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Commentary

Challenges in modulating insulin receptor signalling as a therapeutic strategy for cancer

In spite of dissimilitude in the aetiology of diabetes and cancer, there are several overlapping risk factors such as obesity, lack of physical activity and dietary routines which predispose diabetic patients to cancer. Furthermore, several molecular signalling cascades, especially the deregulated insulin/insulin-like growth factor (IGF) axis pathways, could be evidenced in both these disease conditions. Insulin and IGF can activate the insulin receptor (IR) and insulin-like growth factor receptor (IGF-R), which are expressed as homo/hetero-dimer receptor proteins on the cell membrane, leading to subsequent PI3K-AKT/MAPK signalling resulting in enhanced uptake of glucose into the cell through GLUT-4 for glycolysis[1]. Uncontrolled activation of this signalling cascade results in enhanced proliferation of the cells. When glucose is available to the cells, the glycolytic enzymes would be activated. The association of the phosphorylated forms of glucokinase and BAD (Bcl2 antagonist of cell death) proteins triggers the glycolytic pathway and results in subsequent enhanced cell proliferation. It has been reported that inhibition of insulin/IGF, their receptors or inhibitors of glucose metabolism intermediates such as phospho-BAD, blocks the glycolytic pathway and activates apoptotic signalling, thereby resulting in cell death[2].

Most cancer cells express IR, particularly the A isoform of IR (IRA) and/or IGF-1R, which are shown to stimulate insulin/IGF-mediated mitogenesis. However, activation of IR is capable of inducing cell proliferation independent of IGF-1R[3]. Concomitantly, reports suggest that high levels of circulating insulin increase the cancer risk in diabetes mellitus patients[4]. In this issue, a novel biosynthetic IR antagonist, S961, which is a single-chain peptide with 43 amino acids, has been shown to possess anti-proliferative action against cancer cells that overexpress IRA and IRB. S961 can efficiently block activation of IR even in the presence of insulin. This *in vitro* study on breast cancer cells sheds light on the potential of S961 to be used as an anti-cancer therapeutic agent[5].

There are several challenges to be tackled when we consider a candidate molecule which would inhibit the glucose uptake, thereby acting as an anti-cancer agent. One of the potential challenges with the IR antagonist to be used as an anti-cancer agent would be the effect of its anti-proliferative activity on the pancreatic beta cells and other normal cells, which also express IR. Recent reports involving disruption of IR function in tamoxifen-resistant breast cancer cells using three different approaches, *viz.* IR shRNA, S961 and monoclonal antibodies against IR, successfully blocked insulin-mediated signalling for monolayer proliferation, cell cycle progression and anchorage-independent growth[6,7]. Furthermore, it has been already shown that 100 nmol/l of S961 can block AKT phosphorylation even in the presence of glucose[8]. These reports indicate the evidence for the anti-cancer strategies using IR inhibition. One has to keep in mind that all these studies were done in *in vitro* system, and in-depth *in vivo* experiments and analysis should be performed to corroborate this. This is evident from the studies wherein it was shown that the anti-cancer treatment with IGF-1R monoclonal antibodies failed in patients with endocrine-resistant tumours in phase III clinical trials[9,10]. Since activation of IGF-1R signalling can induce mitogenesis independent of IR, it has to be analyzed whether strategies involving IR blocking would also hinder the IGF-1-mediated signalling in the cancer cells, *in vivo*. Simultaneously, it should also be monitored that insulin action would not be affected in the normal cells. The IGF inhibition is currently a hot topic for sensitizing paclitaxel-mediated anti-cancer activity in breast cancer cells[11]. Such combinatorial therapies are advantageous for the fact that we can reduce the concentration of IR inhibitors, thereby

decreasing the toxicity levels on the IR-expressing normal cells.

As indicated above, clinical trials using anti-IGF-R/IR drugs for anti-cancer activity have not been very promising so far[12]. Inhibition of one pathway would lead to activation of similar pathways because of multiple cross-talks among the mitogenic signalling, which remains to be another challenge that has to be overcome. Moreover, development of drug resistance is a major hurdle in cancer treatment. Resistance to anti-IGF-R/IR drugs is mediated through regulation of IRA in cancer cells and its over-activation by increased secretion of autocrine IGF-II. Thus, there is a need for co-targeting both IRA and IGF-1R to have effective inhibition of proliferation in cancer cells. Targeting IRA, specifically by S961, may also end up in a similar scenario as described above.

Another major challenge would be the concern of glucose uptake by the cancer cells independent of their IR status. Recent studies report that irrespective of the IR status, the cancer cells possess the ability for enhanced glucose uptake[10]. Similarly, in diabetes, it has to be noted that insulin is not the only hormone which can reinstate glucose level. The action of hormone leptin is not restricted to insulin sensitivity but can also normalize glycaemia independently of insulin, which has been proved both in congenital deficiency as well as S961-mediated IR antagonism[13].

Leptins produced by cancer cells and adipocytes are known to activate insulin receptor substrate (IRS) through leptin receptor, independently of IR and the PI3K signalling pathway[13,14]. When we use IR inhibitors, will the leptin-mediated IRS activation be hindered? Since the role of leptins is clearly documented in cancers of the thyroid, liver, colorectum and breast, it has to be analyzed whether leptin-mediated IRS activation would lead to enhanced glucose uptake by the normal cells also[14]. In type I diabetes patients, pancreatic beta cells may also get destroyed in response to S961 if it inhibits IR. On the contrary, S961 can hinder leptin-mediated glucose uptake in *in vitro* conditions[15], which has to be proved in *in vivo* conditions. However, studies using mouse islet cells showed that glucose-induced beta cell proliferation requires IRS2 but not IR[8]. Therefore, it has to be made clear whether a combination of leptin and S961 would save the insulin-responsive normal cells while inducing selective apoptosis of the cancer cells.

Another serious challenge would be that the tricky cancer cells would adapt alternative metabolic pathways for their energy demands. For example, when lactate is used preferentially by certain cancer cells by Warburg effect, other cancer cells within the same tumour may use glucose, as its main source of energy. For their enormous energy needs, cancer cells rely not only on the glucose metabolism but also on the fatty acid metabolism and glutaminolysis, which they opt preferentially based on their requirements and cellular status[16]. Recent researches validate glutaminolysis to counteract glycolysis as the major energy source which the cancer cells utilize for satisfying their nitrogen requirements and energy needs for facilitating the increased cellular proliferation rates.

In comparison with the normal stem cells, cancer stem cells have an enhanced rate of anaerobic glycolysis and high ATP levels, which contribute immensely to their ability in evading the host immune response as well as contributing to an increased resistance towards therapy[17]. Ideally, future IR-targeting strategies should be able to selectively inhibit the tumour stem cells also, without impairing the metabolic effects in the normal cells.

Thus, it can be concluded that the dual targeting of both IGF-1R and IR together, along with the inhibition of IRS, is needed for effective inhibition of insulin signalling in cancer cell proliferation. Targeting glucose uptake by the tumour cells as a means to slow down the metabolism along with the inhibition of mitogenic signalling of IR/IGF-1R would be an ideal strategy for a successful treatment outcome. Furthermore, the ability of cancer cells to utilize the alternative metabolic pathways during extreme conditions should also be tackled. Above all, we might use the combination of all these strategies at a moderate level so that the normal cells would remain unscathed.

***Conflicts of Interest*:** None.

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