Oxidative DNA damage enhances the carcinogenic potential of chronic arsenic exposures

Jordi Bach[1], Jana Peremartí[1], Balasubramanyam Annangi[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.

Chronic arsenic exposures are known to increase the incidence of several cancers in humans. Our previous work demonstrated that environmentally relevant arsenic exposures generate a more rapid accumulation of pre-carcinogen 8-OH-dG DNA lesions in MEF *Ogg1*-deficient cells; nevertheless, it remains unsolved whether this observed arsenic induced oxidative DNA damage (ODD) is certainly important in terms of cancer acquire.

In this study isogenic MEF *wild-type* and *Ogg1*$^{-/-}$ cells were exposed to sub-toxic doses of sodium arsenite. The selected doses were 0.5, 1 and 2 μM and the exposure last for 40 weeks. Hallmarks of cell transformation such as matrix metalloproteinase (MMP) activities measured by zymography, colony formation and promotion of cancer progression evaluated by soft agar assay, and cellular invasiveness measured by transwell assay were assessed. On the other hand intrinsic cancer-like phenotypic changes such as alterations in cellular morphology growth and differentiation status -analysed by real time RT-PCR- were included as complementary measures of transformation.

Results shown that MEF *Ogg1*$^{-/-}$ cells showed a cancer-associated phenotype after 30 weeks of exposure, as indicated by morphological changes, increased proliferation, de-regulated differentiation status, increased MMPs secretion, anchorage independent cell growth and enhancement of tumour growth and invasiveness. Conversely, MEF *wild-type* cells did not present changes in morphology or proliferation, exhibited a milder degree of gene de-regulation and needed 10 weeks of additional exposure to the highest arsenite doses to show tumour enhancing effects.

To sum up our results demonstrate that *Ogg1* genetic background and arsenic-induced 8-OH-dG appear relevant for arsenic-mediated carcinogenic effects. This is the first study directly linking ODD with arsenic carcinogenesis. Implications in human exposed populations need to be explored since individuals carrying variant *OGG1* alleles are expected to be at higher risk.