Oxidative and genotoxic damage drop after arsenic-induced malignant transformation. Involvement of *As3mt* and *Mth1*

Jana Peremartí[1], Jordi Bach[1], Ricard Marcos[1,2], Alba Hernández[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.

Oxidative DNA damage (ODD) plays a crucial role in the carcinogenesis of the widespread and well-known human carcinogen arsenic. The key arsenic biotransformation enzyme As3mt is known to participate in the generation of ROS after a given arsenic exposure. Contrarily, Mth1 sanitizes oxidized dNTP pools to prevent incorporation of damaged bases into DNA.

In the present work, we sought to assess the role of *As3mt* and *Mth1* in the oxidative and genotoxic DNA damage generated throughout the arsenic-related transformation process. Thus, MEF cells previously transformed by 30 weeks of chronic arsenite exposure were monitored for ODD and DNA damage by the comet assay and the micronucleus assay, respectively, at different time-of-exposure intervals for 50 weeks. Expression changes of *As3mt* and *Mth1* were evaluated by real time RT-PCR at equivalent time-points. Epigenetic consequences were also analyzed.

Our results demonstrate that the oxidative and genotoxic damage of chronically exposed MEF cells increased time-dependently up to the point of transformation but dropped drastically afterwards. *Mth1* was responsible for the DNA damage decrease, as mRNA levels increased from basal to 13-33 -fold at the relapse time-point. On the other hand, *As3mt* expression followed a pattern similar to that of DNA damage. Global DNA hypomethylation was observed during the complete duration of the exposure.

As conclusion, we have demonstrated that *As3mt* and *Mth1* have differential roles in the accumulation of DNA damage linked to the transformation process. While *As3mt* acts as a sensor of damage contributing to the genotoxic effects before transformation, *Mth1* prevents the DNA damage fixation after the acquisition of the transformed phenotype. Interestingly, *Mth1* is proposed here as a new biomarker of arsenic carcinogenesis.