PPAR Gamma Antagonists as Monotherapy and in Combination with Checkpoint Inhibitors in Prostate Cancer

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Background: Prostate Cancer (PC) remains a leading cause of cancer mortality and the most successful chemopreventative and treatment strategies for PC come from targeting the androgen receptor (AR). Although AR plays a key role, it is likely that other molecular pathways also contribute to PC, making it essential to identify and develop drugs against novel targets for PC treatment. New studies have identified PPARγ as a novel target in PC and suggest that PPARγ antagonists could be used to treat existing disease and to prevent PC development. PPARγ has also been shown to control inflammatory cytokine production and response to checkpoint inhibitors in bladder cancer, which may extend to PC.

Methods: Growth curves, MTT assays, immunofluorescence, Western blot, and flow cytometry were used to determine the effects of PPARγ antagonists and siRNA on PC cell viability, while luciferase and RT-qPCR assays were used to determine the effects on AR and PPARγ expression and activity. Nude mice were used to determine the effect of PPARγ antagonists on human PC xenograft growth and a syngeneic B6 mouse model was used to determine if PPARγ antagonism can increase response to checkpoint inhibitors and control the growth of RM9 PC tumors.

Results: We found that small molecule inhibition of PPARγ decreases the growth of AR+ and AR- PC cells in vitro and that T0070907, a potent PPARγ antagonist, significantly decreased the growth of human PC xenografts in nude mice. We found that PPARγ antagonists or siRNA do not affect mitochondrial activity nor do they cause apoptosis; instead, they arrest the cell cycle. In AR+ PC cells, antagonists and siRNAs reduce AR transcript and protein levels, which could also contribute to growth inhibition. AR-independent effects on growth appear to be mediated by effects on fatty acid metabolism as the specific FASN inhibitor Fasnall inhibited PC cell growth but did not have an additive effect when combined with PPARγ antagonists. We found that PPARγ inhibition increases inflammatory cytokine expression in PC cells in vitro and in vivo and studies in the RM9 mouse model are ongoing.

Conclusions: Taken altogether, we postulate that PPARγ antagonists directly inhibit PC cell growth and also affect immune cell recruitment to PCs, which can potentially boost the effectiveness of immunotherapies when used in combination. Our studies will help determine the role of PPARγ in PC progression, and whether PPARγ inhibition is an effective strategy for PC treatment.

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