



Close Relationship between Diabetes and Cancer

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Dear Editor-in-Chief

The diabetic individuals are at higher risk of suffering cancers of the colon, pancreas, liver, endometrium and others and it has been also established that high glucose increases the risk of the cancer types (1). Hyperglycemia in diabetic patients activates macrophages and monocytes to produce inflammatory factors such as IL6 and TNF α (2, 3). The cytokines stimulate releasing the free fatty acid (FFA) and the FFA induces adipocytes to produce inflammatory adipokines by the stimulation of toll-like receptor 4 on the adipocytes. The inflammatory adipokines are including MCP-1, IL-6, and TNF- α that leading to insulin resistance (IR) and tumorigenesis (4). Hyperinsulinemia is considered as the primary causative factors for tumor cells (5) and insulin itself induces the release of IL6 from adipocytes (6). Moreover, the inflammatory cytokines by the MAPK or JAK/STAT signaling contribute to tumorigenesis by proliferation, accumulation of mutations, survival and anticancer immunity suppression (1). On the other hand, the cytokines lead to elevated gluconeogenesis in the liver organ of neoplasm patients that is promoted by lactate secreted from the cancer cells (7). Therefore, the inflammation and high glucose feed each other and the inflammation stimulates IR and hepatic gluconeogenesis and the hyperglycemia triggers the inflammation.

In addition, high glucose changes the genes expression that enhances cell proliferation, adhesion and migration (8). High glucose links cancer and diabetes by the stimulation of increased cir-

culating levels of growth factors (insulin/IGF1). On the other hand, tumor cells overexpress the receptors for IGF1 or insulin (IGF1R and IR, respectively) and the activation of these receptors blocks apoptosis and increases proliferation (9). In addition, hyperglycemia is necessary for WNT/ β -catenin pathway, a key cancer-associated signaling pathway (1). Insulin along with high glucose enhances the activation of mTOR, PI3K, and AKT resulting in increased anabolic activity in cancer cells (1).

Furthermore, diabetic patients have immunodeficiency and hyperglycemia changes immune system function. Ascorbic acid is required for proper function of lymphocytes and mitosis, as well as for effective phagocytosis. The immune system response to tumor cells decreases with high glucose; since glucose competitively impairs the transport of vitamin C to immune cells (10). Moreover, hyperglycemia triggers the cell cycle by alterations in the genes expression, including cyclins A and E and E2F (8). On the other hand, the high glucose elevates up-regulated oxidative stress-responsive genes such as thioredoxin-interacting protein that stimulates mutations by an increase in the levels of reactive oxidative species (ROS) (1). The ROS can cause cell death and mutations by elevated DNA damage, accumulation of advanced glycation end products and impaired repair (1).

In addition, high glucose increase protein kinase C α signaling pathway and reduce E-cadherin that resulting in elevated cell motility that accordingly,

induces invasiveness and migration (8). High glucose stimulates the urokinase plasminogen activator expression that promotes migratory and invasive activities. Hyperglycemia induces a key step for tumor progression invasion and migration by the expression up-regulation of chemo-attractant glial cell line-derived neurotrophic factor (GDNF) and its interaction with the RET tyrosine kinase receptor (1). Therefore, there are close relationships between diabetes and cancer.

Conflict of interest

None declared.

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