ID: 00762
Type: COMUNICACIÓN ORAL
Topic: 1. Epigenomic and cancer

BCL7A HAS A TUMOR SUPPRESSOR ROLE IN HEMATOLOGICAL MALIGNANCIES

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INTRODUCTION: Changes in the gene expression patterns are key in cancer cell transformation, through an increase in expression of genes that promote carcinogenesis (oncogenes) and/or a decrease in expression of genes that prevent it (tumor suppressor genes).

SWI/SNF chromatin-remodeling complex uses the energy released upon hydrolysis of ATP to alter the interactions between DNA and histones and modifies the availability of the DNA for the regulatory transcription machinery, and thereby control gene expression. The latest deep-sequencing analysis of tumor genomes has reinforced the important and ubiquitous tumor suppressor role of the SWI/SNF complex in cancer. SWI/SNF complex appears to be mutated in nearly 20% of all tumor samples analyzed.

BCL7A was recently identified as a new dedicated member of the mammalian SWI/SNF complex and some reports found BCL7A expression inactivated in hematological malignancies but rarely in solid tumors, reinforcing a possible tumor suppression role of BCL7A.

OBJETIVES: Given the recent association of BCL7A to the SWI/SNF complex and the high rate of mutation of this subunit in hematological tumours, it became for us a great challenge to elucidate BCL7A biological function and its role in hematologic malignancies, where we hypothesize that BCL7A has a tumor suppressor role.

Specific objectives:

1. Determine BCL7A gene expression inactivation in cell lines derived from hematologic malignancies.

2. Establish a functional model for studying BCL7A activity. The optimal cell line model will be one in which BCL7A expression has been abolished by a genetic or epigenetic alteration.

3. Studying the phenotypic changes after BCL7A expression restoration.

METHODS: A mutational analysis of BCL7A coding sequence was performed at DNA level over a collection of 42 cell lines and 38 patient samples derived from Diffuse Large B-cell lymphoma. Hot spot mutations found at splicing donor sites were subsequent analyzed and shorter BCL7A transcripts were amplified by PCR. Western blot analysis finally confirmed the aberrant expression of a mutated BCL7A protein lacking the amino terminal region.

Then, we used the cell line expressing an aberrant BCL7A as a model to restore its wild-type expression by lentiviral based technology. The resulting phenotype was analyzed by a competition cell growth assay. In order to confirm the tumor suppressor phenotype of BCL7A we performed a xenograft transplantation on NSG mice with cells stably expressing luciferase and expressing or not wild-type BCL7A and mutant-BCL7A. Tumor growth was monitored in vivo by using the IVIS Spectrum photon-counting device optical imaging system.

RESULTS: After screening for BCL7A genetic alterations over a battery of hematological cell lines, we found a set of cell lines harboring critical mutations and chromosomal rearrangements that abolish BCL7A expression.

BCL7A mutations were found in cell lines derived from patients with a specific subtype of Non-Hodgkin lymphoma: Diffuse Large B-cell Lymphoma (DLBCL). To get deeper in BCL7A mutational status in DLBCL we analyzed a panel of 42 cell lines and 38 patient samples derived from DLBCL. BCL7A was mutated in 15.6% of cell lines analyzed. Two different types of mutations were found: missense mutations and mutations in splicing donnor sites.

Interestingly, mutations found in BCL7A are within the amino terminal region, only in the first exon. Furthermore, hot mutations at the splicing site in exon one of BCL7A were found in two different hematological cell lines. These mutations render a mutant-BCL7A, where the amino-terminal region is lost.

BCL7A deficient cell line was used to analyze tumor phenotype changes after BCL7A expression restoration by lentiviral-based technology. Our results show that BCL7A impair proliferation by decreasing its growth. Tumor growth is also reduced after xenograft transplantation of this cell line in NSG mice. Moreover, the tumor suppressor role was shown to fall on the amino terminal region of BCL7A since mutant-BCL7A lacking the amino terminal region is not able to resemble wild-type phenotype.

CONCLUSIONS:

- BCL7A is highly mutated in patients with Diffuse Large B-cell lymphoma.

- BCL7A expression restoration has a tumor suppressor role *in vitro* and *in vivo* xenograft studies.

- BCL7A has critical mutations in the splicing site of exon one. This critical mutation entails a loss of BCL7A tumor suppressor role.