

**TESTOSTERONE/ANDROGEN RECEPTOR-MEDIATED
SIGNALLING PATHWAY DOES NOT MODULATE *in vivo* c-myc
EXPRESSION UP-REGULATED IN ANTIFOLATE/FOLATE-INJURED
MOUSE KIDNEY**

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The remarkable increase in the expression of the gene encoding ornithine decarboxylase (ODC), a key enzyme in polyamine biosynthesis, is a characteristic feature of androgen- and antifolate CB 3717/folate-treated mouse kidney. In the latter model of the injured kidney, the expression of the hepatocyte growth factor (HGF)/c-Met signalling pathway is significantly increased. Signalling pathways activated by testosterone and HGF via the androgen receptor (AR) and c-met receptor, respectively, do not act independently but interact resulting in the negative modulation of ODC gene expression. Thus, testosterone-induced ODC activity and mRNA level are decreased several-fold when the androgen is applied together with CB 3717/folate.

We studied the expression of c-myc mRNA and protein to confirm our working hypothesis, assuming that the negative modulation of ODC expression is the result of an interaction of AR and c-Myc transcription factors activated via the androgen and HGF signalling pathways, respectively. We showed that antifolate/folate induces the elevation of the c-myc transcript level, peaking up to 13-fold after 24h, and persisting for up to 3 days. This increase is accompanied by a significant induction of c-Myc protein, as revealed by Western blot analysis. This is in contrast to the results for testosterone, which does not increase the level of c-myc message. Androgen administration also has no effect on the c-myc mRNA level up-regulated by antifolate/folate. Therefore, a substantial negative regulation of ODC gene expression, a result of the cross-talk between the testosterone- and HGF-activated pathways, appears to not be a consequence of decreased c-myc expression, but rather of direct protein-protein interaction and/or a competition for common coactivators.