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Chapter 8

INFLUENCE OF INSULIN AND METFORMIN ON PROSTATE CANCER

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ABSTRACT

Dietary habit and hormonal factor play a significant role in prostate cancer deregulation in addition to genetic and environmental factor. Non-androgenic growth factor like insulin and insulin growth factor are influences the prostate cancer initiation and progression. Insulin and Insulin-like growth factor regulate various metabolic pathways, cell growth, cellular proliferation and apoptosis. Various epidemiological results point out that insulin not only increased the risk of cardiovascular, macrovascular, and microvascular complications but also at significantly increase the risk of various cancers. The use of metformin, the usually approved drug for type 2 diabetes, was continually linked with the decreased risk of the incidence of a variety of cancers. More than 60 clinical trials of metformin being tested as a treatment for various types of cancer, including breast, colon, prostate, endometrial, and pancreatic cancer. The ability of metformin to lower circulating insulin may be predominantly imperative for the treatment of cancers. Moreover,

metformin inhibiting mammalian target of rapamycin promoted cell growth signaling. In this chapter, the confirmation behind a role for metformin in cancer therapy and its prospective molecular mechanisms of action are discussed.

Keywords: insulin, Metformin, prostate cancer, diabetes

INTRODUCTION

During last decades cancer incidence has emerged remarkably as a global problem. Cancer being the second most common cause of death is exceeded only by cardiovascular disease. Global cancer statistics, 2016 reported that about 16.85 million cancer cases and 5.9 million cancer deaths are predicted to occur in 2016 USA. Prostate, colorectal, female breast and lung cancer rates are 2 to 5 times higher in developed countries as compared to developing countries. Prostate cancer is the second most frequently diagnosed visceral cancer and the sixth leading cause of cancer death in males (Jemal et al., 2011). Diabetes is an important chronic disease with increasing global incidence and though considered as an epidemic (Herman &Zimmet, 2012). The impact of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) is rising parallel worldwide. T1DM or Insulin-dependent diabetes mellitus (IDDM) is a metabolic disorder caused by insulin deficiency with subsequent autoimmune destruction of insulin-producing pancreatic β-cells (Bluestone, Herold, &Eisenbarth, 2010). Epidemiological investigations showed the geographical differences in T1DM incidence. For example the age-adjusted incidence of T1DM varied from 0.1/100,000 per year in China to 40.9/100,000 per year in Finland (Mayer-Davis et al., 2009). The Indian subcontinent has emerged as the capital of this diabetes epidemic. The reported incidence of diabetes in adults between the ages of 20 and 79 is as follows: Bangladesh 9.85%, India 8.31%, Sri Lanka 7.77%, Pakistan 6.72%, and Nepal 3.03%, (Guariguata, Whiting, Weil and Unwin, 2011; Rizvi and Mishra, 2013; Shaw, Sicree, &Zimmet, 2010). Epidemiologic evidence suggests that diabetic induces the risk for different types of cancer development. (http://care.diabetesjournals.org/content/33/7/1674). Insulin, IGF1 and IGF2 signaling through specific receptor can induce tumor initiation, accounting to some degree for the connection between diabetes mellitus and cancer (Singh, Alex, &Bast, 2014).

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Metformin (1, 1-dimethylbiguanide hydrochloride or Begunide) is an antidiabetic drug, but it also reduces development and progression of cancer. Metformin (Metf) is involved in development and progression of prostate cancerby down regulating the insulin/insulin-like growth factor axis. Metf showed AMPK dependent and independent antitumor activity (Anisimov, 2010).High concentration of insulin developed insulin resistance and increased the risk of prostate cancer initiation and progression. Prostate cancer-related mortality risk is increased in individuals with high insulin levels/insulin resistance (Amling et al., 2004). Further, it is also reported that Insulin may affects metabolism and exert a mitogenic effect through Insulin-like growth factor-1 (IGF-1) receptors (Pollak, Schernhammer and Hankinson, 2004). There is a well-established link between metabolic syndrome and prostate cancer. Emerging research is characterizing this relationship further and delineating the specific role of insulin in promoting prostate cancer tumorigenesis.

Metf (Begunide) is a colorless oral hypoglycemic (antihyperglycemic) drug. It is commonly used in the treatment of type 2 diabetes, and is often referred to as an insulin sensitizer. It is also used against insulin resistance, hyperinsulinemia, and hyperglycemia. Metf reduces the circulating insulin levels (Gunton, Delhanty, Takahashi and Baxter, 2003) and improves insulin receptor signaling leading to improvement of insulin resistance, hyperinsulinemia, and hyperglycemia. Moreover, Metf interaction with insulin receptor leads to inhibition of cell proliferation and survival of the cells (Holland, Morrison, Chang, Wiernsperger and Stith, 2004). Anisimov (2010) recommended that Metf mediated downregulation of the insulin/insulin-like growth factor signaling may characterize a new paradigm for the treatment of human malignancies. Moreover, metformin reduces the preliminary cost of therapy and its linked complications.

Metf exert both insulin dependent and independent anticancer effects (Figure 1). The indirect, insulin-dependent effects of metformin are mediated by the adenosine monophosphate-activated protein kinase (AMPK) pathway which inhibits gluconeogenesis in liver and stimulate glucose uptake in muscle thereby reducing blood glucose and insulin level (Cusi, Consoli and DeFronzo, 1996). Insulin has mitogenic activity in cancer cells that led to growth

promoting effects. The direct, insulin-independent effects of Metf originated from liver kinase B1 (LKB1) mediated activation of AMPK and reduction in mTOR (Mammalian Target of the Rapamycin) signaling (Figure 1) (Dowling, Zakikhani, Fantus, Pollak and Sonenberg, 2007).

Table 1. Insulin/IGFs receptor expression on prostate cancer cell lines

Cell lines	IR-A, IR-B	IGF1R	IGF2R
PC3	Yes (Armakolas et al., 2010)	Yes (Kawabata et al., 2011)	Yes (Kawabata et al., 2011)
DU 145	NA	High Expression (Kawabata et al., 2011)	Yes (Kawabata et al., 2011)
LNCaP-FGC	Yes (Giuseppe Pandini, Rossana Mineo, 2005)	Yes (Bidosee, Karry, Weiss Messer and Barkey, 2011)	Yes (Bidosee et al., 2011)
LNCaP-LN-3	NA	Yes (Krueckl et al., 2004; Letsch, Schally, Busto, Bajo and Varga, 2003; Tong da et al.)	Yes (Letsch et al., 2003)
LNCaP-C4	NA	Yes (Krueckl et al., 2004)	Yes (Letsch et al., 2003)
MDA PCa 2a	NA	Yes (Goya et al., 2004)	Yes (Goya et al., 2004)
MDA PCa 2b	NA	Yes (Letsch et al., 2003)	Yes (Goya et al., 2004; Letsch et al., 2003)
22Rv1	NA	Yes (Kawabata et al., 2011)	Yes (Cobb, Mehta and Cohen, 2009; Shukla et al., 2005)

Insulin Receptor A (IRA), Insulin Receptor B (IRB), Insulin Growth Factor Receptor 1 (IGF1R), and Insulin Growth Factor Receptor 2(IGF2R)

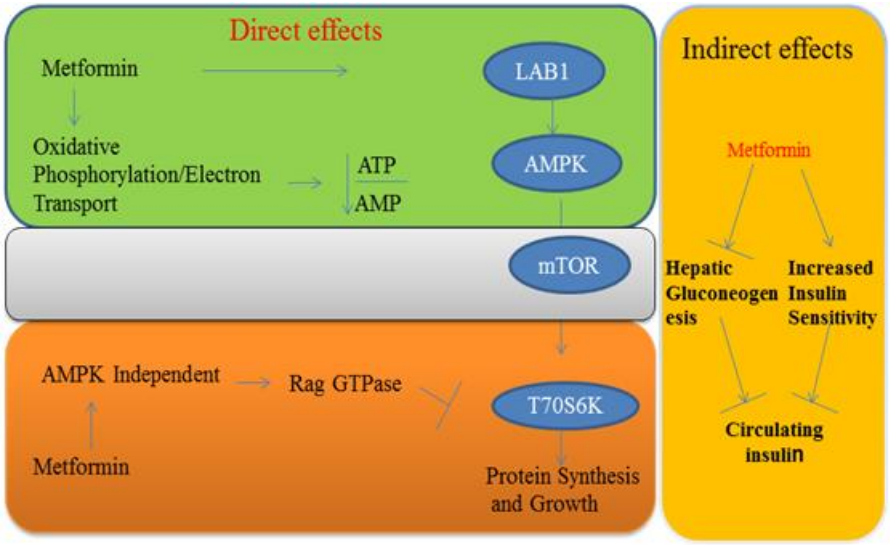

Figure 1. Antitumor mechanisms of Metf action. Metformin may activate AMPK via two mechanisms, the inhibition of oxidative phosphorylation/electron transport and subsequent decrease in the ATP/AMP ratio and the direct activation of LKB1. AMPK activation leads to blocking mTOR cell signaling that ultimately leads to inhibition of cell proliferation and survival.

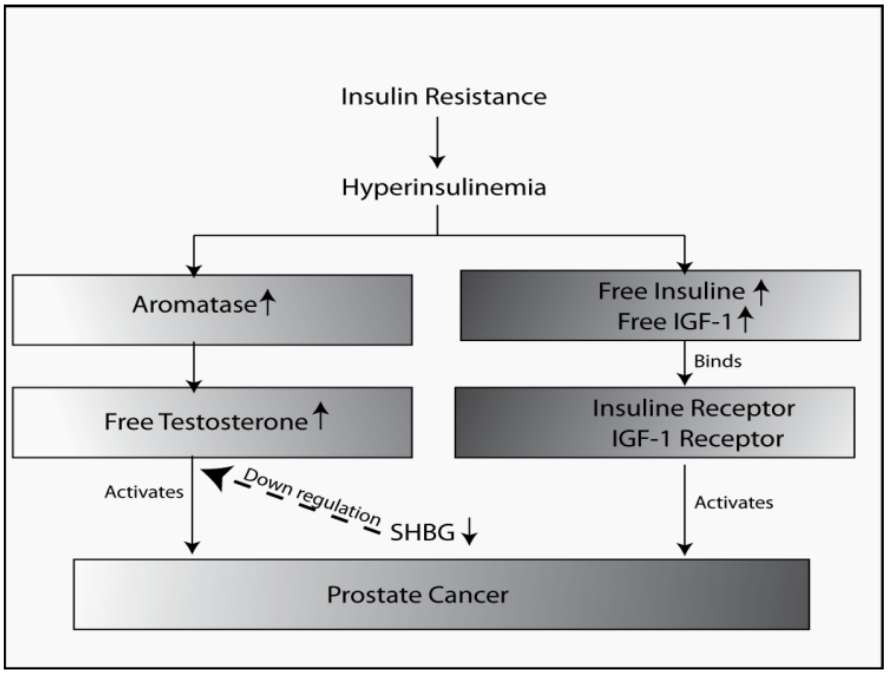

Figure 2. Association of insulin resistance and prostate cancer: high level of insulin binds to IGF axis receptors and initiates mitogenic activity that ultimately leads to the development of prostate cancer in addition to androgen receptor activation.

Prostate cancer is the second most commonly diagnosed visceral cancer and the sixth leading cause of cancer death in males. There is evidence that the metabolic syndrome associated with T2DM is due to the increased insulin levels (Kahn and Flier, 2000) and is related to increased cancer risk worsened cancer prognosis. The insulin affects prostate cancer Growth–IGF signaling axis. There are two mechanisms have been proposed for link between diabetes and pathogenesis of prostate cancer; these are: activation of the insulin and insulin-like growth factor associated signaling pathways, and regulation of endogenous sex hormones. High levels of circulating insulin increase the risk of prostate cancer initiation and progression. Insulin directly affects the cell growth, cell proliferation, survival and ultimately leads to cancer cell resistance. It remains an unlock question as to whether, or to what extent, differences in circulating levels of insulin influence cancer progression. Insulin effects more severely in individuals receiving insulin treatment for diabetes. The exogenous insulin increases the risk of prostate cancer initiation and progression.

Metf is a widely prescribed oral drug available worldwide at low cost. It reduces glucose level and enhances insulin sensitivity reduces insulin resistance. At the same time circulating insulin levels does not induce hypoglycemia and hyperinsulinemia. The growth inhibitory effects of Metf are usually by the AMPK dependent as well as AMPK independent. Serine/threonine protein kinase AMPK activation leads to G1 cell cycle arrest *via* up-regulation of the p53-p21 tumor suppression gene and ultimately results in decrease cancer cell proliferation and growth. During cell proliferation inhibition Metf did not induce apoptosis (Alimova et al., 2009).

The effect of Metf use on consequences of diabetic prostate cancer remains unclear, whereas a decreased incidence of prostate cancer has been reported with type 2 diabetes. Some clinical studies indicated that Metf enhanced survival for cancer patients (Bansal, Bhansali, Kapil, Undela and Tiwari, 2013; Zhang and Li, 2014).Moreover, recent studies have shown that Metf significantly inhibited the proliferation of prostate cancer PC-3 cells via the down-regulation of IGF-1R (Kato et al., 2015). Furthermore, in prostate cancer Metf-induced energy deficiency leads to the inhibition of lipogenesis in PC 3 cells, but in the LNCaP cells, the decrease of essential lipogenic proteins: fatty acid synthase, acetyl-CoA carboxylase, and sterol regulatory element binding protein-1c. The Akt/mTOR pathways have been shown to stimulate lipogenesis through the direct supervision of the expression of fatty acid synthase, acetyl-CoA carboxylase, and sterol regulatory element binding protein-1c(Loubière et al., 2015). Indeed, metformin-mediated AMPK

activation modifies multiple downstream effectors, like the inhibition of mTOR pathway, impairing cancer cell growth (Würth et al., 2016).

The clinically safe, less toxic and low cost of Met make it an ideal candidate for anticancer drug development. Recently epidemiological, clinical and experimental studies support the potential anticancer effect of Metf against human cancer. However, some issues needed further consideration in the development of Metf as anticancer agent. In particular, potential anticancer effects of Metf are only in diabetic patient populations.Both *in vitro* and *in vivo* experiments provide support for anticancer activity of Metf. Metf helps the patients which exhibiting hyperinsulinemia and have the expression of insulin receptor, LKB1, and TSC2. The next question arises that how non-diabetic patients may respond to Metf. Differentiation between direct and indirect effects of Metf treatment is also challenging.

CONCLUSION

Inhibition of insulin signaling is gaining attention as a potential new anticancer therapeutic strategy. Deregulation of insulin and insulin growth factor signaling contribute the mitogenic activity that influences the efficacy of anti-IGFI. It is interesting that metf acts in several ways that may diminish the effect of insulin coupled metabolic changes on prostate cancer cells. 1) Metf lowers insulin levels since insulin can encourage the cell proliferation of prostate cancer cells 2) Metf may increase AMPK activation in cancer cells, resulting in direct growth inhibition 3) Metf may act in AMPK activation independent manner and reduce cancer cell proliferation. Molecular response of Metf in insulin-influenced cancer cells will be a new venture to understand the molecular biology of cancer. Investigation of up/down-regulated insulin signaling molecules in cancer could plausibly re-write the new treatment target and afford the most rational approach to treating diabetic prostate cancer.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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