Prostate cancer is an androgen-dependent disease subject to interactions between the tumor epithelia and its microenvironment. We found epigenetic changes to cancer-associated prostatic fibroblasts (CAF) initiated a cascade of stromal-epithelial interactions that allowed lethal prostate cancer to grow and further develop resistance to androgen deprivation therapy (ADT). We identified that a RAS-GAP gene, RASAL3, is epigenetically silenced in CAF. The resulting increase in oncogenic RAS downstream activity in CAF drove macropinocytosis-mediated glutamine synthesis. Interestingly, ADT further promoted RASAL3 epigenetic silencing and glutamine secretion in prostatic fibroblasts. In a mouse orthotopic xenograft model, subsequent inhibition of macropinocytosis and glutamine transport resulted in antitumor effects and ADT sensitivity. Moreover, stromal glutamine uptake served as a source of energy through anaplerosis of the TCA cycle as well as a neuroendocrine differentiation mediator for prostate adenocarcinoma. In validating these findings, we found that prostate cancer patients on ADT with therapeutic resistance had elevated blood glutamine levels compared to those with therapeutically responsive disease (odds ratio = 7.451, p value = 0.02). Identification of epigenetic regulation of RAS activity in prostatic CAF revealed RASAL3 as a sensor for metabolic and neuroendocrine reprogramming in prostate cancer patients failing ADT.