FRA-1 and MIR-21 involvement 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 and other kinds of cancer. Nonetheless, the mechanisms of action by which chronic arsenic exposure leads to tumor development are not fully known. The *fos-related antigen 1* (FRA-1) is a transcription factor frequently overexpressed in epithelial cancers with a described role in the development of an aggressive tumor phenotype. Its ability to regulate key genes related to the invasion and metastasis processes, as well as different microRNAs such as miR-21, involved in the downregulation of tumor suppressor genes, is well known.

In this work, MEF cells chronically exposed to arsenite were monitored for FRA-1 expression levels at different time-of-exposure intervals for 50 weeks, in order to assess its correlation with the progressive development of an aggressive tumur phenotype. Expression changes of upstream and downstream components of FRA-1 related signaling pathways were evaluated at equivalent time-points.

Our results show a dose-dependent overexpression of FRA-1 from the transformation point of MEF cells, as a response to ERK and p38 activation. This is correlated with an increase in miR-21 levels and a subsequent downregulation of PTEN, PDCD4 and TMP1. Ongoing FRA-1 knock-down experiments could validate its role on miR-21 regulation and its relevance in the initiation of the transformation process and the development of an aggressive tumor phenotype. Therefore, this will be the first work to show that FRA-1 is involved not only in the modulation of arsenic-induced malignant phenotype, but also on its onset through miRNAs regulation.

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