Editorial

Insulin-resistant conditions: A favorable milieu for aggressive drug-resistant malignancies

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Epidemiological studies suggest that the risk of several solid and haematological malignancies (i.e., pancreas, liver, breast and colorectal carcinomas, male and female genitourinary neoplasms and non-Hodgkin's lymphomas) is increased in insulin-resistant diabetic patients with a prevalence that is estimated to be 8-18%. However, the correct assessment of this increased risk needs to take in account a series of potential confounding factors, as conditions associated with insulin resistance and hyperinsulinemia (i.e., physical inactivity, obesity, diabetes treatment types and high-saturated-fat diet), which are also independent risk factors for cancer. Furthermore, insulin-resistant diabetic cancer patients are characterized by a worst outcome compared to non-diabetic cancer patients and this depends on an increased cancer-site specific mortality, which reaches statistical significance for breast, endometrial and colorectal cancers, and a reduced sensitivity to anticancer therapies (1).

It has been suggested that the major mechanism responsible for the increased cancer risk in diabetics and the poor prognosis of patients with malignancies associated to insulin-resistance is the resulting hyperinsulinemia. Chronic hyperinsulinemia, indeed, favors cancer initiation and/or progression due to the direct mitogenic activity of insulin on epithelial cells and its ability to stimulate cells indirectly by increasing the levels of other modulators of proliferation, such as insulin-like growth factor (IGF-1) and sex hormones. In addition, cancer cells are characterized by increased expression of insulin and IGF-1 receptors and by the inability to down-regulate these receptors in response to hyperinsulinemia. Thus, the increased levels of insulin and IGF-1 in diabetic cancer patients lead to abnormal activation of insulin and IGF-1 receptor signaling in tumors cells, potentially explaining the influence of hyperinsulinemia on tumor prognosis and poor response to anticancer therapies. In fact, insulin and IGF-1 are responsible for a strong activation of PI3K/AKT and MAPK pathways and this results in a cascade of proliferative and anti-apoptotic events favoring tumor progression, drug resistance and poor patient's outcome (2). Noteworthy, the same mechanism of insulin resistance and subsequent hyperinsulinemia is likely responsible for the increased cancer risk and the poor prognosis of malignancies associated to other conditions such as obesity and metabolic syndrome (3).

In this issue, Chen et al. present a study which addresses the role of insulin and activation of AKT pathway on oxaliplatin antiproliferative activity in human colorectal cancer cells (4). The authors suggest that high insulin levels in the extracellular environment are responsible for a significant inhibition of oxaliplatin cytotoxic activity, which could be mediated by the activation of the PI3K/AKT pathway. Of note, the selective pharmacological inhibition of PI3K results in the re-establishment of oxaliplatin-induced cytotoxicity. This study highlights two major issues which may be relevant for future clinical management of obesity-associated colorectal cancers: the role played by hyperinsulinemia and activation of PI3K/AKT pathway in favoring drug resistance.

The first issue is relevant in the perspective to design novel strategies to reduce cancer risk in diabetic patients and to improve the activity of anticancer agents in diabetes-associated malignancies. Recently, metformin, a biguanide derivative widely used as first-line therapy for insulin-resistant diabetes, has been proposed as a novel anticancer agent. Metformin is a major activator of AMPK, a kinase

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acting as a central regulator of cellular energy-consuming processes. Of note, metformin-dependent AMPK activation leads to the reversal of hyperglycemia, insulin resistance, hyperinsulinemia and its mitogenic effects, as demonstrated in several human cancer cell models. Metformin's metabolic activity is mediated by its ability to modulate insulin and IGF-1 signaling, to inhibit mTOR kinase pathway, to interfere with tumor angiogenesis and to induce cell cycle arrest and apoptotic cell death. This results in a direct antiproliferative activity on cancer cells and in the enhancement of the chemotherapy-dependent cytotoxicity (2). Extremely relevant in the perspective of rescuing the sensitivity of malignant cells to anticancer agents is the inhibitory activity of metformin on IGF-1 and AKT pathways, leading to inactivation of cell survival and enhancement of drug-induced cell death (2). These evidences are supported by epidemiological study suggesting a reduced risk of cancer in type 2 diabetic patients treated with metformin (5). Based on this rationale several ongoing clinical trials have been designed to investigate the antiproliferative activity of metformin in human solid malignancies as single agent or in combination with traditional chemotherapeutics. In such a perspective the study of Chen et al. provide a strong support in favor of the evaluation of metformin in combination with oxaliplatin in insulin-resistant diabetic colorectal cancer patients.

Finally, the relevance of PI3K/AKT signaling in inducing drug resistance in human colorectal carcinoma cells is emphasized by this study. Indeed, several lines of evidences support the hypothesis that the activation of tyrosine kinase receptor signaling leads to the induction of PI3K/AKT pathway, favoring the activation of survival mechanisms and resistance to apoptosis in cancer cells (6). In such a perspective, the resistance to platin derivatives has been associated with the activation of AKT signaling in several human malignancies (6), as well as the relevance of mitochondrial survival pathways in inducing resistance to oxaliplatin has been demonstrated in colorectal carcinoma cells by our group (7). Furthermore, AKT inhibitors have been proposed as anticancer agents with the aim to re-sensitize tumor cells to cytotoxics and some of them are under clinical evaluation (6). Thus, the results presented by Chen et al. highlight the role of the extracellular milieu as a potential conditioning factor, responsible for a reprogramming of tumor cells at transcriptional and post-transcription levels and potentially favoring proliferation, escape from apoptosis, and drug resistance.

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