The role of Fra-1 in arsenic-induced cell malignant transformation

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Arsenic is a widespread and well-known human carcinogen associated with skin, lung, bladder, liver, kidney, and prostate cancers. However, the mechanism explaining the exact relationship of chronic arsenic exposure and tumor development is unclear.

The transcription factor FOS Related Antigen 1 (Fra-1) is frequently overexpressed in epithelial cancers and has been found to be involved in tumor invasion and metastasis. The present study aims to assess whether Fra-1 plays a role in arsenic-induced malignant transformation.

Thus, MEF cells previously transformed by 30 weeks of chronic arsenite exposure were monitored for Fra-1 expression at different time-of-exposure intervals for 40 weeks. Our results demonstrate that Fra-1 is dose-dependently overexpressed 10 weeks after the acquisition of the cancer-like phenotype at the mRNA and protein level, and that the RAS-ERK1/2 signaling pathway and not MAPK or pP38 are responsible for the maintenance of the elevated Fra-1. Arsenic transformed cells with overexpressed Fra-1 showed morphological, molecular and functional characteristics of myofibroblast trans-differentiation with increased aSma, TGFb and the master EMT regulator Snail, and increased MMP2+9 secretion and invasive potential.

Therefore, this work is the first to show that Fra-1 is involved in the modulation of the malignant phenotype induced by chronic arsenic exposure.