Arsenic exposure disrupts the normal function of the FA/BRCA repair pathway

Jana Peremartí[1], Facundo Ramos[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 exposure is known to enhance the genotoxicity/carcinogenicity of other DNA-damaging agents by inhibiting DNA repair activities. Interferences with nucleotide excision repair (NER) and base excision repair (BER) are well documented, but interactions with other DNA repair pathways are poorly explored so far. The Fanconi anemia FA/BRCA pathway is a DNA repair mechanism necessary for eliminating interstrand crosslinks (ICLs) from DNA, and it is required for maintaining genomic stability and preventing cancer.

We have explore possible interactions between arsenic compounds and the FA/BRCA pathway by using isogenic *FANCD2*$^{-/-}$ (FA/BRCA-deficient) and *FANCD2*$^{+/+}$ (FA/BRCA-corrected) human fibroblasts. To study whether arsenic compounds generate DNA lesions susceptible to be repaired by the FA/BRCA mechanism, both cell lines were exposed to different concentrations of As^{III}, As^{V}, MMA^{III}, MMA^{V} and ATO. The activation of the FA/BRCA pathway was then evaluated, along with the characteristic hipersensitivity and enhanced G2/M arrest of FA/BRCA-deficient cells. To study whether arsenic disrupts the normal FA/BRCA function, *FANCD2*$^{+/+}$ cells were pre-exposed to sub-toxic doses of the above mentioned arsenic compounds for 2 weeks. The cellular response to mitomycin-C (MMC), a typical ICL inducer, was then evaluated and compared to that of *FANCD2*$^{-/-}$ cells.

Our results show that exposures to pentavalent arsenicals As^{V} and MMA^{V} activate the FA/BRCA pathway and produce an effect in FA/BRCA-deficient cells slightly similar to that of MMC, whereas pre-exposure of FA/BRCA-corrected cells to the trivalent arsenic compounds MMA^{III} and ATO induce a cellular FA/BRCA-deficient phenotype, with increased sensitivity to ICLs.

Overall, our data indicate that the FA/BRCA pathway participates in the arsenic-mediated cellular DNA damage response, and demonstrate that chronic arsenic exposure disrupts the normal function of the FA/BRCA activity, therefore supporting a novel source of arsenic co- and carcinogenic effects. Derived implications in arsenic-associated cancer therapy are of interest, as treatment combining ATO with ICL-agents are expected to retrieve a better outcome.