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Metformin: The 'multitasker'

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Metformin was the first drug synthesized to reduce the blood sugar levels, but was overshadowed by the advent of insulin and other drugs. Today, metformin is the primary drug prescribed for the effective treatment of non-insulin dependent diabetes mellitus, obesity and polycystic ovarian syndrome (1). Metformin inhibits hepatic gluconeogenesis through AMP-K dependent regulation of small heterodimer partner (SHP) and the expression of gluconeogenic genes (2). It also increases insulin sensitivity and fatty acid oxidation in skeletal muscle (3). Metformin performs it role as an anti-hypergycemic modulator by suppressing hepatic glucose output, and increasing peripheral utilization and glucose turnover. It also increases translocation of the insulin sensitive glucose transporter GLUT4 into the plasma membrane in adipocytes (4). Metformin regulates insulin mediated functions and increases the number of insulin receptors in various diabetic states, however its blood glucose lowering effect appears to be occurring as an early event in the post-receptor signaling process (5, 6). More recently studies have shown that individuals diagnosed with diabetes and treated with metformin have a reduced risk for developing different types of cancer (7). Use of metformin has also shown enhanced effect of chemotherapy in cancer patients (8, 9). However, the effect of metformin and it's mode of action on cancer has not been demonstrated very clearly. **Hirsch HA *et al* in his paper titled 'Metformin inhibits the inflammatory response associated with cellular transformation and cancer stem cell growth' presents evidence to explain that metformin inhibits the signal transduction pathway that leads to inflammation thereby suggesting a possible mechanism for its role as an anti-cancer agent** (10).

For the study, the authors use a Src-inducible breast cancer model of cellular transformation, MCF10A-ER-Src cells that are induced to transform following treatment with tamoxifen. In these cells a transient inflammatory stimulus initiates an epigenetic switch from a non-transformed to a transformed cancer cell (11). This paper shows that metformin inhibits activation of the NF-κB pathway by inhibiting the nuclear localization of NF-κB and the activity of STAT3, selectively in cancer stem cells. Metformin blocks transformation of cells for 4 days after induction with tamoxifen, however after 5 days all cells looked transformed, indicating that metformin only delays Src-induced cellular transformation. They also observed that metformin inhibits the transformation process only if the cells were exposed to treatment at an early stage.

This paper also shows that metformin selectively inhibits the markers of inflammation in cancer stem cells, blocks tumor growth and prolongs remission on co-treatment with chemotherapeutic agents (12). Interleukin-6 (IL-6) has been shown to play an important role in converting non stem cancer cells (NSCCs) to cancer stem cells (CSCs) and previous studies confirms this as antibodies against IL-6 blocks the conversion of NSCCs to CSCs. IL-6 forms the important link between inflammation and cancer and this positive feedback loop is more pronounced in the cancer stem cells than the NSCCs (11). Metformin decreases plasma insulin concentrations and thereby inhibits insulin mediated effects on cell growth indirectly and insulin and insulin-like growth factor are known to increase cell proliferation and hyperplasia through the activation of the PI3K pathway (13). Therefore metformin probably functions in an anti-tumorigenic manner due to its indirect insulin reducing effect (14). Metformin acts as an inhibitor of pro-inflammatory response by inhibiting NF-κB through the PI3K pathway. Treatment with metformin reduces phosphorylation of Akt and ERK further inhibiting NF-κB translocation and IκB degradation. Metformin treatment also inhibits IL-8 in addition to IL-6 in smooth muscle cells, endothelial cells and macrophages. In addition to the PI3K pathway, it also inhibits IL-1-induced p38 phosphorylation in the MAPK pathway (15).

The authors have shown previously, that in mouse xenografts, use of metformin decreases the dose of chemotherapy and it also synergistically improves the effect of the chemotherapy (16). They also show that metformin selectively kills cancer stem cells and therefore functions synergistically with chemotherapeutic drugs having a significant effect on prolonging remission (12). This is of potential interest especially in tumor cells that are resistant to the conventional drug treatments.

The paper also discusses that metformin inhibits the inflammatory feedback loop by increasing Let-7 expression and the combinatorial therapy is more effective in cell lines that have a more profound inflammatory signature. The human let-7 family contains 13 members located on nine different chromosomes, and is widely viewed as a tumor suppressor. Many human cancers have a deregulated let-7 expression and metformin reverses this suppression of let-7 in the transformed cells (17). In addition to the Let-7 family, metformin also has been shown to upregulate the expression of miR-26a and miR-192 in human pancreatic cancer cells (18). Metformin associated miRNA expression changes have also been observed in miR-146a, miR-100, miR-425 amongst others in prostate cancer (19). It also modulates RNASE III endonuclease DICER which is one of the key enzymes of microRNA biogenesis (20). Therefore metformin probably functions as an anti-cancer agent by regulating the miRNA status of the cancer cells as well.

In summary, Hirsch HA *et al* in this paper and their previous studies have provided various pieces of evidence to show that metformin inhibits the inflammatory pathway and the metabolic stress response. Due to the fundamental role of this pathway

in cancer, it would be applicable to a broad variety of cancers thereby justifying the need for more detailed molecular studies to identify potential targets in this inflammatory axis and also conduct clinical trials to explore metformin as a therapeutic for cancer treatment in more defined target populations.

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