MECHANISMS OF RESISTANCE TO A PI3K INHIBITOR IN GASTROINTESTINAL STROMAL TUMORS: AN OMIC APPROACH AIMED TO IDENTIFY NOVEL DRUGGABLE TARGETS

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Introduction: Gastrointestinal stromal tumors (GIST) represent a worldwide paradigm of target therapy. The introduction of tyrosine kinase inhibitors (TKIs) has deeply changed the prognosis of GIST patients, however, the majority of them acquire secondary mutations and progress. Unfortunately, besides TKIs, no other therapeutic options are available. Therefore, it mandatory to identify novel molecules and/or strategies to overcome the inevitable resistance. In this context, after the promising preclinical data on the novel PI3K inhibitor BYL719, the NCT01735968 trial in GIST patients who previously failed treatment with imatinib and sunitinib started. BYL719 has attracted our attention, and we comprehensively characterized genomic and transcriptomic changes taking place during noticing of resistance.

Material and method: For this purpose, we generated two in vitro GIST models of acquired resistance to BYL719 and performed an omic-based analysis by integrating RNA-sequencing, miRNA and methylation profiling in sensitive and resistant cells.

Results: We didn't identified novel mutations in resistant cell lines. On the contrary, we found a deep deregulation in gene expression levels, as well as in miRNAs and in methylation global profiles. In particular, we observed 95 differentially expressed genes with P-value ≤0.001 and a false discovery rate (FDR) < 0.1. With regard to mRNAs, the array highlighted a total of 44 deregulated miRNA out of the 754 analyzed with a P-value<0.05, however, after adjustment only 13 miRNAs maintained statistical significance. Considering the methylation profile, 3305 differentially methylated CpGs were identified. Among them, 2817 were hypermethylated and 488 hypomethylated; within the hypermethylated CpGs. Finally, we integrated all the data to construct a potential epigenetic network, suggesting the existence of pathways involved in drug resistance and alternative to acquired mutations. Therefore, epigenomics should be taken into account as an alternative adaptive mechanism.

Conclusion: Despite the fact that currently we do not have patients in treatment with BYL719 to verify this hypothesis, the most intriguing results is the involvement of H19 and PSTA1 in GIST resistance, which might represent druggable targets.