Serine and Methionine Metabolism: Vulnerabilities in Lethal Prostate Cancer

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Altered metabolism is a common feature of new and recurring malignancy. In this issue of Cancer Cell, Reina-Campos and colleagues report upregulation of the serine, glycine, one-carbon (SGOC) metabolic network is required for neuroendocrine prostate cancer, a castration-resistant aggressive form of the disease, and presents a targetable vulnerability.

Acquired and intrinsic resistance to targeted therapies including androgen deprivation in prostate cancer is often lethal. Thus, understanding resistance mechanisms or non-oncogenic vulnerabilities such as dysregulated cellular metabolism is important for the development of new therapeutic strategies. Indeed, targeting metabolism in cancer is a promising approach. However, establishing a therapeutic window requires the identification of specific pathways and contexts where it may be effective. In this issue of Cancer Cell, Reina-Campos and colleagues define a mechanism whereby loss of protein kinase C (PKC) λ/ι and subsequent upregulation of the serine, glycine, one-carbon (SGOC) metabolic network in early-stage prostate cancer leads to the development of neuroendocrine prostate cancer (NEPC), an aggressive, particularly lethal form that lacks effective therapeutic options (Figure 1). Of significance, targeting the SGOC metabolic network is effective in reducing NEPC formation in a murine prostate cancer tumor model, providing proof-of-concept that SGOC metabolism is a viable target in aggressive prostate cancer (Reina-Campos et al., 2019).

Using bioinformatics, the authors examined the expression of the PKCλ/ι-coding gene, PRKCI, in human prostate tumors. Intriguingly, PRKCI expression was lower in patients with NEPC, an aggressive form of late-stage prostate cancer, compared to earlier-stage prostate adenocarcinomas. This led the authors to propose that prostate cancer progression and NEPC development can occur in response to PKCλ/ι deficiency. Consistent with this hypothesis, knockout of Prkci in a mouse prostate cancer model and PRKCI ablation in human prostate cancer cell lines recapitulated histological, gene expression, and disease outcome profiles found in NEPC patient tumors. These results provided compelling evidence that loss of PKCλ/ι in prostate cancer leads to a more aggressive form of the disease.

The authors then investigated how PKCλ/ι loss may lead to NEPC formation. Using transcriptomic, proteomic, and biochemical approaches, they identified a sequence of events whereby PKCλ/ι deficiency leads to ATF4-mediated transcriptional reprogramming with mTORC1 activation as an intermediate. In addition to upregulating genes required for NEPC differentiation, ATF4 also promoted the expression of numerous genes in the SGOC network including PHGDH, PSAT1, and MTHFD2, suggesting this metabolic pathway may play a causal role in NEPC development. Importantly, stable isotope tracing and mass spectrometry confirmed increased flux through the SGOC pathway when PKCλ/ι was deleted.

Having established that PKCλ/ι loss leads to NEPC formation via an mTORC1/ATF4/SGOC axis that was consistent with a previous report (Ben-Sahra et al., 2016), the authors aimed to understand how upregulation of SGOC metabolism could possibly drive NEPC development. Because the SGOC network can sometimes be coupled to the methionine cycle, which is important for generating the methyl donor S-Adenosylmethionine (SAM) used by histone and DNA methyltransferase enzymes, the authors hypothesized that changes in chromatin biology directly contributed to NEPC formation. Indeed, genome-wide increases in DNA methylation levels were observed in PKCλ/ι-deficient cells compared to control, which were correlated with NEPC transcriptional changes and could be rescued by knockdown of the enzyme PHGDH, which is the first committed step in serine synthesis. Of particular interest,
the differentially methylated regions in PKC\(\lambda\)\(i\) null cells significantly overlap with CpG areas found hypermethylated in NEPC patients and highly aggressive prostate cancers. Finally, the authors demonstrate targeting DNA methyltransferase activity or the SGOC pathway was sufficient to reduce NEPC formation.

In all, the study by Reina-Campos et al. is a compelling example of how alterations in cellular metabolism are relevant to cancer pathology. It is well established that cancer cells have different nutritional requirements due to enhanced metabolic demands and that alterations of metabolic networks can lead to growth and fitness advantages. As demonstrated by this study, rewiring of metabolism by cancer cells can be used to circumvent targeted therapies.

Reina-Campos and colleagues describe a mechanism whereby nutritional status drives disease by regulating chromatin biology. In this manuscript, the authors reported the cellular availability of the methionine-derived metabolite SAM as one of the major causative factors of aggressive prostate cancer development. The levels of SAM were elevated in response to upregulation of the SGOC metabolic network and promoted hypermethylation of DNA, which ultimately led to transcriptional programming that favored NEPC formation. These findings extend the cancer contexts in which this mechanism has been attributed to the pathogenesis of cancer. Previous reports have identified similar SGOC pathway-mediated epigenetic alterations upon loss of LKB1 in a type of pancreatic cancer (Kottakis et al., 2016) and the evolution of chemoresistance in breast cancer (Debold et al., 2018).

These studies also raise the intriguing possibility that dietary interventions could have therapeutic consequences. For example, histone methylation is dynamically regulated by SAM levels, which can be controlled by the manipulation of dietary methionine intake (Mentch et al., 2015). Moreover, inhibition of histone methylation has been shown to reduce prostate cancer development and increase therapeutic response (Ku et al., 2017). Thus, it would be interesting to explore how dietary methionine availability could influence the formation and progression of this cancer. Furthermore, it is tempting to speculate that change to dietary amino acid intake such as serine, glycine, or methionine could influence prostate cancer outcome—possibly through these proposed mechanisms. Indeed, dietary depletion of serine and glycine produces therapeutic responses in aggressive pre-clinical cancer models (Maddocks et al., 2017).

Finally, this work opens additional research directions for the role of the SGOC metabolic network in the progression of prostate and other cancers. Besides contributing to methylation reactions, the SGOC network is important for redox balance and the biosynthesis of nucleotides, proteins, and lipids (Mehrmohamadi et al., 2014), all of which are required for cell viability and proliferation and may be co-opted by aggressive cancers. Moreover, the SGOC enzyme PHGDH has been shown to be coupled to the anabolic fluxes of the TCA cycle and pentose phosphate pathway in certain contexts (Reid et al., 2018). Whether this occurs in response to PHGDH upregulation during NEPC development is intriguing and may lead to further therapeutic considerations. Furthermore, the closely related PKC\(\lambda\) family member, PKC\(\zeta\), was previously shown to negatively regulate the SGOC enzyme PHGDH and exhibit control over glutamine metabolism (Ma et al., 2013). Accordingly, it would be important to explore other metabolic changes that may occur during progression of cancer or in response to drug resistance. Finally, while gene expression analyses which account for overall network expression can sometimes be sufficient to characterize the activity of metabolic pathways (Mehrmohamadi et al., 2014), other approaches such as metabolomics and metabolic flux analysis can quantitatively measure metabolic phenotypes and warrant future consideration in contexts where metabolic vulnerabilities may be identifiable.

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DECLARATION OF INTERESTS

The authors hold patents related to the use of serine and methionine metabolism and related pathways for cancer therapy.

REFERENCES

**Therapeutic Clues from an Integrated Omic Assessment of East Asian Triple Negative Breast Cancers**

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In this issue of *Cancer Cell*, Jiang et al. report a genomic and transcriptional analysis of triple negative breast cancers (TNBCs) from an East Asian population. Their study shows minor differences with published studies of European and North American populations and suggests a therapeutic decision tree for treatment of TNBC.

Breast cancer treatment strategies typically are determined by underlying molecular characteristics of the cancers. Historically, ductal breast cancers have been managed based on a limited number of markers as: triple negative (TN) (HER2−, ER−, PR−), hormone receptor (HR) or luminal (HER2−, ER+, PR−), or HER2+, which is frequently divided based on hormone receptor status into HR+/HER2+ (HER2+, ER+, PR+), HR−/HER2+ (HER2+, ER−, PR−), and HR−/HER2− (HER2−, ER−, PR−). Management of ductal breast cancer based on these subtypes has both prognostic and therapeutic relevance contributing substantively to improved outcomes for breast cancer patients. Large-scale molecular profiling beginning with gene expression measurements enabled further refinement of ductal breast cancers into molecularly distinct subtypes with different regulatory pathway usage that dictates response to pathway-targeted therapies. Initial work defined five molecular subtypes designated luminal A, luminal B, HER2, basal-like, and normal-like based on measurements of gene expression profiling (Perou et al., 2000) (Figure 1). Ongoing classification efforts based on measurements of additional molecular endpoints (genome, epigenome, microRNA, protein, etc.) are further refining the classification into different subtypes (Cancer Genome Atlas, 2012; Curtis et al., 2012).

The TN subgroup of breast cancer (TNBC) is of special interest due to their aggressive nature and poor outcome. Importantly, the TNBC subgroup is not a single disease but a set of diverse diseases (Cancer Genome Atlas, 2012; Curtis et al., 2012) that display epigenomic heterogeneity, phenotypic plasticity, and often harbor DNA repair defects (homologous recombination deficiency [HRD]), as well as mutations of TP53, BRCA1, and BRCA2 (Cancer Genome Atlas, 2012; Curtis et al., 2012). Their diversity and epigenomic plasticity have hindered the development of effective therapeutic approaches, although their high prevalence of BRCA1 and BRCA2 mutations and HRD has led to implementation of PARP inhibitors and platinum-based therapy. The heterogeneity of TNBC has spawned...