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PROSTATE CANCER

Mechanisms of cancer metabolism: mTORC1 mediates AMD1

New data suggests that mechanistic target of rapamycin complex 1 (mTORC1) mediates S-adenosylmethionine decarboxylase 1 (AMD1) stability, which in turn affects decarboxylated S-adenosylmethionine (dcSAM) production and polyamine synthesis. Thus, AMD1 provides a potential therapeutic target for treating prostate cancer.

Analysis of metabolic alterations in the prostate at the onset of prostate intraepithelial neoplasia and invasive prostate cancer revealed increases in metabolites related to polyamine synthesis in *Pten*-null mice and human prostate cancer tissue. Fate-tracing investigations using radiolabelled methionine showed elevated levels of dcSAM and increased polyamine synthesis, suggesting that the enzyme catalysing dcSAM decarboxylation, AMD1, could be responsible for the observed metabolic changes.

Ectopic expression of AMD1 in prostate cancer cell lines increased dcSAM levels, foci formation, and anchorage-independent growth in these cells, and tumour growth *in vivo*. Treatment with AMD1-targeting, doxycyclin-inducible short hairpin RNA reduced dcSAM expression and 2D and anchorage-independent growth, and tumour growth *in vivo*. Furthermore, pharmacological inhibition of AMD1 resulted in similar effects to genetic silencing without overt toxicity. Elevated AMD1 protein levels were observed in *Pten*-null mice and human prostate cancer tissue, and re-expressing *PTEN* in *PTEN*-deficient LNCaP cells reduced AMD1 levels.

Only mTORC1 inhibitors decreased AMD1 and pro-AMD1 protein (but not mRNA) levels *in vitro*, with accompanying decreased dcSAM expression. *In vivo*, treating *Pten*-null mice with an mTORC1 inhibitor reduced Amd1 and dcSAM levels, an effect that was ameliorated by a proteasome inhibitor. Phosphoproteomic analysis identified a single phosphorylated residue on AMD1 and pro-AMD1 compatible with a consensus site on mTORC1, and phosphorylation of this site on pro-AMD1 could be controlled by mTORC1, promoting pro-AMD1 stability.

In human tissue samples, AMD1 levels were higher in specimens of prostate cancer exhibiting increased mTORC1 than in BPH specimens. Moreover, p70S6K phosphorylation positively correlated with AMD1 levels. Furthermore, samples from patients treated with everolimus, an mTORC inhibitor, displayed reduced AMD1 immunoreactivity compared with pretreatment biopsy samples of the same lesion, and only AMD1 exhibited decreased immunoreactivity in patients who responded to this therapy.

These results demonstrate that increased polyamine synthesis is associated with oncogenic signalling in prostate cancer. Furthermore, control of this metabolic programme is downstream of mTORC, which regulates AMD1 and dcSAM production. Thus, AMD1 could be therapeutically targeted for prostate cancer treatment.

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