**GASS lncRNA Modulates the Action of mTOR Inhibitors in Prostate Cancer Cells**

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Background

There is a need to develop new therapies for castrate-resistant prostate cancer (CRPC) and growth arrest-specific 5 (GAS5) long non-coding RNA (lncRNA), which riborepresses androgen receptor action, may offer novel opportunities in this regard. GAS5 lncRNA expression declines as prostate cancer cells acquire castrate-resistance, and decreased GAS5 expression attenuates the responses of prostate cancer cells to apoptotic stimuli. Enhancing GAS5 lncRNA expression may therefore offer a strategy to improve the effectiveness of chemotherapeutic agents. GAS5 is a member of the 5' terminal oligopyrimidine gene family, and we have therefore examined if mTOR inhibition can enhance cellular GAS5 levels in prostate cancer cells. In addition, we have determined if GAS5 lncRNA itself is required for mTOR inhibitor action in prostate cancer cells, as recently demonstrated in lymphoid cells.

Method

The effects of mTOR inhibitors on GAS5 lncRNA expression and cell proliferation were determined in a range of prostate cancer cell lines. Transfection of cells with GAS5 siRNA and plasmid constructs was performed to determine the involvement of GAS5 lncRNA in mTOR inhibitor action.

Results

Treatment with rapamycin and rapalogues increased cellular GAS5 levels and inhibited culture growth in both androgen-dependent (LNCaP) and androgen-sensitive (22Rv1) cell lines, but not in androgen-independent (PC-3 and DU145) cells. GAS5 silencing in both LNCaP and 22Rv1 cells decreased their sensitivity to growth inhibition by mTOR inhibitors. Moreover, transfection of GAS5 lncRNA sensitized PC-3 and DU145 cells to mTOR inhibitors, resulting in inhibition of culture growth.

Conclusion

mTOR inhibition enhances GAS5 transcript levels in some, but not all, prostate cancer cell lines. This may in part be related to endogenous levels of GAS5 expression, which tend to be lower in prostate cancer cells representative of advanced disease, particularly since current findings demonstrate a role for GAS5 lncRNA in mTOR inhibitor action in prostate cancer cells.