Editorial Commentary

Key players of neuroendocrine differentiation in prostate cancer

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We read with interest the article entitled "Increased Serine and One-Carbon Pathway Metabolism by PKCλ/ι Deficiency Promotes Neuroendocrine Prostate Cancer" recently published by Reina-Campos *et al.* on *Cancer Cell* (1), in which a pathogenetic hypothesis focusing on the protein kinase C (PKC)λ/ι loss that would favor the acquisition of neuroendocrine (NE) differentiation in prostate cancer (PC) models has been investigated.

Molecularly-based personalized interventions represent the "Holy Grail" for cancer researchers worldwide. Although several steps forward have been made on the route to precision medicine in PC (2-5), a complete comprehension of the processes of carcinogenesis, tumor progression and acquired drug resistance is still so far. These mechanisms include wide simultaneous genomic rearrangements that results into double-strand DNA breaks ("chromoplexy") (6), *de novo* monoclonal seeding of daughter metastases (7), metabolic alterations in tumor cells (8,9) and the transdifferentiation to a NE-like phenotype characterized by tumor cell proliferation and invasion (10). On this background, NE features seem to play a significative role. NE differentiation can vary within a single patient along the natural history of PC and results highly prevalent in men treated with prolonged androgen-deprivation therapy (ADT), in which represents a mechanism for hormonal escape or androgen receptor (AR) independence (11,12).

The process of acquisition of NE differentiation has been poorly molecularly characterized due to the lack of tumor specific therapies but requires a series of key players that includes inflammation and autophagy. Indeed, in PC microenvironment, Tumor-Associated Macrophages (TAMs) secrete Interleukin (IL)-6 and promote the NE differentiation of PC cells (13,14). On the other hand, autophagy is involved in PC progression and modulates the sensitivity of this tumor to chemotherapy (12,15).

Thus, targeting NE differentiation may be the key to modulate tumor aggressiveness and response to therapy. Among emerging targets, Prostate Specific Membrane Antigen (PSMA) is demonstrating to be an ideal candidate for the diagnosis and treatment of PC (16,17). PSMA is an androgen-regulated membrane bound glycoprotein and is variably expressed in NE prostate cancer (NEPC). PSMA can act as a target for antibody-drug conjugated (ADC) therapies. At this regard, Petrylak *et al.* investigated the efficacy and safety of PSMA-ADC at 2.5 mg/kg in patients with taxane-refractory metastatic castration-resistant PC. Prostate-specific antigen (PSA) decline of ≥30% was observed in 36% of enrolled patients while Circulating Tumor Cell (CTC) decline of ≥50% was noticed in more than 70%, with an acceptable toxicity profile (11), thus supporting the development of further studies in this field.

On this scenario, the results published by Reina-Campos *et al.* (1) focused on PKCλ/ι loss open the way to a novel promising therapeutic strategy. The authors primarily demonstrated that in PC datasets

the gene expression of *PRKCI* (coding for PKCλ/ι) was downregulated in metastases and correlated with a negative prognosis. Hence, both in primary and metastatic samples, PKCλ/ι downregulation appeared to be associated with NEPC phenotype, and also in a cohort of *de novo* hormone-naive NEPC samples lower PKCλ/ι levels were displayed. Likewise, in enzalutamide-resistant PC cell lines with related NE differentiation, PKCλ/ι was reduced as well. Of interest, in PC mouse lines the authors observed that the concomitant deletion of PTEN and PKCλ/ι drove to aggressive disease development and gain of NE features. On the same line, in two androgen-resistant cell lines, knock down of PKCλ/ι elicited NE markers in *in vitro* cells and *in vivo* tumor xenografts. In *in vitro* kinase assay, PKCλ/ι was able to inhibit mTORC1 activation through directed LAMTOR2 phosphorylation, the latter identified as a likely link among PKCλ/ι and mTORC1. The authors observed that in C42B cell lines with inactivation of PKCλ/ι (sgPKCλ/ι), mTORC1 turned out to be activated as displayed by western blot of three downstream effectors (p4EBP1, pS6K, and cMYC), and to play a crucial role toward NEPC differentiation. Along this line, through gene expression analysis on the same cellular model PKCλ/ι-deficient, ATF4 resulted as the main upstream regulator of the transcriptional changes, and its increase was confirmed by western blot analysis. In sgPKCλ/ι cells, knock down of ATF4 was associated with decreased NEPC levels and slowed cell proliferation. Furthermore, gene set enrichment analysis pointed out meaningful enrichment in sgPKCλ/ι cells of a metabolic serine, glycine, one-carbon pathway (SGOCP), which is of paramount importance for sustaining cell proliferation and epigenetic changes through S-adenosyl methionine (SAM) production. The mTORC1/ATF4 axis definitely induced a metabolic cell reprogramming to enhance the flux of methyl donors SGOCP-stimulated finally fostering NE differentiation. Again, in a comparison among human samples of adenocarcinoma and NEPC both with mTORC1 iperexpression, higher PHGDH levels were detected in *de novo* NEPC tissues and in NEPC lesions developing after therapy, so underlining also the role of PHGDH in the mTORC1/ATF4 axis. Of clinical relevance, the authors observed that DNA methylated regions in sgPKCλ/ι cells exhibited a significant overlapping with hypermethylated areas in NEPC tumors and in lethal PC subtypes as well. Lastly, the authors explored a therapeutic target involving SGOCP and DNA methylation. In detail, sgPKCλ/ι cells treated with decitabine inhibitor of DNA methyltrasferase activity or with cycloleucine inhibitor of SAM production proved a strong reduction of NEPC markers along with a remarkable anti-proliferative effect.

In conclusion, the study led by Reina-Campos *et al.* showed that targeting PKCλ/ι may be feasible in order to modulate the NE differentiation of PC cells and, as a consequence, to reduce tumor aggressiveness and drug resistance. The possibility to sequence or combine PKCλ/ι -targeted approaches with current and future hormonal therapies and chemotherapies should be further investigated in randomized clinical trials.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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