INTRODUCTION

Prostate Cancer occurs in about 1 in every 6 men and remains to be the second leading cause of cancer death in men. Although the survival rate for early-stage prostate cancer is nearly 100%, this statistic plummets to 31% when the cancer becomes advanced. Since Judah Folkman discovered that tumors promote the growth of new blood vessels to bring in extra-tumoral nutrients and oxygen in a process called angiogenesis, researchers have been trying to find a way to exploit the inhibition of angiogenesis to starve tumors of the critical nutrients they need to grow1. While angiogenesis inhibitors were initially promising and have shown efficacy in some cancers, they have underperformed expectations in many cancers, including prostate cancer2. The reason for disparate efficacies between cancers remains unclear. While studying the kinase Ca2+/calmodulin-dependent protein kinase kinase 2 (CAMKK2), a direct androgen receptor (AR) target gene and known driver of prostate cancer progression1-3, we observed a significant increase in angiogenesis upon CAMKK2 knockout. We hypothesize that because CAMKK2 can activate AMPK, a master regulator of energy homeostasis, tumors rely on angiogenesis to bring in nutrients and to maintain energetic balance when CAMKK2 activity is lost. Here, we introduce the idea that co-targeting CAMKK2 in combination with angiogenesis could increase the efficacy of both treatments in the clinic.

RESULTS

Figure 2: Angiogenesis is a primary mechanism of resistance to CAMKK2 inhibition.
After KO of CAMKK2 in a CRPC subcutaneous tumor model, CAMKK2 tumors eventually grew out and exhibited an (a-b) hemorrhagic phenotype. (c) Staining for CD-31, a marker for endothelial cells, is expressed more highly in both CAMKK2 KO cohorts which further validates angiogenesis as a mechanism of resistance to CAMKK2 inhibition. ***P<0.001

Figure 3: Clinical cohorts consistently exhibit inverse correlation between CAMKK2 expression and angiogenesis.
(a) Angiogenesis score, the expression of a set of genes that predict the likelihood of angiogenesis, is inversely correlated with CAMKK2 expression in several clinical cohorts (4 of 8 shown).

Figure 4: Co-targeting of angiogenesis increases efficacy of CAMKK2 inhibition in vivo.
(a) Avastin (bevacizumab) is a mAb that binds the angiogenesis promoter Vascular Endothelial Growth Factor A (VEGF-A) and prevents it from binding to the VEGF receptor (VEGF-R) (b) While both Avastin and CAMKK2 loss alone prolong survival in a CRPC xenograft model, combination therapy nearly doubles survival time compared to WT alone. ****P<0.0001

Figure 5: Analyzing molecular data from in vivo experimentation.
(a) Infographic of procedure for collecting molecular data, Created with BioRender.com. (b) CD31 and TUNEL IHC staining of prostate tumor tissue and subsequent QuPath imaging (c) PbCreCAMKK2 Castrated with CAMKK2 KO demonstrated increased angiogenesis (d) Thrombospndin-1 decreases with Avastin treatment.

CONCLUSIONS

- Combo therapy of CAMKK2 inhibition and angiogenesis inhibitors could increase efficacy of both therapies in the clinic.
- CAMKK2 could be a predictive biomarker for response to anti-angiogenic therapy.
- Alternative anaplerotic disruptors might also increase efficacy of angiogenesis inhibitors.

FUTURE DIRECTIONS

- Conduct metabolomics to understand if combo inhibition of CAMKK2 and angiogenesis could deplete TCA cycle metabolites synergistically.
- Test combo therapy of anaplerotic pathway inhibitors with Avastin (bevacizumab) in vivo.

REFERENCES