PGC-1alpha controls an onco-metabolic program to limit prostate cancer aggressiveness

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Purpose:
Prostate cancer (PCa) is the third cause of cancer death in men and deaths are due to advanced metastatic PCa. Metabolic reprogramming has been shown to play a major role in cancer aggressiveness; however, the metabolic pathways implicated in the formation of metastasis are poorly understood. In this context, we chose to study peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) which plays a major role in cell metabolism and more specifically the regulation of Oxidative Phosphorylation. PGC-1α is a master regulator of mitochondrial biogenesis and a recent paper suggests that low levels of PGC-1α may be associated with a poor prognosis in PCa. Then, we decided to study the role of PGC-1α on PCa aggressiveness and metabolism.

Experimental Design and Results:
We performed a knockdown (KD) of PGC-1α in prostate cancer cell lines using different shRNA. PGC-1α KD enhanced PCa cell proliferation, migration and invasion of LNCaP and DU145 cells. Conversely, overexpression of PGC-1α decreased cell migration. To determine the molecular mechanism implicated in this phenotype, we analyzed the expression of several genes controlling oncogenesis and metabolism. We found that c-myc and some other genes implicated in glutaminolysis were up regulated in PGC1-α KD cells. We then performed proliferation and transwell migration assay using c-myc inhibitors. These inhibitors reversed the pro-proliferative and the pro-migratory effects induced by the downregulation of PGC-1α. To characterize the metabolic modifications modulated by PGC-1α, we performed a steady-state metabolomic analysis. We demonstrated that the polyamine pathway (putrescine, spermine) is significantly up-regulated in cells where PGC1-α is downregulated. In accordance, the ornithine decarboxylase (ODC), a rate limiting enzyme of this pathway controlled by c-myc, is up-regulated in PGC-1α KD cells. We then decided to inhibit ODC with DFMO (α-difluorométhylornithine) and performed migration assay. We showed that the pro-migratory effects of PGC-1α KD cells are blocked by DFMO. Finally, in accordance with the results presented here, we demonstrated that the expression of PGC-1α is significantly downregulated in PCa patients and logically, c-myc and ODC are up regulated.

Conclusion:
Altogether, our results demonstrate that the downregulation of PGC1α increased c-myc expression and up-regulated polyamine synthesis. These onco-metabolic modifications are directly implicated in PCa aggressiveness.