Dysregulated metabolism: a relevant player in prostate cancer progression and clinical management

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It is well accepted that cancer cells have different metabolic programme compared to normal cells (1). Rapidly replicating tumor cells requirements to support inappropriate cell proliferation and maintain growth is reflected at least in part by a metabolic shift towards aerobic glycolysis, a phenomenon known as Warburg effect and a modification in gene expression for enzymes involved in other pathways supporting proliferation (2,3). Increased glucose uptake lead to modifications of many metabolites mainly associated with cell growth and stress (4,5).

Currently, still little is known about the mechanisms linking deregulated metabolism and cancer aggressiveness. Prostate cancer (PCa) is a particularly suitable model to investigate this aspect. In fact, healthy prostate exhibit a unique metabolism, leading to production of the components of prostatic fluid: prostate specific antigen (PSA), spermine, myo-inositol, and citrate. Such a physiological condition is completely altered in neoplastic cells due to the alteration of glandular framework, leading to zinc loss and subsequently citrate accumulation. Therefore, prostate tumors display unique metabolomic signature (6).

Khan et al. (7) analyzed global metabolic profiling of benign and malignant prostate, allowing the creation of a comprehensive catalog of metabolic alterations. Such analysis allows not only a better understanding of biological basis of tumor development and progression, but also a platform for the identification of metabolites such as sarcosine, uracil, kynurenine, glycerol-3-phosphate, leucine and proline, which increase with disease progression and may represent new diagnostic and prognostic biomarkers. Metabolomic analysis of biological fluids are minimally invasive and easily accessible, providing a potential useful tool for cancer diagnosis and prognosis. Previously reports indicated citrate, myo-inositol and the polyamine spermine as metabolic markers of PCa in prostatic secretions (8) and metabolic differences between PCa patients and healthy subjects blood samples (9,10).

Increased glucose use by cancer cells is the basis for cancer detection by the uptake of the glucose analogue, fluorine-18-labeled 2-deoxy-2-fluoro-D-glucose (¹⁸F-FDG) which can be visualized by positron-emission tomography (PET). PCa cells have a dominant uptake of fatty acid over glucose, alternative tracers have been proposed and PET scanning in PCa is still developing (11). Imaging with PET tracers with ¹¹C acetate and ¹¹C choline have shown sufficient sensitivity in the detection not only of primary site, but also of metastasis and recurrence (12). Unfortunately, both of the tracers were not able to reveal small metastatic sites (13). Of note, the study of altered metabolic pathway in PCa led to the identification of potential therapeutic target. Particular attention has received key lipogenic enzymes, such as Fatty acid synthase (FASN) and S⁰ adenosine monophosphate-activated protein kinase (AMPK). It has been recently demonstrated a decreased of PCa onset among subjects taking statin in the...
Finnish Prostate Cancer Screening Trial, independently of circulating PSA values (14). Metformin is a derivative of guanidine and is able to activate AMPK, partly explaining its anti-tumor effect. Accordingly, several trials treating patients with a combination of chemotherapeutic agents and metformin in low risk PCa patients has been planned. Recent studies indicated that patients receiving metformin together with androgen deprivation therapy (ADT) have benefits in terms of cell proliferation beyond metabolic phenotype (15).

Overall, literature data suggest that targeting lipid metabolism provides an interesting road to take. Metabolic reprogramming of PCa cell represents a promising way to explore investigation for the identification of new diagnostic and therapeutic strategies in PCa (Figure 1), as shown by the results obtained by Liss et al. (16). Particularly, worthy of attention seems to be fatty acid metabolism studies, potentially able to provide in future useful tools for personalized medicine.

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Footnote

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References


