P17 p300 and CBP targeting in castration therapy resistant prostate cancer

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Introduction & Objectives: p300/CBP are two highly homologous coactivators containing a histone acetyltransferase (HAT) domain and a bromodomain (Bd). Both are involved in key processes like migration, invasion, apoptosis and DNA damage repair. Recent work could also show that targeting the HAT and Bd of p300/CBP via small molecular inhibitors is effective in prostate cancer and castration resistant disease. Here the aim is to reveal downstream pathways of p300/CBP and their function in cancer proliferation and resistance.

Materials & Methods: The effect of the p300/CBP HAT inhibitor C646 and the Bd inhibitor ICBP-112 on viability, mRNA, protein and AR activity was tested. Several PCa cell lines with different AR expression levels and resistance status were used. Resistant cells were derived from DUCaP and LNCaP cells chronically treated with Enzalutamide. Gene expression in parental and resistant DUCaP and LNCaP cell lines after inhibitor treatment was analyzed with RNAseq. CX-5461, an inhibitor of RNA polymerase I was used to inhibit ribosomal biogenesis.

Results: Increased sensitivity to inhibitors was observed in Enzalutamide resistant cell lines relative to parental cells. Moreover, expression of the AR target genes FKBP5, PSA and TMPRSS2 was reduced after p300/CBP inhibition. Whilst less pronounced, this regulation was also observed at the protein level. Similarly, AR activity was reduced in resistant cells. Inhibition of p300/ CBP reduced androgen-, myc- and parts of an EMT-signature, which are likely involved in the development of Enzalutamide resistance. RNAseq showed differences between DUCaP and LNCaP regarding development of resistance. Interestingly, we observed overexpression of ribosomal proteins in Enzalutamide resistant cells. This overexpression could be reversed in DUCaP cells by using p300/CBP inhibitors. CX-5461, an inhibitor of ribosomal biogenesis, was also significantly more effective in Enzalutamide resistant cells.

Conclusions: Enzalutamide resistant cell lines were increasingly susceptible to inhibitors of p300/CBP, although differences between cell lines suggest that the AR background and other factors influence their effectivity. A common factor of resistance is the overexpression of ribosomal proteins, which are downstream targets of Myc. Inhibition of the ribosomal biogenesis itself was also more effective in Enzalutamide resistant cells, thus suggesting its important role in resistance.