Journal of
Clinical and Experimental Pharmacology

Buac and Dou, Clin Exp Pharmacol 2013, 3:1
DOI: 10.4172/2161-1459.1000116

Commentary Open Access

At the Center of the Metabolism and Cancer Web: AMP-Activated Protein Kinase (AMPK)

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That cancer cells display an altered metabolism was first recognized almost a century ago by Otto Warburg who noted that tumors display a shift in glucose metabolism from oxidative phosphorylation to glycolysis [1]. Since then, many reports have documented the importance of glycolysis in supplying much of the energy, proteins, and nucleotides required to fuel the largely metabolically demanding process at the core of all cancer causation: uncontrolled cell division [2-4]. Therefore, the importance of targeting cellular metabolism for cancer therapy has attracted much attention over the last decade and much of the research has primarily focused on three areas: i) metabolic and growth signaling pathways, ii) metabolic enzymes, and iii) diet and exercise. It was not until recently, however, that the major cellular energy sensor, Adenosine Monophosphate-Activated Protein Kinase (AMPK), emerged in the spotlight as a novel therapeutic target in the treatment of various cancer types. AMPK is a ubiquitously expressed tumor suppressor protein, which functions as a heterotrimeric enzyme and is activated in response to a variety of stress signals defined by a drop in the cellular ATP: AMP ratio [5,6]. Upon activation, energy consuming processes are shut down, while energy producing processes are turned up. In this way AMPK serves as a unique target for therapeutic intervention in a cancer setting as it integrates cellular growth factor signaling pathways with cellular metabolism.

The idea of AMPK as a novel target for cancer therapy really took off after the release of data from a 10 year-long epidemiological study, which revealed that type II diabetic patients on a regular regimen of the drug metformin (glucopage®) have a 30% less chance of developing a broad range of cancer types in their lifetime as opposed to those not taking metformin [7]. Also important to note is Libby et al. finding that metformin users who did develop cancer had a survival advantage over their non-taker counterparts [7]. This sprouted immediate curiosity into what the anti-cancer mechanism of metformin may be. It is no surprise then that the literature includes a plethora of metformin related studies in which its affects have been assessed in a wide range of cancer types including breast, colon, lung, prostate and ovarian from cancer laboratories all over the world [8-11]. Although its exact mechanism of action still remains to be determined, AMPK activation is well accepted to be the key and required event for its reported anti-tumor effect, summarized nicely in a recent review by Pierotti et al. [12]. However, there are several drawbacks to using metformin for cancer therapy. The most important is that there is no telling if the established therapeutic doses used in the clinic for the treatment of type II diabetes will translate effectively in cancer patients. For this reason, there are currently 146, either open and/or completed, cancer related clinical trials listed on the *clinicaltrials.gov* website investigating metformin's cancer fighting potential around the United States and Canada. Along these lines, the *in vitro* potency of metformin poses a major limitation to its bench to bedside translational potential, as it is optimally effective in the millimolar range. Therefore, the search for more potent AMPK activating agents could prove to be a rewarding avenue in cancer drug discovery and molecular therapeutics.

Recently, Chen et al. published 3,3'-Diindolylmethane (DIM), a by-product of the ingestion of indole-3-carbinol from cruciferous vegetables, and analogs of Epigallocatechin Gallate (EGCG), a green tea polyphenol, to be effective AMPK activators both *in vitro* and *in vivo* in a prostate or breast cancer model system, respectively [13,14]. The use of natural compounds as anti-cancer agents is an age-old idea. Many of the chemotherapeutic agents used in the clinic today are synthetic derivations based on naturally occurring agents found in plants, plant by-products and bacteria. Metformin itself actually comes from the *French lilac* flower and so it is no surprise that naturally occurring compounds such as DIM and EGCG, widely available in our daily food and drink, should have such cancer fighting powers. Based on their findings Chen et al. report, for the first time, that B-DIM can activate the AMPK signaling pathway, associated with suppression of the Mammalian Target Of Rapamycin (mTOR), down-regulation of Androgen Receptor (AR) expression and induction of apoptosis in both androgen-sensitive LNCaP and androgen-insensitive C4-2B prostate cancer cells. These results were further translated *in vivo* where B-DIM induced a similar effect in C4-2B prostate tumor xenografts in SCID mice [13]. Similarly, Chen et al. also showed synthetic EGCG analogs to be more potent AMPK activators than metformin and EGCG (micromolar range), resulting in inhibition of cell proliferation, up-regulation of the cyclin-dependent kinase inhibitor p21 and down-regulation of mTOR pathway in MDA MB 231 breast cancer cells [14]. These findings suggest that natural and synthetic compounds are a valuable source for the development of novel, potent, and specific AMPK inhibitors. However, as with all natural compounds, bioavailability is indeed the major limitation to their use. Due to biologically inactivating processes and instability issues in a physiologic setting, derivatives of such compounds are commonly designed to improve bioavailability as is the case with EGCG. Nevertheless, the issue of sufficient and efficient concentration as well as effectiveness in combination with other currently established chemotherapeutics also needs to be addressed. It has been reported that green tea polyphenols counteract some chemotherapy regimens and whether or not this can be avoided with synthesis of derivatives should be determined [15,16].

In conclusion, it should be noted that although the great majority of the work published is in favor of AMPK activation as a potential novel approach in cancer therapy, there are those who report conflicting results with its activation [17-19]. In addition, it still remains widely debatable whether or not continuous activation of the enzyme is more favorable than activation in spurts, similar to that during

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Received January 22, 2013; **Accepted** January 25, 2013; **Published** January 27, 2013

Citation: Buac D, Dou QP (2013) At the Center of the Metabolism and Cancer Web: AMP-Activated Protein Kinase (AMPK). Clin Exp Pharmacol 2: 116. doi:10.4172/2161-1459.1000116

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strenuous exercise. Finally, it should also be mentioned that there are twelve possible isoforms of AMPK, $\alpha_1\beta_1\gamma_1$ being most common [20]. As mentioned earlier, it is present in all cells and indeed, certain isoforms are exclusive to certain tissue types. The effect of prolonged activation could therefore have pleiotropic systemic effects that may be unfavorable, for example in the brain where pharmacologic activation of AMPK has been reported to have undesirable side effects on the ability to differentiate between hunger and satisfaction suggesting obesity risk [21-23]. For now, the study of AMPK's tumor suppressing abilities is an exciting area of research which has the potential to bridge several large gaps in knowledge on the link between metabolism, obesity and cancer; thus it is overall an attractive molecular drug target for the treatment of cancer. Those off-target concerns, however, will absolutely need to be addressed before its capacity can be fully appreciated.

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