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BRG1 deficient cells are sensitive to the inhibition of specific lysine demethylases (KDMs) in lung cancer

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The standard treatment of non-small cell lung cancer (NSCLCs) is surgery. New therapeutics, such as tyrosine kinase inhibitors or immunotherapy may improve survival, but these treatments are only effective in small cohorts of patients. Thus, hopes of improving survival of lung cancer patients are related to the advent of novel therapeutic strategies. The classic epigenetic research focuses in the reversion of gene promoter DNA hyper methylation or histone code modifications, using a battery of unspecific drugs addressed to modify the global epigenetic code in cancer cells. In our previous work, we identified frequent inactivating mutations in the epigenetic gene BRG1, (about 20% of NSCLC) which were mutually exclusive with amplifications in the MYC oncogenic family. Cells that lack BRG1 were refractory to the administration of glucocorticoids (GC) and retinoic acid (RA). In other hand BRG1-mutant cancer cells were also not able to respond to certain epigenetic therapies, alone or in combination with hormones. In contrast cancer cells carrying MYC amplification, which are BRG1 proficient, appear to be highly sensitive to these combinations of treatments. These results show that MYC amplification could be used as a **prognostic biomarker for a specific personalized therapy**. This idea of Cancer Epigenetic Reprogramming emerged as the rational combination, of target specific epigenetic drugs, with the combinations of appropriate environmental stimuli (hormones and vitamins) depending of the specific mutational background at the different epigenetic effectors in each cancer type. In this project we observed that the mutational status of BRG1, directly correlates with the expression levels of several Lysine methyltransferases (KMTs) and Lysine demethylases (KDMs) in cancer cells. Interestingly we also found that at genetic level, inactivating mutations in KDMs and KMTs tend to be mutually exclusive with inactivating mutations in BRG1, mutations in other SWI/SNF members and mutations in MYC oncogenic genes. Thus, we focused on targeting histone-modifying enzymes, in BRG1 proficient or deficient lung cancers cell lines. For this propose we integrate state of the art technology like genome-wide chromatin modification and transcriptome analysis, using human cell lines and preclinical models for lung cancer, including *in vivo* models of mice such as xenografts, to **design a personalized epigenetic treatment with high efficacy and low toxicity**. Our results showed that BRG1 directly regulates KDMs expression in lung cancer and demonstrates that inactivating mutations in BRG1 sensitizes cancer cells to the histone H3K27me3 demethylase inhibitor GSK-j4. We also noticed that co-treatment with RA in BRG1 proficient cells promotes an enhancing of H3K4me1 mark at gene promoter level. This indicates that the mechanistic cooperation between KDM6A and MLL4/KMT2B or MLL2/KMT2B, by which the removal of repressive marks and the simultaneous deposition of active marks leads to the activation of a target gene expression, is dependent of a proficient BRG1 in lung cancer cells. The results will be of great value for the stratification of lung tumors according to their genetic or epigenetic background for tailored treatments. The development of an epigenetic-based therapeutic prediction model will hopefully set the basis for future treatment of lung cancer as well as of other epithelial cancers

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