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Autotaxin exacerbates tumor progression by enhancing MEK1 and overriding the function of miR-489-3p

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ABSTRACT

Upregulated expression of autotaxin, a secreted phospholipase and phosphodiesterase enzyme, appears in malignant disease. The identification of a circulating miRNA signature should distinguish autotaxin-mediated disease and also elucidate unknown molecular mechanisms that rationalize its malignant potential. Using female transgenic 'AT-ATX' mice, whereby human wild-type autotaxin is expressed in liver under the control of the alpha-1 antitrypsin promoter, transgenic animals express augmented autotaxin in circulation and a percentage develop tumors. Serum collected at necropsy had circulating miRNAs analyzed for statistical significance. The ensuing autotaxin-mediated miRNome differentiated between groups: healthy FVB/N mice versus AT-ATX mice with and without tumors. Intriguingly, miR-489-3p was sharply increased in AT-ATX tumor-bearing mice. Tissue analysis showed a correlation between miR-489-3p expression in tumors and surrounding milieu with autotaxin concentration in circulation. Sequence alignment suggested miR-489-3p targets MEK1, which was confirmed through *in vitro* studies. Exogenously added miR-489-3p, which decreases MEK1 in normal cells, dramatically increased MEK1 expression in cells stably expressing autotaxin. Taken together, this suggests that autotaxin overrides the normal regulatory function of miR-489-3p to inhibit MEK1 via coordinately increased miR-489-3p appearing in serum.