AS3MT AND *MTH1* GENES AS NEW MARKERS IN THE ARSENIC-INDUCED MALIGNANT TRANSFORMATION

Barguilla I.[1], Peremartí J.[1], Bach J.[1], Marcos R.[1,2], Hernández A.[1,2]

[1]Grup de Mutagènesi, Departament de Genètica i de Microbiologia, Facultat de Biociències, Universitat Autònoma de Barcelona, Bellaterra, Spain

[2]CIBER Epidemiología y Salud Pública, ISCIII, Spain.

irene.barguilla@uab.cat

Arsenic is a widespread and well-known human carcinogen associated with different kinds of cancer. Although the mechanisms of action by which chronic arsenic exposure leads to tumor development are not fully unveiled, it has been found that oxidative DNA damage plays an important role in the process. AS3MT is a key enzyme in arsenic biotransformation known to participate in the generation of ROS after a given arsenic exposure, while MTH1 has a role sanitizing oxidized dNTP pools and preventing the incorporation of damaged bases into the DNA.

In this work, MEF cells were chronically exposed to arsenite and monitored for oxidative and genotoxic DNA damage at different time-of-exposure intervals for 50 weeks, in order to assess the role of *As3mt* and *Mth1* in the arsenic-related transformation process. Thus, expression changes of these genes were evaluated by real-time RT-PCR at equivalent time-points.

Our results demonstrate that the oxidative and genotoxic damage increased time-dependently up to the cell's transformation point -reached after 30 weeks of exposure- but dropped drastically afterwards. Ongoing knock-down experiments could elucidate *As3mt* and *Mth1*'s role on the transformation process, validating the correlation found between their mRNA levels and the DNA damage pattern observed during arsenite exposure.

In conclusion, the study of the differential role of *As3mt* and *Mth1* in the accumulation of DNA damage linked to the transformation process has shown that *As3mt* acts as a damage sensor, contributing to the genotoxicity observed before transformation, while *Mth1* prevents the DNA damage fixation after the acquisition of the transformed phenotype and it is proposed as a new biomarker of arsenic carcinogenesis.