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“Direct targeting of the energy sensor AMPK inhibits prostate cancer cell growth through blockade of the lipogenic switch: novel therapeutic implications”

SUMMARY OF RESEARCH
It is well established that the process of cancer development and growth involves major alterations of cell metabolism. In addition to triggering signaling cascades involved in proliferation and survival, oncogenes such as Ras, c-Myc or Akt, also induce concomitant metabolic changes, mostly aerobic glycolysis and lipogenesis in order to transform the cell. Even if the metabolic reprogramming of cancer cells has been described more than a century ago, only recently, attention has been regained on metabolic changes and metabolic regulators in cancer cells. During my post-doctoral training I explored the role of alterations in lipid metabolism, which together with deregulation of mTORC1 pathways are the most common features of primary and advanced Prostate Cancer (PCa). Since activation of the energy sensor AMPK regulates cell metabolism and growth through the negative regulation of these two anabolic pathways, I explored its potential as novel therapeutic target in PCa. To overcome non-specificity issues of the current AMPK activators, we performed a chemical screening of 10,000 small molecules and we identified MT63-78, a novel highly specific direct activator. We proved that AMPK activation per se inhibits PCa cell growth, induces G2-M cell cycle arrest and apoptosis. In vivo, significant delay in tumor development was observed. Despite the inhibition of mTORC1, our data showed that de novo lipogenesis blockade is the key responsible mechanism for the anti-cancer effect of MT 63-78. Indeed, addition of exogenous palmitate and/or mevalonate but not reactivation of mTORC1 pathway rescues cell growth. On this basis, we performed $^{11}$C-acetate PET to establish in vivo efficacy of AMPK activation by measuring tumor uptake of this lipid precursor. Finally, we derived a 123-gene signature by combining gene expression profiling data from prostate cell lines, engineered to increase lipogenesis and deactivate AMPK, and six human prostate cancer microarray databases. This signature can be
utilized to select patients that might benefit from either AMPK activators or inhibitors of lipid synthesis.

**IMPACT**

We demonstrate that direct targeting of the metabolic hub, AMPK, represents a valid therapeutic strategy in prostate cancer. In-depth biochemical characterization identified inhibition of lipogenesis as the effector arm of AMPK activation in prostate cancer. Selection of patients via a molecular signature of the “lipogenic phenotype” and subsequent monitoring of drug efficacy by non-invasive imaging with $^{11}$C-acetate provide the foundation for a novel therapeutic approach in prostate cancer.
Overview of AMPK targeted-therapy approach in prostate cancer

**Metabolic targeted therapy**

Gene expression profiling for lipogenic phenotype

PCa patients

**Direct activators**

Active AMPK!

MT 63-78

HMG-CoA Reductase

HMG-CoA

Mevalonate

Cholesterol

Lipo genesis

Cell signaling and membrane synthesis

Protein synthesis

**Cell growth**