival benefit derived from chemotherapy is different according to both MSH2 and ERCC1 expression (chemotherapy strongly prolonged long-term survival in the combined MSH2-negative/ERCC1-negative subgroup compared to observation (adjusted hazard ratio for death, 0.65; 95%CI, 0.47 to 0.91; P=0.01). This observation suggest that lung cancers presenting high expression of DNA repair biomarkers might be a different disease compared to cancers with low expression profiles.

There are at least 6 major pathways of DNA repair in a cell, each processing a particular type of DNA damage: DR (Direct Repair), NER (Nucleotide Excision Repair), BER (Base Excision Repair), MMR (mismatch repair, or mismatch repair), HRR (Homologous Recombination Repair,) and NHEJ (Non-Homologous End-Joining). Despite a high complexity of DNA damage signalling and connexions between different DNA repair pathways, it is generally possible to highlight one or two (MMR), BRCA1/2 (HRR) and DNA-PKcs (NHEJ). We are actually pursuing our investigations using an integrated approach to characterize DNA repair dysfunctionality in lung cancer cells and in patients. This is achieved by means of CGH and measurement of the aberrant genome index in tumor samples, and also by a functional test allowing the dynamic measure of the global number cisplatin-induced DNA adducts

IHC evaluation of ERCC1, BRCA1, MSH2 and PARP1 clearly demonstrate that loss or low protein expression of these proteins is observed in 38% to 53% of around 650 resected NSCLC samples. Further, using an independent cohort of lung cancer patients, we also found a significant association between the level of ERCC1 immunohistochemical status and genomic instability measured by CGH arrays.

In conclusion, DNA damaging-based therapy could be chosen according to individual tumor evaluation of DNA repair dysfunctionality.