Dependencies of CRPC cell fitness on ERG levels

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Despite the survival benefits given to castration resistant prostate cancer (CRPC) patients by second-generation androgen receptor (AR) pathway inhibitors, the emergence of resistance and the applicability of alternative therapies only in a minority of cases highlight the importance of discovering novel therapeutic strategies. Toward this end, the technological advances in next generation sequencing have allowed the deep genomic and epigenomic characterization of localized PCa (prostate cancer) and CRPC tumor samples. Although described as an early event in PCa tumorigenesis and considered a prominent feature of primary tumors, the fusion of an AR-regulated gene to proto-oncogenes of the ETS family is among the most frequent genomic aberrations in metastatic CRPCs. Specifically, ERG fusions mainly involving TMPRSS2 (hereafter defined as T2ERG fusion) are found in about 40% of mCRPCs. Furthermore, the dependence of models of advanced PCa endogenously bearing the T2ERG fusion on ERG activity renders ERG an attractive, yet challenging, therapeutic target.

By using metastatic PCa cells and an inducible system to overexpress ERG, here we show that their fitness decreases in presence of high ERG levels. ERG DNA binding and transcriptional activity are necessary to induce this phenotype since prolonged overexpression of a mutant form of ERG, which is not able to bind DNA, does not affect cell viability. Furthermore, overexpression of ERG in AR-negative PCa cell lines show that ERG does not rely on AR to reduce cellular fitness. Interestingly, levels of ERG overexpression comparable to those of VCaP cells that endogenously harbor the T2ERG fusion are compatible with PCa cell viability. Altogether, these results suggest a biphasic cell response to ERG activity; where ERG levels canonically reached in tumors via gene fusion with AR-regulated genes increase cell invasion and limit AR-mediated differentiation, higher levels of ERG reduce cellular fitness. The identification of the mechanisms underlying this biphasic response is under investigation and could provide novel therapeutic opportunities for the treatment of ERG-positive CRPC patients.

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