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Commentary Open Access

Furthering Molecularly Targeted Strategies Agent Combinations against Cancer Cell Proliferation

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Commentary

Several functional signaling pathways submodules that control the cancer cell proliferation participate simultaneously in the cell growth, cell survival, cell differentiation, intracellular senescence and death programs, and in appropriate interaction with angiogenesis, cell micro-environment regulation and immunologic system signaling pathways. Selective targeted drugs of hub molecules may optimize patient's treatment efficacy, such as de use of CDK4/6 inhibitors that improve the outcomes of patients with HR+ breast cancer (BC) [1].

Recent translational oncology research has progress in the identification of genomic, epigenomic and metabolomic markers that drive in the susceptibility and development different cancer types (and subtypes), these biomarkers could be used as targets in the clinic therapeutic interventionism. Metabolic intermediates and signaling molecules abnormalities together with aging-somatic and epigenomic alterations of mammalian tissue in breast cancer will be the issue of these brief commentary.

Age, family history, reproductive factors, estrogen and life style are the main risk factors breast cancer developing [2]: Cancer biology may be seen as analogue of aging process, exemplifying how a linear accumulation of somatic mutations cause a rapid rise in morbidity and mortality [3]. Inherited oversensitivity (genomic and metabolomic) of breast cancer is partially attributed to *BRCA1* and *BRCA2* mutations. Environmental related metabolomics such as reproductive factors as early menarche, late menopause, late age at first pregnancy and low parity increases the risk of BC, and are associated with the ER status; lengthy endogenous or exogenous estrogens increase BC risk; dietary fat intake, body mass index, smoking, excessive alcohol consumption offer to a higher risk on BC occurrence. These BC-risk factors participate as an asymmetric impact in the personalized developing of BC patient.

The majority breast cancers are carcinomas that originate from cells lining milk ducts and start from ductal hyperproliferation. Estrogen receptor-α (ER) is expressed in approximately 75% of breast cancers. More than 15 years ago, for the BC histological evaluation, pathologists have used gene expression profiling analysis (using immunohistochemistry (IHC) or microarrays), resulting in the identification of four BC molecular subtypes: luminal A, luminal B, HER2-like and basal-like. Each BC intrinsic subtype has a main biological profile, such has IHC surrogate, chromosomal CNAs, recurrent gene mutations, treatment vulnerability and prognosis: for example, subtype luminal A has ER+, PR+ HER2+, increased-CNA (1q, 16p, 16q), decreased (8p11-12, 11q13-14, etc.), 20q13 amplification; PIK3CA, GATA3, MAP3K1, TP53 y CDH1, endocrine treatment, and good prognosis, respectively; Luminal B has an intermediate prognosis, and HER-2 enriched/Basal-like (TNBC) have poor prognostic [2]. This BC first-generation prognosis gene signature could be increase by the use of stroma/immune cells derived prognostic predictor. BC next-generation prognostic approaches using metabolic intermediates, epigenetic profiles, gene expressing profiles, and signaling molecules assessment may furthering the individualized diagnosis, prognosis and treatments and improve treatments outcomes [4].

Many of the advances in deciphering and targeting mutations in BC have achieved by DNA sequencing studies [5-7], which in these days use as therapeutic and prognostic clinical guide. Recently, BC research and translation studies have analyzed transcription factor dynamics, transcriptome, epigenome, metabolome and signalosome profiles. Oncogenic transcription is induced by mutations affecting regulatory elements or chromatin conformation, and more than 49 genes have been identified that directly or indirectly are involved in transcription process [8].

Tumorigenesis is initiated through specific altered genomic, epigenomic and metabolomic factors. In majority of sporadic cancers, the tumorigenesis dependent on the reprogramming of cellular metabolism is influenced by lifestyle habits. The alterations of intracellular and extracellular metabolites that can accompany cancer-associated metabolic reprogramming have profound effects on gene expression, cellular proliferation and differentiation of their parenchymal cells and their different stromal tissue microenvironment cells. Altered metabolic pathways are considered the pipelines to supply altered metabolic cofactors of epigenetic modifiers and drive the deregulation of the functional epigenomic changes which cooperates with aging accumulated mutations to the information gathering process for the oncogenic transcriptome generation, oncogenic proteome generation and finally the neoplastic phenotype cellular generation [9].

Metabolic reprogramming in cancer is considered one of the non-genetic factors to alter the epigenetic landscape. Cancer metabolic changes adaptation drives to epigenetic modifies, at least by three mechanisms:

- Alteration of metabolite levels by reprogramming metabolic pathways.
- Nuclear production of metabolites by enzymes translocated to the nucleus.

- Generation of oncometabolites that regulate the activity of epigenetic enzymes [10].

One of the main features of cancer metabolism is the increased uptake of glucose and some amino acids (glutamine, serine, etc.) compared to that in quiescent normal cells. Changes in acetyl-CoA level by glucose availability preferentially control histone acetylation associated with the genes for cell proliferation. Upregulated glycolysis in cancer cells works as metabolic hub which interconnect and branching with other metabolic pathways as the pentose phosphate pathway, the hexosamine pathway, and serine biosynthesis pathways, these allow the balance of the ribonucleotide/NADPH, the UDP-N-acetylglucosamine for protein glycosylation and the SAM and NADPH biosynthesis, respectively. Glutamine acts as the nitrogen donor for anabolic pathways to synthesize nucleotides, amino acids and hexosamine in cells [10].

Specific metabolic changes in transformed cells have been identified to affecting their epigenetic landscapes such as an elevated acetyl-CoA production in cancer cells that upregulates histone acetylation, an accumulation of metabolic inhibitors of histone deacetylases such as butyrate and lactate, a reduced αKG and SAM levels that alter the regulation of DNA/histone methylation, a nuclear production of metabolites that provide epigenetic cofactors in cancer cells, as ATP citrate lyase and acetyl-CoA synthetase, and that TCA-enzymes mutation promotes oncometabolite production to affect DNA/histone methylation, preferably the isocitrate dehydrogenases 1 and 2, the succinate dehydrogenases and the fumarate hydratase.

Substantial but limited progress has been made about the mechanisms and biological consequences associated with metabolic reprogramming in carcinoma cells. Gene expression programs are tightly and dynamically regulated by the metabolome, either at the level of chromatin modification and transcription factor activities [11].

DeBerardinis and Chandel [12] have noted four key principles that take place in cancer metabolism of the the bioenergetic, biosynthetic and redox biochemical pathways:

- Malignant cells survive and grow using conventional metabolic pathways to produce energy, synthesize biosynthetic precursors and maintain redox balance;
- Metabolic reprogramming is the result of mutations in oncogenes and tumor suppressors (or epimutations);
- Alterations in metabolite levels (oncometabolites) can affect cellular signaling, epigenetics and gene expression;
- New approaches to assess metabolism will improve our ability to understand how metabolic reprogramming is regulated and will drive to hold opportunities to improve care of cancer patients.

Much details remains to be identified on the bidirectional relationship between metabolism and gene transcription (epigenetic landscape and transcription factor regulation) for a more integrated understanding of cellular adaptations during carcinogenesis and cancer progression [11].

Modern translational cancer studies have obtained different advances in cancer metabolism, and have started to simultaneously identify somatic mutations/epimutations, gene expression, metabolomic changes and oncogenic signaling pathways as much as precancerous lesions, early invasive phase, local/progressive phase, metastatic phase, treatment-refractory phase, clonal evolution phases, and a long list of other biological conditions. Some BC modern translational studies analysis can serve as an example of these advances [12].

As we have mentioned, BC molecular subtypes, luminal A, luminal B, HER2-like and basal-like (TNBC), have different positive expression profile such as hormone receptor status ER, PR, HER2, but also overexpression of different oncoproteins such as MYC. Elevated MYC expression is present in BC basal like and in high-grade breast cancers. The oncoprotein MYC is a master regulator of many cellular signaling (promote tumor growth) and metabolic pathways (glutamine and lipid metabolism), its overexpressing is associated with the accumulation of the oncometabolite 2-hydroxyglutarate, and has been implicated in drug resistance in BC and poor prognosis [13]; like this, targeting MYC will be a logical strategy to apply in drug resistant breast cancer. However, due to the lack of pharmacological efficacy of direct MYC inhibitors, researchers have shifted their focus on understanding the target genes and pathways downstream of MYC activation. Camarda et al. [14] showed *in vitro* and *in vivo* targeted metabolomic approach that in TNBC-MYC overexpression (MO-TNBC) models, the fatty acid oxidation (FAO) intermediates were noticeably upregulated, implicating that FAO is a dysregulated pathway critical for TBNC metabolism. They find that MO-TNBCs are sensitive to pharmacologic FAO inhibition in a MYC-dependent manner, and that FAO inhibition abrogates growth of distinct models of MO-TNBC, then FAO inhibitors could be used as a novel therapeutic strategy for these tumor subtypes [14,15]. Likewise, FAO promotes sprout-endothelial cell proliferation in angiogenesis and lymphangiogenesis by producing nucleotide biomass as well my mediating epigenetic changes of histone acetylation, which promotes transcription of key lymphatic genes. Carnitine palmitoyltransferase I (CPT1) catalyzes the rate limiting step of FAO. The current understanding of FAO and CPT1 in cancer provide theoretical basis for this enzyme may be a target in cancer therapeutic intervention [16].

BC and lung cancer show increased expression and mutations in EGFR that enhance signaling and resistance to targeted-therapy. Post-translational modification of some proteins (as EGFR) by attachment of palmitate serves as a mechanism to regulate their protein localization and function. The role of palmitoylation in cancer has mostly focused on the palmitoylation of H-Ras, N-Ras proteins and recently to EGFR, this last is palmitoylated by the palmilotyltransferase-DHHC20. Dysregulation and inappropriate activation of the receptor tyrosine kinase EGFR are example of use of signaling pathways interventionism against EGFR signaling for cancer cells. Given the essential role that palmitoylation plays in cancer cell signaling, approaches that target palmitoylated proteins and palmitoyl acyltransferases have potential for therapeutic intervention in cancer [17]. Runkle et al. [18] show that inhibiting the palmitoyltransferase-DHHC20 (PT-DHHC20) sensitizes cells to EGFR tyrosine kinase inhibition, and causes a signal regulation and susceptibility to EGFR inhibitor-induced cell death. TNBC patients with mutations within the C-terminal tail of EGFR resistant to gefitinib may be treat targeting to PT-DHHC20 inhibitor (2-bromopalmitate, small molecule) in combination with EGFR TK inhibitors (gefitinib) as an effective clinical approach. Likewise, there are no effective therapeutic strategies to K-Ras driven cancers, but reducing expression of PT-DHHC20 increases cell death induced by gefitinib in some K-Ras and EGFR mutant cell lines. When EGFRC1025A and K-RasG12V are expressed in cell, the EGFR inhibitor together with the 2-bromopalmitate, act synergistically to induce cell death [19].

Comprehensive and integral molecularly studies of BC signaling pathways in living tumors, particularly in metabolic and epigenetic profiles and signaling molecules and its biological interactions, together with previous and new genomic clinical background information may improve our pathogenic mechanisms understanding, and its will be conductive to improve care of cancer patients.

References

1. Valdespino VM, Valdespino-Castillo VE, Valdespino-Castillo PM (2017) Increasing the potential targets and molecularly targeted agent combinations against cancer cell proliferation. J Cell Signal 2: 139.
2. Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, et al. (2017) Risk factors and preventions of breast cancer. Int J Biol Sci 13: 1387-1397.
3. Martincorena I, Campbell PJ (2015) Somatic mutation in cancer and normal cells. Science 349: 1483-1489.
4. Ades F, Tryfonidis K, Zardavas D (2017) The past and future of breast cancer treatment-from the papyrus to individualized treatment approaches. Ecancermedicalscience 11: 746.
5. Santarpia L, Bottai G, Kelly CM, Gyorffy B, Szekelv B, et al. (2016) Deciphering and targeting oncogenic mutations and pathways in breast cancer. Oncologist 21: 1063-1078.
6. Hou L, Chen M, Wang M, Cui X, Gao Y, et al. (2016) Systematic analyses of key genes and pathways in the development of invasive breast cancer. Gene 593: 1-12.
7. Shi H, Zhang L, Qu Y, Hou L, Wang L, et al. (2017) Prognostic genes of breast cancer revealed by gene co-expression network analysis. Oncol Lett 14: 4535-4542.
8. Zacksenhaus E, Liu JC, Jiang Z, Yao Y, Xia L, et al. (2017) Transcription factors in breast cancer-lessons from recent genomic analyses and therapeutic implications. Adv Protein Chem Struct Biol 107: 223-273.
9. Pavlova NN, Thompson CB (2016) The emerging hallmarks of cancer metabolism. Cell Metab 23: 27-44.
10. Kim JA, Yeom YI (2018) Metabolic signaling to epigenetic alterations in cancer. Biomol Ther 26: 69-80.
11. Martin-Martin N, Carracedo A, Torrano V (2018) Metabolism and transcription in cancer: merging two classic tales. Front Cell Dev 5: 119.
12. DeBerardinis RJ, Chandel NS (2016) Fundamentals of cancer metabolism. Sci Adv 2: e1600200.
13. Terunuma A, Putluri N, Mishra P, Mathe EA, Dorsey TH, et al. (2014) MYC-driven accumulation of 2-hydroxiglutarate is associated with breast cancer prognosis. J Clin Invest 124: 398-412.
14. Camarda R, Zhou Z, Kohnz RA, Balakrishnan S, Mahieu C, et al. (2016) Inhibition of fatty oxidation as a therapy for MYC-overexpressing triple breast cancer. Nat Med 22: 427-432.
15. Fallah Y, Brundage J, Allegakoen P, Shajahan-Haq AN (2017) MYC-driven pathways in breast cancer subtypes. Biomolecules 7: e53.
16. Qu Q, Zeng F, Liu X, Wang QJ, Deng F (2016) Fatty acid oxidation and carnitine palmitoyltransferase I: emerging therapeutic targets in cancer. Cell Death Dis 7: e2226.
17. Resh MD (2017) Palmitoylation of proteins in cancer. Biochem Soc Trans 45: 409-416.
18. Runkle KB, Kharbanda A, Stypulkowski E, Cao XJ, Wang W, et al. (2016) Inhibition of DHHC20-mediated EGFR palmitoylation creates a dependence on EGFR signaling. Mol Cell 62: 385-396.
19. Kharbanda A, Runkle K, Wang W, Witze ES (2017) Induced sensitivity to EGFR inhibitors is mediated by palmitoylated cysteine 1025 of EGFR and requires oncogenic Kras. Biochem Biophys Res Comun 493: 213-219.