ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 36 (2018) 327–337

UROLOGIC ONCOLOGY

Review article

Metabolic changes in bladder cancer

Benjamin L. Woolbright, Ph.D., Matthew Ayres, B.S., John A. Taylor III, M.D., M.S.*

Department of Urology, University of Kansas Medical Center, Kansas City, KS

Received 2 March 2018; received in revised form 5 April 2018; accepted 17 April 2018

Abstract

Introduction and Objective: Bladder cancer is a common solid tumor. Outcomes are poor in advanced disease, with few novel clinical therapeutics introduced over the previous several decades. Otto Warburg's original hypothesis that cancer cells use aerobic glycolysis to produce ATP instead of traditional oxidative phosphorylation in the mitochondria was a landmark discovery in its time. Recent studies indicate metabolic changes in cancer are far more complex than originally anticipated though. The purpose of this review is to understand metabolic changes that occur in bladder cancer, how targeting these changes could potentially be used therapeutically, and the current treatments that target these metabolic changes

Methods: A literature review on recent advances in cancer metabolism with an emphasis on bladder cancer was performed.

Results: Significant metabolic change occurs in bladder cancer; however, these changes associated are not yet well understood. Therapeutic development in this area is growing and a diverse array of actionable targets such as mitochondrial DNA, mitochondrial metabolic enzymes and cellular signaling proteins have been identified. Many of these proteins may also be involved in chemoresistance.

Conclusion: Metabolism is a growing area of therapeutic interest in bladder cancer, but more studies are required to advance therapeutic development in this area.

Keywords: Bladder; Cancer; PDK4; Metabolism; Glycolysis; Mitochondria

1. Introduction

Bladder cancer is among the most common tumors and a major source of morbidity and mortality worldwide. Treatment for bladder cancer is largely dependent on stage and grade, which are also tightly linked to patient outcomes [1]. Nonmuscle invasive bladder cancer is typically treated with resection and use of intravesicle agents such as Bacillus Calmette-Guerin immunotherapy; whereas, muscle invasive bladder cancer requires more aggressive approaches including radical cystectomy coupled with chemotherapy [1]. Used in the neoadjuvant and adjuvant settings, chemotherapy can improve outcomes yet utilization remains low [2]. This may be due in part to inherent issues with these regimens, including the fact that up to 50% of all patients are natively resistant to cisplatin-based chemotherapy, and a significant percentage of those whom are eligible for cisplatin develop chemoresistance during treatment [1,2]. Checkpoint inhibitors represent a recently approved second-line treatment with potential to change the landscape of bladder cancer treatment. Unfortunately, recent enthusiasm over checkpoint inhibitors has been tempered by the fact that only 20% to 30% of patients show a clinical response and long-term data suggest no improvement in disease-specific survival [3]. Given the successes of combination therapy in other modalities, new therapeutics that can serve as adjuvants for either cisplatin-based chemotherapy or as adjuvants to checkpoint inhibitor mediated therapy are sorely needed.

Cancer cells exist in an environment with varying degrees of acidosis and hypoxia that requires alteration of cellular metabolism in order to continue production of sufficient concentrations of adenosine triphosphate (ATP) and necessary metabolic intermediates for survival. This phenomenon was first established in the 1920s and later coined the Warburg effect [4]. Since its initial description, a significant amount of effort has been spent in an attempt to better understand this phenomenon. Modern understanding of Warburg metabolism indicates that the relative degree of

* Corresponding author. Tel.: +1-913-588-9184; fax: +1-913-588-7501.
E-mail address: jtaylor27@kumc.edu (J.A. Taylor III).

https://doi.org/10.1016/j.urolonc.2018.04.010
1078-1439/

glycolysis is highly variable between tumors, likely dependent partially on the state of hypoxia [5]. Perhaps more importantly, many tumors still undergo oxidative phosphorylation and thus have a bimodal metabolic capacity. The degree to which many tumors, including bladder, specifically undergo a major shift toward Warburg effect-like metabolism and reliance on glycolysis is not well understood. Moreover, alterations in cancer metabolism have been found to fundamentally alter production of necessary metabolites for other pathways such as purine synthesis that can alter growth kinetics [6]. Recent advances in both methodologies, and the scientific understanding of metabolism, have led to novel studies of how alterations in metabolism specifically affect bladder cancer tumors. Agents targeting cellular energetics in multiple pathways and in multiple organelles have been developed and are currently being evaluated in different solid tumors. These agents may be able to substantially potentiate the effects of current treatments by targeting the cellular population with the most dysregulated metabolic state, as the dysregulation of the metabolic state is strongly tied to the proliferative potential of cancer cells [7]. This may be especially efficacious in the case of drugs like cisplatin wherein metabolic alterations have been associated with chemoresistance in bladder cancer [8]. This review will assess recent advances in the understanding of how altered cellular metabolism can promote bladder cancer, and how targeting of these same pathways be can used therapeutically.

2. Cellular bioenergetics and metabolism in cancer cells

To produce energy in the form of ATP, cells take up glucose via glucose transporters such as glucose transporter 1 (GLUT1) [9]. Normal cells produce pyruvate from glucose through the well-described glycolysis pathway. Pyruvate is then converted to acetyl-CoA by the pyruvate dehydrogenase complex (PDH) and directed to the tricarboxylic acid cycle (TCA) where it is converted to electron carriers such as NADH and other cellular intermediates. The high energy electron carriers fuel ATP production by oxidative phosphorylation via complex I-complex V in the mitochondria. These processes produces 36 ATP per glucose, a number of necessary intermediate precursors for synthesis of critical biomass, and is the major source of reactive oxygen species (ROS) production in normal cells [10]. These processes, glycolysis, the TCA cycle, and mitochondrial oxidative phosphorylation, occur when oxygen is plentiful in healthy tissue and constitute what is largely considered normal energy (ATP) and metabolite production.

Cancer cells are known to undergo a fundamental shift in metabolism where energy production is shunted away from the normal pathway, and ATP is generated partially by aerobic glycolysis in the cytoplasm. This can be especially pertinent under prolonged periods of hypoxia wherein activation of the transcription factor hypoxia inducible factor 1α (HIF-1α) upregulates a number of genes involved in glycolysis [11]. The Warburg effect occurs both in the presence of reduced mitochondrial function, and relatively normal mitochondrial ATP production, dependent on the individual tumor [7,12,13]. The associated changes in metabolism are partially mediated by increased expression at the transcriptional level of proglycolytic enzymes, including glucose transporters, glucose metabolizing genes, and mitochondrial enzymes responsible for controlling pyruvate flux and metabolism [14–16]. This fundamental shift in metabolism is thought to have 2 major effects: (1) increased energy production in rapidly growing tumors and (2) increased production of functional metabolites necessary for cellular proliferation through noncanonical metabolic pathways [7,17,18]. Thus, the precise role of aerobic glycolysis and its usefulness therapeutically may differ substantially between tumor types depending on their rate and use of glycolysis vs. oxidative phosphorylation, and their use of noncanonical metabolic pathways. Understanding the relative role of glycolysis vs. oxidative phosphorylation and the compensatory pathways associated with this change is critical for understanding how bioenergetics and metabolism can be addressed therapeutically in all cancers, including bladder cancer. Direct measurements of glycolysis and oxidative phosphorylation are not widely available in tumor specimens; however, a number of studies have investigated the effects of inhibition of relevant pathway members and their potential therapeutic benefit.

3. Glycolysis and bladder cancer

3.1. Transcriptional control of glycolysis

The enzymatic pathway that mediates glycolysis has been intensely studied and is well-described. Dysregulation of energy production, and a potential therapeutic role for a number of genes in the glycolysis pathway, has been implicated in bladder cancer and is directly related to a number of the primary oncogenic mutations that initiate transformation. Many of the primary oncogenic drivers of bladder cancer such as PI3K, KRAS, and c-Myc activate and upregulate genes involved in glycolysis [19,20]. Activation of protein kinase B (Akt) associated with PTEN mutation upregulates glycolysis through a HIF-1α dependent mechanism [21,22]. Many oncogenic transformations either directly stimulate, or mimic the effects of, activation of HIF-1α protein and its downstream components [18,19]. This is not surprising as upregulation of energy production via multiple mechanisms is a normal response to nutrient deprivation [11,23]. In normal cells, HIF-1α is continually processed by prolyl hydroxylases that result in degradation of HIF-1α by the proteasome [11,24]. In the hypoxic tumor environment, HIF-1α is stabilized by the lack of molecular oxygen leading to expression of HIF-1α target genes [11].