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Review Article

Betting on Metformin and their Signature Modality in Realm of Cancer Therapy

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Introduction

Natural products and their synthetic analogs have played an integral role in drug discovery, mostly for cancer and other infectious diseases and over 60% of currently available anticancer drugs are from natural sources [1,2]. Plant-based compounds that show antitumor properties belong to various groups of compounds, such as alkaloids, diterpenes, diterpenoquinone, purine-based compounds, lactonic sesquiterpene, peptides, cyclic depsipeptide, proteins, and macrocyclic polyethers. One of the most famous plant-based drugs is metformin, used as antihyperglycemic drug, which was isolated from *Galega officinalis* [3,4].

Metformin has been receiving wide attention as a potential anticancer treatment following retrospective results in improving the overall survival rate in cancer patients with diabetes using metformin as a primary medication than non-metformin treatment [5]. The major effects of metformin as an anticancer agent are due to the inactivation of oxidative phosphorylation in mitochondria and activation of AMPK [6,7]. Activation of AMPK directly inhibits mTOR pathway via phosphorylation of TSC1/2, a tumor suppressor gene that negatively regulates mTOR [7,8]. Metformin-mediated AMPK activation increases the expression of p53, a tumor suppressor gene that promotes apoptosis and autophagy by inactivating Akt and mTOR protein. Metformin-mediated MAPK activation increases the expression of p53, a tumor suppressor gene that promotes apoptosis and autophagy by inactivating Akt and mTOR protein [9]. Furthermore, metformin inhibits receptor tyrosine kinases EGFR, ErbB2, and IRS1; IRS1 activates IGF1R and PI3/Akt pathway [10-12]. Metformin also inhibits the growth of cancer stem cells and tumor-initiating cells by targeting the sphere-forming ability of CD44+CD24−, CD61highCD49fhigh, CD133+, ALDH1+, EpCAM+, CD133+CD44+, and CD44+ CD117+ subpopulations in breast, pancreatic, glioblastoma, CRC, and ovarian cancer models. Metformin has also been reported to target various microRNAs (miRNAs), proteins associated with the miRNA biogenesis pathway. As such, metformin inhibits the proliferative capability of breast cancer cells by downregulating miR-27a [13] and upregulating miR-193 (miR-193a-3p and miR193b) [14], which in turn increased AMPKα and decreased FASN levels, respectively. Specificity protein transcription factors (Sp1, Sp3, and Sp4) are non-oncogene addict genes that are highly expressed in solid tumor-derived cells, including pancreatic cancer cells that regulate cancer cell growth, survival, migration/invasion, and inhibit apoptosis [15,16]. Several anticancer agents, including metformin, inhibit colon cancer growth in both *in-vitro* and *in vivo* models by downregulating Sp1, Sp3, and Sp4 and Sp-regulated pro-oncogenes such as mTOR and subsequent mTOR downstream genes [17]. This highlights the important chemotherapeutic aspect of metformin, suggesting a huge potential as an anticancer agent against several cancers.

Studies in a combination of metformin with several FDA-approved chemotherapeutics such as gefitinib and cisplatin have demonstrated a significant reduction of tumor burden in mice with lung cancer xenograft models [18]. Few studies performed in pancreatic cancer cells reported that metformin increased the sensitivity of pancreatic cancer cells to gemcitabine treatment by decreasing CD133+ cell populations and inhibiting phosphorylation of ERK/P70S6K signaling and reversing EMT through regulation of miR-663 [19,20]. Several clinical trials are underway to evaluate the therapeutic efficacy of metformin as a single or in combination with FDA-approved drugs in breast, pancreatic, endometrial, lung, colon, and prostate cancers and drugs in combination such as

cyclophosphamide, doxorubicin, docetaxel, epirubicin, everolimus, exemestane, trastuzumab, atorvastatin, letrozole, megestrol acetate, carboplatin, and fluorouracil (5-FU). The therapeutic efficacy of these drugs combined with metformin is not remarkable because of either minimal to no effect on tumor burden or concern with systemic toxicities [21].

A completed Phase II trial of metformin and medroxyprogesterone acetate combination treatment in endometrial cancer showed modest outcomes with no severe toxicities [22]. Several concerns are against these trials and needed attention. To understand the potential anticancer effects of metformin in clinical settings, the efficacy of metformin as a chemotherapeutic agent still needs investigation.

Despite the potential anticancer effects, the bioavailability of metformin and/or its uptake by cancer cells is too low to exert its antitumor effects in humans. The anticancer effect of metformin in invitro usually falls within the range of 5 to 10 mM, which is much higher than steady-state range levels in the plasma of patients with T2DM, which is around 10 μM and can reach 40 μM when standard prescribed dose is given [23]. *Invitro* studies show that this low dose is not sufficient to trigger AMPKα activation [24]. Another study highlights the unfavorable pharmacokinetic profile of metformin, suggesting slow and incomplete absorption from the gastrointestinal tract [25].

The pharmacokinetics properties of metformin are determined by its hydrophilic character, and the positive charge under physiological conditions made it difficult for passive diffusion in cells [26]. Organic cation transporters (OCTs) 1, 2, and 3 shuttle metformin inside the cell, and the expression of these transporters are in varying levels in different organs, including the liver, muscle, ovary, and kidney [27,28]. OCT2 is highly overexpressed in the kidney and is primarily responsible for eliminating metformin via urine [29]. Patients with compromised kidney function seemed to have a short half-life of metformin followed by a wide range of peak to trough drug levels [27,29]. Several studies have demonstrated the decreased nephrotoxicity when OCT2 inhibitor cimetidine is treated in patients with cisplatin by restricting the effect of cisplatin in the kidney [30-32]. Another study highlights the interindividual genetic variability of OCT1 leading to gastrointestinal side effects [33].

Efforts to improve and enhance the potency of metformin involved modification of structure by attaching alkyl or aromatic groups, but very few showed improved anticancer potency and pharmacokinetics [34]. Another biguanide, phenformin shows 50-fold higher anticancer potency than metformin, however, it was removed from the market due to the high risk of fatal lactic acidosis [35]. Drugs inhibiting the OCTs transporter could eventually increase the plasma concentration of metformin, however, it could also lead to metformin-induced lactic acidosis (MALA) [36]. Sulfonamide and sulfenamide derivatives of metformin showed increased potency than the parent molecule in breast and colon cancer models. Similarly, another derivative, HL156A, and triphenylphosphonium cation showed a potential effect in oral squamous cell carcinoma and pancreatic cancer cells via a ROS induction mediated activation of AMPKα and subsequent inhibition of insulin-like growth factor/AKT/mTOR pathway [37,38]. It seems that the antitumor activity of metformin requires higher dose, which exceeds the normal dose required for diabetes patients and that could lead to systemic toxicity.

The collective evidence on the anticancer effects of metformin and its lack of therapeutic concentration in the plasma is summarized here to raise the enthusiasm for further investigation. Several important issues need to be addressed before designing pre-clinical and clinical studies. Metformin analog, NT1014, a novel orally bioavailable drug with increased AMPK activity and increased affinity towards OCT1 and OCT3 showed anticancer activity in *in vivo* ovarian cancer model [39]. Another analog, HL156A is in a preclinical stage for treating solid tumors [40]. This information suggests that functional derivatives of metformin alone or in combination with other FDA-approved drugs have a huge potential to move forward as an anticancer drug.

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