Title:
Hypoxia changes lipid metabolism in advanced Prostate Cancer

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Abstract:
Prostate Cancer (PCa) is the second most common cancer and a major cause of cancer related deaths in males worldwide. Intratumoral hypoxia is common in PCa and it alters lipid metabolism. Since cholesterol biosynthesis inhibitors, statins, have been shown to improve PCa patient outcome, we investigated the effects of hypoxic conditions in combination with statins on cell growth and viability, lipid accumulation and for changes in lipid expression in treatment-resistant PCa cell lines.

We used our in-house developed VCaP cell lines modelling different stages of clinical PCa progression to determine these changes. These include testosterone-dependent, castration-resistance modelling and both castration-resistant and enzalutamide-resistant cell lines. We assessed the changes in hypoxic response under the influence of simvastatin through cell proliferation and viability, lipid accumulation and lipidomic profiling.

Proliferation and cell viability was reduced in both testosterone-dependent and enzalutamide-resistant with simvastatin in hypoxia. castration-resistant was not affected. Simvastatin or fatostatin exposure did not have a cumulative effect on proliferation with hypoxia in any tested cell line. Additionally, we observed multiple differences between cell lines in both normoxic and hypoxic conditions. This would suggest that treatment resistance alters how PCa cells react to hypoxia. Lipid accumulation also increased as a response to hypoxia, with greatest increase in enzalutamide-resistant.

Based on this evidence, changes in lipid metabolism are a part of PCa progression. Identifying processes that function during hypoxia and statin exposure in these *in vitro* models can result in the discovery of novel mechanisms that can be utilized in future in PCa treatment.