Molecular Determinants of Retinoic Acid Sensitivity in Pancreatic Cancer

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**Background:** Response to retinoic acid towards cell proliferation versus death depends on the relative expression of two proteins, FABP5 and CRABP2, which transport retinoic acid to two different nuclear receptors, resulting in opposite outcomes.

**Aim:** We tested the responsiveness of various pancreatic cancer cell lines to all trans-Retinoic Acid (ATRA), in light of this new finding.

**Observations:** We found that the sensitivity of these cell lines to ATRA, indeed, depended on the differential expression of FABP5 and CRABP2 proteins. High expression of FABP5 causes resistance, while high expression of CRABP2 causes apoptosis in response to ATRA. Furthermore, there was an increase in migration and invasion upon ATRA treatment, in high FABP5 expressing cell lines. The phenotype of CRABP2<sup>low</sup> FABP5<sup>high</sup> cell line was reversed upon ectopic expression of CRABP2. Expression of CRABP2 also increased in CRABP2<sup>low</sup> FABP5<sup>high</sup> cell lines, by exposure to decitabine and trichostatin A, by relieving the promoter methylation of CRABP2 promoter. This encourages the future use of ATRA and decitabine combination in clinic. ATRA treatment was also found to be very effective in inhibiting the growth of gemcitabine-resistant xenograft tumor in the athymic mouse model. Immunohistochemical staining of FABP5 in archival human tissue microarrays identifies a subset of cases which are negative for FABP5 staining in tumor cells.

**Conclusion:** This suggests that it is possible to screen patients suitable for retinoic acid therapy based on the tumor expression of FABP5. ATRA alone or in combination with various other drugs can be used for the treatment of such FABP5-negative patients for a successful clinical outcome.