REVIEW

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

New insights in the molecular pathways linking obesity, type 2 diabetes and cancer

ADINA POPA[1)], MILENA GEORGESCU[2)], SIMONA GEORGIANA POPA[1)], ADRIANA ELENA NICA[3)], EUGEN FLORIN GEORGESCU[4)]

[1)]*Department of Diabetes, Nutrition and Metabolic Diseases, University of Medicine and Pharmacy of Craiova, Romania*

[2)]*Department of Plastic Surgery, Emergency County Hospital, Craiova, Romania*

[3)]*Department of Anesthesiology and Intensive Therapy, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[4)]*Department of Surgery, University of Medicine and Pharmacy of Craiova, Romania; Department of Surgery, Emergency County Hospital, Craiova, Romania*

Abstract

Steadily, cancer is becoming the first cause of mortality, with over 9 million deaths estimated in 2018. Increasing evidence supports a direct association between obesity, type 2 diabetes mellitus (T2DM) and cancer, with a higher risk of cancer mortality especially for some of the most common malignancies, such as breast, colon, and rectal cancers. So far, several mechanisms underlying the cancer–diabetes relationship have been investigated revealing dysregulations of the insulin–insulin-like growth factor (IGF) system as the most important paradigm. Other molecular mechanisms that seem to play a role in the association cancer–T2DM consist of alteration of the signaling pathways activated by inflammatory cytokines, adipocytokines or adhesion molecules. The overall aim of this review is to provide an overview of the molecular mechanisms linking obesity, T2DM and cancer, as related to the receptors and signaling pathways involved in these associations.

Keywords: insulin-like growth factor system, adipocytokines, G protein-coupled receptors, tyrosine kinase receptors, signaling.

Introduction

Cancer is overtaking cardiovascular disease as the first leading cause of death worldwide, according to the latest data published by the *World Health Organization* (WHO) and the *International Agency for Research on Cancer* (IARC), with an estimated 9.6 million cancer deaths in 2018, making cancer the most important barrier to increasing life expectancy in the 21st century [1, 2]. Furthermore, *IARC* estimates there will be 18.1 million new cancer cases in 2018, with the highest incidence in Asia (48.4%), followed by Europe accounting for 23.4% of these new cases, Americas (21%) and Africa (5.8%) [1]. Regarding mortality, the highest percentage of cancer deaths in 2018 was also observed in Asia (57.3%), this share being higher than the cancer incidence share. The same pattern was observed for Africa, where 7.3% of cancer deaths were reported. The mortality shares reported by this study for Europe and Americas were 20.3% and 14.4%, respectively [1]. The type of cancer with the highest mortality reported for 2018 was lung cancer, responsible for 18.4% of all cancer deaths, followed by colorectal cancer, accounting for 9.2% of all cancer deaths. Other forms of cancer with increased mortality were stomach and liver cancers, each responsible for 8.2% of all cancer deaths. The second highest incidence (11.6% of all cancer cases) was reported for female breast cancer, which was accountable for 6.6% of all cancer deaths [1].

It has been long known that 30–50% of all cancers can be prevented, by avoiding pollution, occupational carcinogens and some viral or bacterial infections [2]. Nevertheless, both obesity and type 2 diabetes mellitus (T2DM) are increasingly recognized to be associated with higher cancer mortality. For instance, it is clearly demonstrated that T2DM is an aggravating factor for cancer mortality in patients suffering from colon cancer or pancreatic cancer, as well as breast cancer in females and liver cancer or bladder cancer in males [3, 4].

As such, the involvement of obesity and T2DM in the pathogenesis of different types of cancer is generally accepted. While this relationship is known for more than 80 years [3], the exact mechanisms linking these conditions remain largely unknown or underinvestigated. In this paper, we review the molecular mechanism linking obesity, T2DM and cancer, with focus on the signaling pathways activated by plasma-membrane receptors.

Obesity and diabetes. Metabolic syndrome

Worldwide, an estimated 650 million adults suffered from obesity in 2016 (numbers which have nearly tripled since 1975), with an overall prevalence of obesity of about 13% (11% in males and 15% in females); even more worrisome is data showing that over 340 million children and adolescents in 2016 were overweight or obese [5]. Studies analyzing the trends in obesity estimate that the prevalence of obesity will reach 18% in males and 21% in females by 2025 [6].

The epidemic of T2DM parallels the epidemic seen in obesity. Indeed, in most, though not all, individuals with obesity there is a condition known as the metabolic

syndrome (MetS) found in the continuum between simple obesity and T2DM and often considered a "pre-diabetes" entity [7]. Different manifestations of MetS have different diagnostic criteria, but most include an increased waist circumference, dyslipidemia, hypertension and even elevated fasting plasma glucose. Although MetS and T2DM are associated with older age, family history of diabetes, history of gestational diabetes, physical inactivity and race/ethnicity, the most critical risk factors in developing T2DM are obesity or MetS.

According to data published by the *International Diabetes Federation* (IDF), in 2017, there were 425 million people living with diabetes in the world, number that is estimated to increase by 45%, reaching 629 million cases by 2045 [8]. The estimates for Europe show that in 2017 there were 58 million people living with diabetes with an estimated increase to 67 million by 2045 [8].

The epidemiology of MetS is more difficult to establish, given the different criteria used for its definition. It is estimated that the worldwide prevalence of MetS varies from 10% to 84% depending on the population studied and the definition used in the study. Epidemiological studies performed in Europe showed that about one-fourth of the adult population has MetS [9], while the prevalence reported in the United States was 38.5% [10].

Genome-wide association studies (GWASs) have identified genetic variants associated with an increased risk of developing T2DM. Some of these genetic variants have also been studied in relation to the risk of different cancers, such as pancreas, colon, rectum, prostate and breast cancers [11–15]. Furthermore, genetic studies have also shown a connection between obesity and breast cancer and colon cancer, potential overlaps being proposed with chromosomes 18q for colon cancer and 11p and 16q for breast cancer, when obesity gene maps are superimposed with cancer gene maps [16, 17]. Recent studies have demonstrated a great potential for micro-ribonucleic acids (miRNAs) as cancer biomarkers and therapeutic targets in different types of cancer [18]. Furthermore, studies showed that miRNAs may have an altered expression in cancers associated with obesity and MetS [19, 20]. miRNAs, such as let-7, miR-27, and miR-143 have an altered expression both in cancer and obesity and may play a role in obesity-linked breast cancer [19].

Diabetes and cancer

Studies show that there is a direct association between T2DM and cancer, independent of the effects of obesity. In a retrospective population-based cohort study of 32 247 patients with T2DM, Gini *et al.* showed a 30% increased overall risk of cancer in patients with T2DM, both for males and females, and the strongest association between T2DM and cancer was with pancreatic cancer. In this study, T2DM was also highly associated with liver, endometrium, colorectal, bladder, female breast, kidney and urinary tract cancers [21].

A recent study conducted using *UK Clinical Practice Research Datalink* (1988–2012) showed that patients with T2DM had higher incident rates for liver, pancreatic and colon cancers, compared to subjects without diabetes [22]. However, the same study did not find different incident rates regarding rectal, gastric and biliary cancers between patients with T2DM and subjects without diabetes.

The association T2DM–breast cancer is highly studied. For instance, breast cancer risk is significantly increased in women with prediabetes [23, 24], raising awareness regarding prevention of both T2DM and breast cancer from the diagnosis of prediabetes. As single entity, diabetes was found to be accountable for 293 300 cancer cases, as 25.8% of diabetes-related cancers were attributable to the increases in diabetes prevalence since 1980 [25]. Pearson-Stuttard *et al.* estimated population attributable fractions for 12 types of incident cancers attributed to obesity and diabetes for 175 countries by gender and age, showing that the combined effects of the two risk factors were responsible for 5.7% of all incident cancers, in 2012 [25].

Given the increasing prevalence of T2DM, as well as the parallel increase in diabetes-related cancers, higher emphasis should be placed on preventing T2DM in order to decrease both diabetes and cancer burden.

Obesity and cancer

Epidemiological large-cohort studied established that high body mass index (BMI) was responsible for 544 300 incident cancer cases worldwide, in 2012; furthermore, the increase in obesity prevalence since 1980 was attributed 31.9% of all obesity-related cancers [25].

Based on experimental, epidemiological and clinical data, *IARC* has concluded that excessive body weight is associated with at least 16 types of cancer: adenocarcinoma of esophagus, pancreas, liver, colorectum, mouth, pharynx, larynx, cardia, gallbladder, prostate, postmenopause breast cancer, endometrium, kidney, ovary, cervix [26], placing obesity after smoking as the second leading cause of malignancy [27, 28]. There are conflicting data regarding the relationship between obesity and lung cancer, studies suggesting that smoking behavior may play a role as mediator in this association [29, 30]. Paradoxically, there is an inverse association between lung cancer mortality and obesity [31].

If the current trends will continue, excessive adiposity may overtake smoking as the main cancer risk factor in the next years [2].

Mechanisms incriminated in the association obesity, T2DM and cancer

Hyperglycemia

Hyperglycemia was proposed as a risk factor for cancer development, taking into account that cancer cells take up glucose and use it for both energy production and different synthesis. A meta-analysis conducted by de Beer *et al.* showed that chronic hyperglycemia, evaluated by hemoglobin A1c (glycated hemoglobin) (HbA1c) levels, was correlated with an increased risk of breast, pancreatic, gastric and liver cancer, and did not correlate with prostate cancer risk [32]. Furthermore, hyperglycemia was associated with chemotherapy resistance and reduced overall survival (OS) in breast cancer [33, 34]. Several glucose-associated pathways were described in the association hyperglycemia–cancer: autoxidation, oxidative phosphorylation, glycosylation, and glycosamine pathways, inducing free peroxides

radicals formation required for increased cell division [35]. Interestingly, cancer cells present an altered glucose metabolism, relying mostly on anaerobic glycolysis, known as the Warburg effect [36, 37], which in turn leads to a glucose uptake increase in cancer cells [36].

However, studies have shown that hyperglycemia in the absence of hyperinsulinemia is not associated with tumor growth [36], proving that increased levels of insulin and insulin-like growth factor (IGF) as it happens in insulin resistant states, such as obesity, MetS and T2DM create a favorable tumor microenvironment in the cells, which will become more susceptible to cancer development [35, 36].

Molecular mechanism

Dysregulations of the insulin–IGF system

Insulin and IGFs signaling contribute to metabolic signaling pathways, but also play important roles in cell survival and proliferation. Insulin, together with IGF-I and IGF-II, are ligands of the insulin–IGF (IIGF) system, which includes three cell surface receptor tyrosine kinases (RTKs): insulin receptor (IR), IGF-IR and IGF-IIR [38–41], as well as at least seven IGF-binding proteins (IGFBPs). The IR and IGF-IR are well-studied transmembrane RTKs, and their downstream cellular signal pathways are well known, while the IGF-IIR has no tyrosine kinase enzymatic activity and is the mannose-6-phosphate receptor [36].

Both the IR and IGF-IR are expressed on the cell surface as two $\alpha\beta$ chains dimmers, with each monomer containing seven extracellular domains, joined by disulfide bridges forming a heterotetrameric complex [41–43]. These RTKs have a high homology of their amino acid sequences, with a 45–69% homology in the ligand-binding site and a 60–80% homology in the substrate recruitment and tyrosine kinase domains [41, 44–47]. However, the expression of these receptors is tissue specific, IR being found in higher levels in liver and adipose tissue, whereas although IGF-IR has an ubiquitous expression, it is found at low levels in adipose tissue and is almost absent in the liver. These differences, together with structural differences found in the β-subunit, resulting in specific activation of substrates and signaling pathways, may explain in some measure the preferential effects of insulin on metabolic homeostasis [42].

In unphosphorylated state, the IGF-IR catalytic activity is very low as a result of the inhibitory conformation of the activation loop, which is a domain of the kinase region that impedes tyrosine phosphorylation and adenosine triphosphate (ATP)-binding, acting as a pseudosubstrate which arrests the active site [41]. Classically, the binding of the ligand (IGFs) leads to a conformational change and activation of the IGF-IR, the dimeric subunit partner trans-phosphorylating the tyrosines of the activation loop [40]. The activation of the IGF-IR leads to two main downstream signaling pathways, mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K).

The α subunits of the IR present two binding sites for the ligands, one with low affinity and a second one with high affinity. Insulin binds to the low-affinity site of one α subunit and then to the high affinity site of the other α subunit, while a second insulin molecule binds to both sites of β subunit, leading to the dissociation of the first insulin molecule [44]. These trigger the tyrosine kinase activity of β subunits, leading to a cascade of phosphorylation of intracellular proteins participating in cell growth and survival, as well as cell metabolism [44, 48].

The IR is encoded by a gene located in chromosome 19p13.2, the coding region including 22 exons [44, 49]. Two structurally different IR isoforms are generated by alternative splicing of exon 11, IR-A and IR-B, which differ by the length of the alpha-C-terminal (αCT) segment, the latter including 12 amino acids derived from exon 11, being the mature isoform, whereas the former, which does not include these amino acids, is the fetal isoform [43, 44]. Furthermore, the IR isoforms have a different tissue expression, with IR-A being mainly expressed by embryo and fetal tissues, hematopoietic cells, central nervous system as well as cancer cells, and IR-B being predominantly expressed in the liver, adipose tissue and muscle (insulin target tissues) [43, 44, 49, 50]. Furthermore, IR-B is also expressed in differentiated cells, such as mammary gland cells, epithelial intestinal cells, kidney cells, thyroid cells, liver cells, adipocytes, while IR-A is mainly expressed in the precursor cells of all these cell types [44], suggesting that IR-A is involved in regulating tissue development and prenatal growth, studies showing that only IR-A binds with high affinity growth factors, such as proinsulin and IGF-II, whereas IR-B plays an important role in adults in glycemic metabolism [43, 44].

Recent studies support the theory that the physiological roles of the IR isoforms are not regulated by their different affinities for insulin, but by their different affinities for IGFs, mostly for IGF-II [43, 49]. Furthermore, the diversification of the IIGF system actions and signaling in various tissues could be explained both by differential expression of the IR isoforms, as well as by the association IR–IGF-IR in order to form hybrid receptors (HRs) [43, 51]. The proportion of HRs found in a tissue is given by the amount of IR isoforms and IGF-IR expressed by each cell [52]. Regarding their roles, HRs can act as growth-promoting receptors with poor insulin activation, but HRs containing IR-A may also respond to hyperinsulinemia [52].

With regard to the IR signaling pathways, the activation of the IR leads to both metabolic and mitogenic effects. The activated IR is involved in glucose, lipid and protein metabolism by the PI3K/v-akt murine thymoma viral oncogene homolog (protein kinase B) (AKT) pathway. This pathway is regulated by the phosphatase and tensin homolog deleted on chromosome 10 (PTEN), which dephosphorylates phosphatidylinositol-3,4,5-trisphosphate, molecule that is responsible for 3-phosphoinositide-dependent protein kinase 1 and AKT activation [52]. The mitogenic pathway stimulated by the activated IR is rat sarcoma virus/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase kinase/extracellular-regulated kinase (RAS/RAF/MEK/ERK) cascade, having as a final effect the phosphorylation of cytosolic proteins, which will translocate to the nucleus, regulating gene expression and cell growth [52]. Although these signaling pathways are used by all the receptors of the IIGF system, there are some differences depending on both the receptor and ligand involved [52]. Therefore, we can explain the different effects of insulin when it binds to the two isoforms of the

IR, as well as the different effects given by the activation of IR-A by either insulin or IGF-II [52].

It is generally accepted that hyperinsulinemia and insulin-resistant states, such as obesity and T2DM, are associated with different forms of cancer, such as carcinomas of the gastrointestinal tract, liver, pancreas, kidney, breast, endometrium cancer [3, 53–55], an important role in these associations being played by the IR-B/IR-A ratio and HRs. Furthermore, higher levels of insulin/C peptide lead to a reduced apoptosis and an increased cell proliferation, having a promoting effect on malignancies [3, 54]. Additionally, mitogenic properties of insulin, particularly in the liver and the pancreas that are exposed to high quantities of endogenous insulin, were demonstrated [3, 56–58], leading to the hypothesis that hyperinsulinemia may have a stimulating effect on cancer growth and their progression to metastatic disease.

Over the years, many studies showed that the IR is overexpressed in many forms of cancer (breast, prostate, endometrium, ovarian, liver, bladder, lung, colon, thyroid, osteosarcoma), breast cancer being one of the most studied, where the content of IR is six-fold higher than in the normal breast tissue [44]. Studies performed in the last years confirmed that this overexpression associated with hyperinsulinemia is responsible for the high incidence of breast cancer among women with obesity or T2DM [44].

The role of IGF-IR in promoting and sustaining the malignant phenotype is also generally accepted and overexpression of IGF-IR in gastric, colorectal, breast and endometrial cancers, which was correlated with cancer development, aggressiveness, poor outcome and resistance to therapy is clearly demonstrated [59]. Yet, the recognition of the role of IGF-IR in the association cancer–diabetes is still in its infancy as only recently it was concluded that IGF-IR had a higher expression in the patients having breast cancer and T2DM compared to those without diabetes [60], while for other cancer types this association is still under investigation. Figure 1 summarizes the role played by IIGF system together with other important molecular mechanism in the association T2DM and cancer.

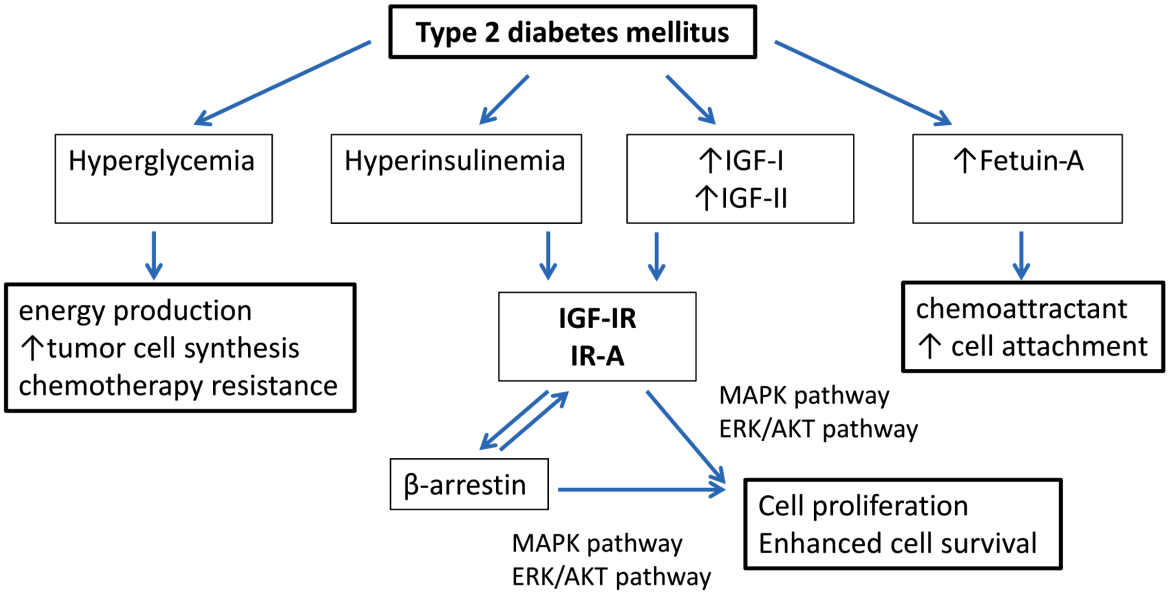

Figure 1 – ***The main molecular mechanism involved in the association T2DM–cancer. ERK/AKT: Extracellular-regulated kinase/v-akt murine thymoma viral oncogene homolog (protein kinase B); IGF-I: Insulin-like growth factor-I; IGF-II: Insulin-like growth factor-II; IGF-IR: Insulin-like growth factor-I receptor; IR-A: Insulin receptor A; MAPK: Mitogen-activated protein kinase; T2DM: Type 2 diabetes mellitus.***

G protein-coupled receptors

G protein-coupled receptors (GPCRs) are one of the most studied groups of cell signaling receptors, with more than 800 being reported in humans [61]. According to their structure, different authors classified them either into five families (rhodopsin, adhesion, secretin, glutamate, frizzled) [62] or into four classes (A, B, C, F) [63], class A (rhodopsin family) being the most widely characterized.

Representatives of class A and B receptors are proposed active targets for diseases, such as diabetes, cardiovascular diseases, neurological disorders and cancers [14, 64].

Fatty acid receptor family GPCRs, belonging to class A GPCRs, were studied for their possible roles in the relationship cancer–T2DM. The most studied free fatty acid receptors (FFARs) are FFAR1, FFAR2, FFAR3 and FFAR4, FFAR1 and FFAR4 being activated by medium- to long-chain fatty acids, while FFAR2 and FFAR3 are activated by short-chain fatty acids [64].

Both FFAR1 and FFAR4 play an important role in glucose metabolism, FFAR1 being expressed by β-cells, enhancing glucose-induced insulin secretion and cell glucose uptake, while FFAR4 are implicated in insulin signaling at the level of adipocytes, taste buds and macrophages [64], their dysregulation being associated with T2DM in animal studies.

Interestingly, studies show that FFAR1 and FFAR4 have opposing effects in terms of tumorigenesis and migration, the loss of FFAR1 in pancreas cancer cells and melanoma cells stimulating migration, while FFAR4 loss inhibiting this process [65, 66].

Other cell culture models showed that activation of both FFAR1 and FFAR4 exhibited inhibitory effects on proliferation and migration in prostate cancer and breast cancer [64].

Furthermore, colorectal cancer tissue FFAR4 expression was correlated with advanced clinical stage and poor differentiation, FFAR activation in these cells being associated with increased migration and angiogenesis [67]. Additionally, recent studies showed that FFAR4 activation may play a role in chemotherapy resistance [64].

Beta-arrestin

Beta-arrestin 2 (β-arr2) is an important cell regulator, with a crucial role in signaling downstream of GPCRs [68–70]. Recent studies showed that the pathways mediated by β-arr2 are involved in pathological processes, such as tumorigenesis and T2DM.

Jing *et al.* showed overexpression of β-arr2 in adriamycin (ADM) multidrug-resistant breast cancer cell, as well as partly restored sensitivity to cancer drugs after β-arr2 silencing, suggesting β-arr2 as a new molecular target for drug-resistant breast carcinoma [70].

Furthermore, β-arrestin system plays a role in IGF-IR signaling, studies showing that β-arr1 binding to IGF-IR has as a final effect additional MAPK/ERK signaling and protects cancer cells against anti-IGF-IR therapies [69].

Pang *et al.* showed in mice studies that β-arr2 was able to improve glucose uptake and insulin sensitivity in diabetes [68].

PTEN

Discovered in 1997, PTEN is a tumor suppressor whose expression is frequently lost in tumors [71]. Gremline mutations in *PTEN* gene are known to cause cancer-predisposition syndromes [72].

PTEN genetic inactivation was seen in melanomas, glioblastomas, endometrium, prostate, bladder and colon cancers, while in lung and breast cancer a reduced PTEN expression was observed [72, 73].

PTEN is a protein tyrosine phosphatase, which is capable to dephosphorylate inositol lipids, as well as proteins [74]. PTEN acts as a tumor suppressor trough its ability to negatively regulate AKT, an oncogenic protein involved in tumor cell growth, survival, migration and differentiation [75].

With regard to insulin resistance and T2DM, animal studies showed that PTEN inhibition might be appropriate in T2DM, this protein being able to counteract insulin signaling [74]. Selective PTEN-knockout mice in muscle cells, pancreatic cells or adipocytes were protected for insulin resistance and T2DM, in the absence of cancer [74]. Furthermore, diminished total PTEN levels reversed hyperglycemia and insulin resistance in diabetic mice [74].

Interestingly, PTEN seems to play a role in the development of chronic complications of diabetes. Diabetes is one of the leading causes of chronic kidney disease, which is rapidly becoming public a health burden and recent studies associate PTEN dysregulations with renal fibrosis in diabetic nephropathy [76–78].

Fetuin-A

Discovered almost 75 years ago, fetuin-A is a glycoprotein synthesized by the liver. Fetuin-A is a multifunctional protein, with proven roles in normal and pathological processes, such as insulin resistance, bone metabolism, vascular calcification, etc. Recent *in vivo* studies have shown that fetuin-A also plays a role in tumor cell growth and progression [79, 80]. Furthermore, it was demonstrated that pancreatic, glioblastoma, prostate tumor cells are able to secrete an ectopic fetuin-A, with roles in tumor progression [80].

Srinivas *et al.* demonstrated that fetuin-A is an inhibitor of the IR tyrosine kinase, inhibiting by 40% the insulin-induced phosphorylation of the β-subunit of the IR [81], resulting in a decreased glucose transport, which might be a source of insulin resistance [80]. Several recent meta-analysis showed an association between higher circulating fetuin-A levels and increased risk of T2DM [82–84]. Mechanistically, direct cancer-promoting roles for fetuin-A, were demonstrated, such as enhanced exosomes production that in turn promotes cell spreading and adhesion [55]. It should be noted here that levels of serum autoantibodies against fetuin-A are proven as useful biomarker for early-stage detection of breast cancer [85].

Chronic inflammation

Obesity and T2DM are associated with chronic inflammation [86, 87], being characterized by increased production of pro-inflammatory cytokines [interleukin (IL)-6, tumor necrosis factor (TNF), IL-1]. Circulating C-reactive protein (CRP), a marker of inflammation, was studied in relationship with different types of cancer. Zhou *et al.* concluded that pre-diagnosis levels of CRP, but not IL-6 levels, are associated with an increased risk of colorectal cancer [88].

Animal studies showed that in obesity white adipose tissue presents an increased proportion of proinflammatory M1 macrophages, which leads to increased production of inflammatory cytokines and decreased adiponectin levels having as a result further adipose tissue dysfunction by increased release of free fatty acids (FFAs) [89]. The high levels of FFAs determine reactive oxygen species-induced deoxyribonucleic acid (DNA) damage, as well as upregulation of p53 tumor suppressor [89, 90], further promoting inflammation and insulin resistance, which is believed to create an appropriate microenvironment for tumor cell growth and progression [89].

Abnormal adipocytokine production

Abnormal adipocytokine production is numbered among the different hypotheses proposed to explain the association between adiposity, T2DM and cancer, as shown in Figure 2.

Adiponectin, one of the most studied adipocytokines, was also studied in cancer starting 2003 when Miyoshi *et al.* showed that its levels are decreased in breast cancer [91, 92]. Beyond its protective roles against T2DM, MetS, cardiovascular diseases, hypertension, etc., adiponectin seems to have protective effects against carcinogenesis through its anti-proliferative, anti-migration and pro-apoptotic properties, suggesting that this adipokine could be an important regulator of carcinogenesis and cancer progression [92–95]. Furthermore, studies have indicated that decreased levels of adiponectin are associated with an increased risk of cancer at different sites (colorectal, prostate, endometrium, leukemia).

Additionally, experimental studies have suggested a possible link between adiponectin and IGF-I in the tissues that express receptors for these proteins [96]. A study which analyzed the relationship between adiponectin and IGF-I in patients with obesity after weight loss showed an increase in the levels of both IGF-I and adiponectin after by-pass surgery, but their levels were not correlated [97].

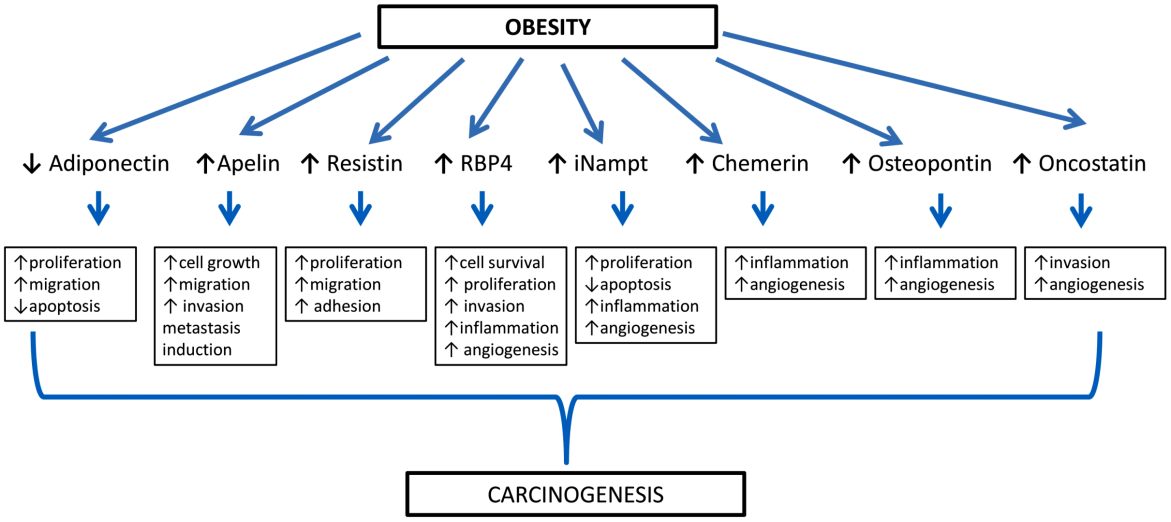

Figure 2 – ***The roles played by adipocytokines in obesity-related cancers. iNampt: Intracellular nicotinamide phosphoribosyl-transferase; RBP4: Retinol-binding protein 4.***

Recently, studies associated low adiponectin levels with concomitant dysregulations of IGF-I, with an increased risk of developing obesity-related malignancies and more aggressive phenotypes [96, 98]. Studies showed that in breast cancer there seems to be a cross-talk between adiponectin and IGF-IR [98]. It was proposed that adiponectin is capable to modulate the stimulatory effects of IGF-I in breast cancer cells in relationship with estrogen receptor alpha (ERα) status, low concentrations of adiponectin potentiating the anchorage independent growing induced by IGF-I in ERα-positive cells [93].

Many studies have focused on the role of leptin in cancers, but the results are discordant. Until now, a few meta-analyses showed higher levels of leptin in women with obesity and breast cancer, as well as an increased risk for endometrial cancer [99, 100].

Apelin, a novel adipokine, was identified and named after the orphan GPCR angiotensin II receptor-like 1 (APJ), to which acts as a ligand. The apelin/APJ system seems to be regulating many physiological processes, such as blood pressure, fluid homeostasis, cardiac contractility, energy metabolism, angiogenesis, as well as many pathological processes like obesity, diabetes, cardiovascular diseases and cancer [101]. Many types of cancer (cholangiocarcinoma, gastroesophageal, prostate, endometrium, ovarian, lung, oral) have been associated with higher levels of apelin, which was proposed as a cancer progression marker [93, 101]. Furthermore, apelin may play a role in tumor cell growth, migration, invasion and metastasis induction [93, 101].

Other novel adipokines [visfatin, chemerin, resistin, retinol-binding protein 4 (RBP4), osteopontin, oncostatin, omentin-1, etc.] were also studied in the association obesity, T2DM and malignancy.

Visfatin, also known as nicotinamide phosphoribosyltransferase (Nampt) or pre-B-cell colony enhancing factor, is a novel adipokine having insulin-mimetic effects, which studies have associated with obesity related cancers, such as colorectal, breast and endometrium cancer, its upregulation in these forms of cancer being associated with advanced stage and grade as well as worse prognosis [93, 102, 103]. This protein presents two forms, extracellular (eNampt) and intracellular (iNampt), both being associated with cancers [102, 104]. eNampt plays proliferative, anti-apoptotic, pro-inflammatory and pro-angiogenic roles, leading to the upregulation of important signaling pathways, such as MAPK, ERK-1, ERK-2, Notch-1, p38 [93, 105, 106]. Regarding iNampt, its overexpression was reported by histopathological studies in many forms of cancer including breast, endometrium, ovary, prostate, colorectal, gastric, pancreatic cancers, etc., its upregulation being associated with increased cancer grade, higher tumor stage and poor survival [102].

Described as an adipokine with higher concentrations in subjects with obesity and MetS in 2007 [107, 108], chemerin is a protein with roles in adipocyte metabolism, adipogenesis and immunity [93, 109]. Recent studies showed that chemerin may also play a role in obesity-induced cancers, increased levels of this protein being identified in patients with gastric, esophageal and colorectal cancers [93, 100, 110]. Wang *et al.* focused on the roles played by chemerin in gastric cancer and showed that this protein is present in significantly higher concentration in patients with gastric cancer, starting from stage 1, compared to healthy controls [100]. The same study proved that chemerin increases invasiveness and spread of gastric cancer cells, but not their proliferation, leading thus to the progression of gastric cancer [100]. Zhang *et al.* evaluated the prognostic significance of plasma chemerin levels in patients with gastric cancer, showing that patients with gastric cancer who had higher preoperative levels of chemerin had a poor prognostic and disease-free survival (DFS) and OS [111].

Identified as an adipokine in 2001, resistin was associated with insulin resistance and was thought as a link between obesity and T2DM [112]. Studies analyzing resistin since 2001 showed that this protein has pro-inflammatory effects, activating p38, MAPK and nuclear factor-kappa B (NF-κB), leading to an increased production of TNF-α and IL-12 [93, 113–115]. Resistin was proposed as a link between chronic inflammation, obesity, T2DM and malignancy, due to its proinflammatory, proangiogenic, antiapoptotic and proliferative effects [113]. Studies have investigated the levels of resistin in different forms of

cancer, such as breast, prostate, liver, colorectal cancers [109]. In a recent meta-analysis, Gong *et al.* observed significantly higher resistin levels in patients with obesity related cancers, suggesting that resistin is an independent biomarker, but not a predictor of obesity-related malignancy risk [114].

Osteopontin is another pro-inflammatory adipokine, which produces its effects through matrix metalloproteinase (MMP)-2 and MMP-9 activation [93]. This adipocytokine is also involved in tumorigenesis, being able to modulate the expression of genes which play a role in cell proliferation, invasion and migration, as well as angiogenesis [115]. Different types of cancers, including breast, ovarian, stomach, colorectal, lung and melanoma are associated with an overexpression of osteopontin [93, 116, 117]. A 2013 study conducted by Thorat *et al.* concluded that overexpression of osteopontin in breast cancer subtypes overexpressing human epidermal growth factor receptor 2 (HER2) may be associated with increased aggressiveness and proposed osteopontin as a prognostic and diagnostic biomarker in breast cancer [118]. Furthermore, a meta-analysis analyzing the role of osteopontin as a biomarker for cancers showed that high levels of osteopontin were associated with a poor prognosis, with decreased DFS and OS [119].

Produced mainly by the liver and with secondary site by adipocytes, RBP4 acts as a vitamin A/retinol acid carrier, whose overexpression of RBP4 from adipose tissue was associated with different forms of cancer, including breast, endometrium, liver, pancreas, colon cancers [93, 120, 121]. RBP4 exerts its oncogenic effects by binding to its receptor, signaling receptor and transporter of retinol STRA6, leading to recruitment and activation of tyrosine kinases Janus kinases (JAKs), which phosphorylate the oncogenic transcription factors STATs (signal transducers and activators of transcription) having as a final result inflammation, oncogenic transformation, cell survival, cell proliferation, invasion, as well as angiogenesis [121].

Another adipocytokine, which promotes carcinogenesis through JAK/STAT signaling, as well as MAPK signaling, is oncostatin M [93, 122]. Studies associated the production of oncostatin M from adipose tissue with breast cancer progression, the upregulation of JAK/STAT3 pathway being incriminated as the responsible mechanism [122]. A study published in 2012 has associated high oncostatin M expression with poor outcome in patients with breast cancer by downregulation of the ER [123]. Furthermore, a recent breast cancer mouse model study suggested that this protein plays a very important role in metastasis and progression of breast cancer, peritumoral injection of recombinant human oncostatin M increasing the lung metastases and the numbers of circulating tumoral cells and reducing survival [124].

Described for the first time in 2006, omentin-1, also known as intelectin-1, is an adipocytokine that enhances the effects of insulin *via* AKT signaling [125]. In pathological conditions, such as obesity, MetS, hypertension, lower levels of omentin-1 were identified, suggesting the possible use of this protein as cardiovascular risk marker [93]. Regarding the roles played by omentin-1 in oncogenesis, studies have associated omentin-1 with better outcomes in gastric and colorectal cancers [93, 125–127], which led to the belief that this protein might have a protective role against cancers.

Conclusions

Over the last decades, chronic diseases, which include cancer, diabetes, cardiovascular diseases, have become a major public health problem, as they cause premature mortality. Obesity is also an important public health issue, being responsible for several comorbidities, including cancers. As we are just begin to understand the mechanisms linking cancer, obesity and T2DM and in the context of the continuously raising their prevalence, a general prevention program addressing obesity and T2DM might also have beneficial effect on decreasing cancer prevalence and mortality. Further research is essential for a better understanding of the mechanisms linking these conditions, which will open the road for novel therapeutic strategies addressing diabetes-related and obesity-related cancers. Both classical molecular pathways involved in these associations (such as IGF system, adipokines, chronic inflammation), as well as newly described mechanisms (involving PTEN, GPCRs, β-arr signaling), are already in study and hopefully, in the near future, promising molecules targeting cancer will be developed.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018, 68(6):394–424.

[2] World Cancer Research Fund (WCRF) / American Institute for Cancer Research (AICR). Diet, nutrition, physical activity and cancer: a global perspective. Continuous Update Project (CUP) Expert Report 2018. Available online: dietandcancer report.org (accessed on 18th October 2018).

[3] Garg SK, Maurer H, Reed K, Selagamsetty R. Diabetes and cancer: two diseases with obesity as a common risk factor. Diabetes Obes Metab, 2014, 16(2):97–110.

[4] Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol, 2004, 159(12):1160–1167.

[5] World Health Organization (WHO). Obesity and overweight. Available online: http://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweigh (accessed on 18th October 2018).

[6] NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet, 2016, 387(10026):1377–1396.

[7] Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H, Eckel RH. The metabolic syndrome. Endocr Rev, 2008, 29(7):777–822.

[8] International Diabetes Federation (IDF). IDF Diabetes Atlas. 8th edition, 2018. Available online: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8th-edition.html (accessed on 12th October 2018).

[9] Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol, 2008, 28(4):629–636.

[10] Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. J Diabetes, 2010, 2(3):180–193.

[11] Pierce BL, Austin MA, Ahsan H. Association study of type 2 diabetes genetic susceptibility variants and risk of pancreatic cancer: an analysis of PanScan-I data. Cancer Causes Control, 2011, 22(6):877–883.

[12] Cheng I, Caberto CP, Lum-Jones A, Seifried A, Wilkens LR, Schumacher FR, Monroe KR, Lim U, Tiirikainen M, Kolonel LN, Henderson BE, Stram DO, Haiman CA, Le Marchand L. Type 2 diabetes risk variants and colorectal cancer risk: the Multiethnic Cohort and PAGE studies. Gut, 2011, 60(12): 1703–1711.

[13] Sainz J, Rudolph A, Hoffmeister M, Frank B, Brenner H, Chang-Claude J, Hemminki K, Försti A. Effect of type 2 diabetes predisposing genetic variants on colorectal cancer risk. J Clin Endocrinol Metab, 2012, 97(5):E845–E851.

[14] Machiela MJ, Lindström S, Allen NE, Haiman CA, Albanes D, Barricarte A, Berndt SI, Bueno-de-Mesquita HB, Chanock S, Gaziano JM, Gapstur SM, Giovannucci E, Henderson BE, Jacobs EJ, Kolonel LN, Krogh V, Ma J, Stampfer MJ, Stevens VL, Stram DO, Tjønneland A, Travis R, Willett WC, Hunter DJ, Le Marchand L, Kraft P. Association of type 2 diabetes susceptibility variants with advanced prostate cancer risk in the Breast and Prostate Cancer Cohort Consortium. Am J Epidemiol, 2012, 176(12):1121–1129.

[15] Zhao Z, Wen W, Michailidou K, Bolla MK, Wang Q, Zhang B, Long J, Shu XO, Schmidt MK, Milne RL, García-Closas M, Chang-Claude J, Lindstrom S, Bojesen SE, Ahsan H, Aittomäki K, Andrulis IL, Anton-Culver H, Arndt V, Beckmann MW, Beeghly-Fadiel A, Benitez J, Blomqvist C, Bogdanova NV, Børresen-Dale AL, Brand J, Brauch H, Brenner H, Burwinkel B, Cai Q, Casey G, Chenevix-Trench G, Couch FJ, Cox A, Cross SS, Czene K, Dörk T, Dumont M, Fasching PA, Figueroa J, Flesch-Janys D, Fletcher O, Flyger H, Fostira F, Gammon M, Giles GG, Guénel P, Haiman CA, Hamann U, Harrington P, Hartman M, Hooning MJ, Hopper JL, Jakubowska A, Jasmine F, John EM, Johnson N, Kabisch M, Khan S, Kibriya M, Knight JA, Kosma VM, Kriege M, Kristensen V, Le Marchand L, Lee E, Li J, Lindblom A, Lophatananon A, Luben R, Lubinski J, Malone KE, Mannermaa A, Manoukian S, Margolin S, Marme F, McLean C, Meijers-Heijboer H, Meindl A, Miao H, Muir K, Neuhausen SL, Nevanlinna H, Neven P, Olson JE, Perkins B, Peterlongo P, Phillips KA, Pylkäs K, Rudolph A, Santella R, Sawyer EJ, Schmutzler RK, Schoemaker M, Shah M, Shrubsole M, Southey MC, Swerdlow AJ, Toland AE, Tomlinson I, Torres D, Truong T, Ursin G, Van Der Luijt RB, Verhoef S, Wang-Gohrke S, Whittemore AS, Winqvist R, Pilar Zamora M, Zhao H, Dunning AM, Simard J, Hall P, Kraft P, Pharoah P, Hunter D, Easton DF, Zheng W. Association of genetic susceptibility variants for type 2 diabetes with breast cancer risk in women of European ancestry. Cancer Causes Control, 2016, 27(5):679–693.

[16] Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. Annu Rev Med, 2010, 61:301–316.

[17] Basen-Engquist K, Chang M. Obesity and cancer risk: recent review and evidence. Curr Oncol Rep, 2011, 13(1):71–76.

[18] Ling H, Girnita L, Buda O, Calin GA. Non-coding RNAs: the cancer genome dark matter that matters! Clin Chem Lab Med, 2017, 55(5):705–714.

[19] Kasiappan R, Rajarajan D. Role of microRNA regulation in obesity-associated breast cancer: nutritional perspectives. Adv Nutr, 2017, 8(6):868–888.

[20] De Luca P, Dalton GN, Scalise GD, Moiola CP, Porretti J, Massillo C, Kordon E, Gardner K, Zalazar F, Flumian C, Todaro L, Vazquez ES, Meiss R, De Siervi A. CtBP1 associates metabolic syndrome and breast carcinogenesis targeting multiple miRNAs. Oncotarget, 2016, 7(14):18798–18811.

[21] Gini A, Bidoli E, Zanier L, Clagnan E, Zanette G, Gobbato M, De Paoli P, Serraino D. Cancer among patients with type 2 diabetes mellitus: a population-based cohort study in north-eastern Italy. Cancer Epidemiol, 2016, 41:80–87.

[22] de Jong RGPJ, Peeters PJHL, Burden AM, de Bruin ML, Haak HR, Masclee AAM, de Vries F, Janssen-Heijnen MLG. Gastrointestinal cancer incidence in type 2 diabetes mellitus; results from a large population-based cohort study in the UK. Cancer Epidemiol, 2018, 54:104–111.

[23] Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE. Diabetes mellitus and breast cancer: a retrospective population-based cohort study. Breast Cancer Res Treat, 2006, 98(3): 349–356.

[24] Onitilo AA, Stankowski RV, Berg RL, Engel JM, Glurich I, Williams GM, Doi SA. Breast cancer incidence before and after diagnosis of type 2 diabetes mellitus in women: increased risk in the prediabetes phase. Eur J Cancer Prev, 2014, 23(2):76–83.

[25] Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter MJ, Ezzati M. Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment. Lancet Diabetes Endocrinol, 2018, 6(6):e6–e15.

[26] WCRF / AICR. Body fatness and weight gain and the risk of cancer. CUP Expert Report 2018. Available online: dietand cancerreport.org (accessed on 18th October 2018).

[27] Ulrich CM, Himbert C, Holowatyj AN, Hursting SD. Energy balance and gastrointestinal cancer: risk, interventions, outcomes and mechanisms. Nat Rev Gastroenterol Hepatol, 2018, 15(11): 683–698.

[28] Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer – viewpoint of the IARC Working Group. N Engl J Med, 2016, 375(8):794–798.

[29] Demetrian C, Demetrian A, Meunier JP, Naffaa N, Olaru M, Pleşea RM, Pleşea IE. A profile of lung carcinomas: study on 364 cases. Rom J Morphol Embryol, 2013, 54(4):1005–10017.

[30] Carreras-Torres R, Johansson M, Haycock PC, Wade KH, Relton CL, Martin RM, Davey Smith G, Albanes D, Aldrich MC, Andrew A, Arnold SM, Bickeböller H, Bojesen SE, Brunnström H, Manjer J, Brüske I, Caporaso NE, Chen C, Christiani DC, Christian WJ, Doherty JA, Duell EJ, Field JK, Davies MPA, Marcus MW, Goodman GE, Grankvist K, Haugen A, Hong YC, Kiemeney LA, van der Heijden EHFM, Kraft P, Johansson MB, Lam S, Landi MT, Lazarus P, Le Marchand L, Liu G, Melander O, Park SL, Rennert G, Risch A, Haura EB, Scelo G, Zaridze D, Mukeriya A, Savić M, Lissowska J, Swiatkowska B, Janout V, Holcatova I, Mates D, Schabath MB, Shen H, Tardon A, Teare MD, Woll P, Tsao MS, Wu X, Yuan JM, Hung RJ, Amos CI, McKay J, Brennan P. Obesity, metabolic factors and risk of different histological types of lung cancer: a Mendelian randomization study. PLoS One, 2017, 12(6):e0177875.

[31] Zhang X, Liu Y, Shao H, Zheng X. Obesity paradox in lung cancer prognosis: evolving biological insights and clinical implications. J Thorac Oncol, 2017, 12(10):1478–1488.

[32] de Beer JC, Liebenberg L. Does cancer risk increase with HbA1c, independent of diabetes? Br J Cancer, 2014, 110(9): 2361–2368.

[33] Villarreal-Garza C, Shaw-Dulin R, Lara-Medina F, Bacon L, Rivera D, Urzua L, Aguila C, Ramirez-Morales R, Santamaria J, Bargallo E, Mohar A, Herrera LA. Impact of diabetes and hyperglycemia on survival in advanced breast cancer patients. Exp Diabetes Res, 2012, 2012:732027.

[34] Zeng L, Biernacka KM, Holly JM, Jarrett C, Morrison AA, Morgan A, Winters ZE, Foulstone EJ, Shield JP, Perks CM. Hyperglycaemia confers resistance to chemotherapy on breast cancer cells: the role of fatty acid synthase. Endocr Relat Cancer, 2010, 17(2):539–551.

[35] Chang SC, Yang WV. Hyperglycemia, tumorigenesis, and chronic inflammation. Crit Rev Oncol Hematol, 2016, 108: 146–153.

[36] Kang C, LeRoith D, Gallagher EJ. Diabetes, obesity, and breast cancer. Endocrinology, 2018, 159(11):3801–3812.

[37] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science, 2009, 324(5930):1029–1033.

[38] Gallagher EJ, LeRoith D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. Physiol Rev, 2015, 95(3):727–748.

[39] Crudden C, Ilic M, Suleymanova N, Worrall C, Girnita A, Girnita L. The dichotomy of the insulin-like growth factor 1 receptor: RTK and GPCR: friend or foe for cancer treatment? Growth Horm IGF Res, 2015, 25(1):2–12.

[40] Sun Y, Sun X, Shen B. Molecular imaging of IGF-1R in cancer. Mol Imaging, 2017, 16:1536012117736648.

[41] Girnita L, Worrall C, Takahashi S, Seregard S, Girnita A. Something old, something new and something borrowed: emerging paradigm of insulin-like growth factor type 1 receptor (IGF-1R) signaling regulation. Cell Mol Life Sci, 2014, 71(13): 2403–2427.

[42] Dupont J, LeRoith D. Insulin and insulin-like growth factor I receptors: similarities and differences in signal transduction. Horm Res, 2001, 55(Suppl 2):22–26.
[43] Belfiore A, Malaguarnera R, Vella V, Lawrence MC, Sciacca L, Frasca F, Morrione A, Vigneri R. Insulin receptor isoforms in physiology and disease: an updated view. Endocr Rev, 2017, 38(5):379–431.
[44] Vella V, Milluzzo A, Scalisi NM, Vigneri P, Sciacca L. Insulin receptor isoforms in cancer. Int J Mol Sci, 2018, 19(11):3615.
[45] Whittaker J, Groth AV, Mynarcik DC, Pluzek L, Gadsbøll VL, Whittaker LJ. Alanine scanning mutagenesis of a type 1 insulin-like growth factor receptor ligand binding site. J Biol Chem, 2001, 276(47):43980–43986.
[46] Ullrich A, Gray A, Tam AW, Yang-Feng T, Tsubokawa M, Collins C, Henzel W, Le Bon T, Kathuria S, Chen E, Jacobs S, Francke U, Ramachandran J, Fujita-Yamaguchi Y. Insulin-like growth factor I receptor primary structure: comparison with insulin receptor suggests structural determinants that define functional specificity. EMBO J, 1986, 5(10):2503–2512.
[47] LeRoith D, Werner H, Beitner-Johnson D, Roberts CT Jr. Molecular and cellular aspects of the insulin-like growth factor I receptor. Endocr Rev, 1995, 16(2):143–163.
[48] Sciacca L, Prisco M, Wu A, Belfiore A, Vigneri R, Baserga R. Signaling differences from the A and B isoforms of the insulin receptor (IR) in 32D cells in the presence or absence of IR substrate-1. Endocrinology, 2003, 144(6):2650–2658.
[49] Belfiore A, Frasca F, Pandini G, Sciacca L, Vigneri R. Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. Endocr Rev, 2009, 30(6):586–623.
[50] Frasca F, Pandini G, Scalia P, Sciacca L, Mineo R, Costantino A, Goldfine ID, Belfiore A, Vigneri R. Insulin receptor isoform A, a newly recognized, high-affinity insulin-like growth factor II receptor in fetal and cancer cells. Mol Cell Biol, 1999, 19(5):3278–3288.
[51] Pandini G, Frasca F, Mineo R, Sciacca L, Vigneri R, Belfiore A. Insulin/insulin-like growth factor I hybrid receptors have different biological characteristics depending on the insulin receptor isoform involved. J Biol Chem, 2002, 277(42):39684–39695.
[52] Vigneri R, Goldfine ID, Frittitta L. Insulin, insulin receptors, and cancer. J Endocrinol Invest, 2016, 39(12):1365–1376.
[53] Poloz Y, Stambolic V. Obesity and cancer, a case for insulin signaling. Cell Death Dis, 2015, 6:e2037.
[54] Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L, Renehan AG; Diabetes and Cancer Research Consortium. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia, 2012, 55(6):1607–1618.
[55] Murphy N, Cross AJ, Abubakar M, Jenab M, Aleksandrova K, Boutron-Ruault MC, Dossus L, Racine A, Kühn T, Katzke VA, Tjønneland A, Petersen KE, Overvad K, Quirós JR, Jakszyn P, Molina-Montes E, Dorronsoro M, Huerta JM, Barricarte A, Khaw KT, Wareham N, Travis RC, Trichopoulou A, Lagiou P, Trichopoulos D, Masala G, Krogh V, Tumino R, Vineis P, Panico S, Bueno-de-Mesquita HB, Siersema PD, Peeters PH, Ohlsson B, Ericson U, Palmqvist R, Nyström H, Weiderpass E, Skeie G, Freisling H, Kong SY, Tsilidis K, Muller DC, Riboli E, Gunter MJ. A nested case-control study of metabolically defined body size phenotypes and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). PLoS Med, 2016, 13(4):e1001988.
[56] Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer, 2008, 8(12):915–928. *Erratum* in: Nat Rev Cancer, 2009, 9(3):224.
[57] Giorgino F, Belfiore A, Milazzo G, Costantino A, Maddux B, Whittaker J, Goldfine ID, Vigneri R. Overexpression of insulin receptors in fibroblast and ovary cells induces a ligand-mediated transformed phenotype. Mol Endocrinol, 1991, 5(3):452–459.
[58] Ish-Shalom D, Christoffersen CT, Vorwerk P, Sacerdoti-Sierra N, Shymko RM, Naor D, De Meyts P. Mitogenic properties of insulin and insulin analogues mediated by the insulin receptor. Diabetologia, 1997, 40(Suppl 2):S25–S31.
[59] Motallebnezhad M, Aghebati-Maleki L, Jadidi-Niaragh F, Nickho H, Samadi-Kafil H, Shamsasenjan K, Yousefi M. The insulin-like growth factor-I receptor (IGF-IR) in breast cancer: biology and treatment strategies. Tumour Biol, 2016, 37(9): 11711–11721.
[60] Xin C, Jing D, Jie T, Wu-Xia L, Meng Q, Ji-Yan L. The expression difference of insulin-like growth factor 1 receptor in breast cancers with or without diabetes. J Cancer Res Ther, 2015, 11(2):295–299.
[61] Hoque M, Ali S, Hoda M. Current status of G-protein coupled receptors as potential targets against type 2 diabetes mellitus. Int J Biol Macromol, 2018, 118(Pt B):2237–2244.
[62] Kolakowski LF Jr. GCRDb: a G-protein-coupled receptor database. Receptors Channels, 1994, 2(1):1–7.
[63] Fredriksson R, Lagerström MC, Lundin LG, Schiöth HB. The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. Mol Pharmacol, 2003, 63(6):1256–1272.
[64] Houthuijzen JM. For better or worse: FFAR1 and FFAR4 signaling in cancer and diabetes. Mol Pharmacol, 2016, 90(6):738–743.
[65] Fukushima K, Yamasaki E, Ishii S, Tomimatsu A, Takahashi K, Hirane M, Fukushima N, Honoki K, Tsujiuchi T. Different roles of GPR120 and GPR40 in the acquisition of malignant properties in pancreatic cancer cells. Biochem Biophys Res Commun, 2015, 465(3):512–515.
[66] Ishii S, Hirane M, Kato S, Fukushima N, Tsujiuchi T. Opposite effects of GPR120 and GPR40 on cell motile activity induced by ethionine in liver epithelial cells. Biochem Biophys Res Commun, 2015, 456(1):135–138.
[67] Wu Q, Wang H, Zhao X, Shi Y, Jin M, Wan B, Xu H, Cheng Y, Ge H, Zhang Y. Identification of G-protein-coupled receptor 120 as a tumor-promoting receptor that induces angiogenesis and migration in human colorectal carcinoma. Oncogene, 2013, 32(49):5541–5550.
[68] Pang Y, Zhu H, Xu J, Yang L, Liu L, Li J. *β*-Arrestin-2 is involved in irisin induced glucose metabolism in type 2 diabetes *via* p38 MAPK signaling. Exp Cell Res, 2017, 360(2):199–204.
[69] Suleymanova N, Crudden C, Shibano T, Worrall C, Oprea I, Tica A, Calin GA, Girnita A, Girnita L. Functional antagonism of *β*-arrestin isoforms balance IGF-1R expression and signalling with distinct cancer-related biological outcomes. Oncogene, 2017, 36(41):5734–5744.
[70] Jing X, Zhang H, Hu J, Su P, Zhang W, Jia M, Cheng H, Li W, Zhou G. *β*-Arrestin 2 is associated with multidrug resistance in breast cancer cells through regulating *MDR1* gene expression. Int J Clin Exp Pathol, 2015, 8(2):1354–1363.
[71] Chen CY, Chen J, He L, Stiles BL. PTEN: tumor suppressor and metabolic regulator. Front Endocrinol (Lausanne), 2018, 9:338.
[72] Ortega-Molina A, Serrano M. PTEN in cancer, metabolism, and aging. Trends Endocrinol Metab, 2013, 24(4):184–189.
[73] Hollander MC, Blumenthal GM, Dennis PA. PTEN loss in the continuum of common cancers, rare syndromes and mouse models. Nat Rev Cancer, 2011, 11(4):289–301. *Erratum* in: Nat Rev Cancer, 2011, 11(6):458.
[74] Pulido R. PTEN inhibition in human disease therapy. Molecules, 2018, 23(2):285.
[75] Manning BD, Toker A. AKT/PKB signaling: navigating the network. Cell, 2017, 169(3):381–405.
[76] Zhang Y, Zhao S, Wu D, Liu X, Shi M, Wang Y, Zhang F, Ding J, Xiao Y, Guo B. MicroRNA-22 promotes renal tubulo-interstitial fibrosis by targeting PTEN and suppressing autophagy in diabetic nephropathy. J Diabetes Res, 2018, 2018: 4728645.
[77] Zhu L, Zhao S, Liu S, Liu Q, Li F, Hao J. PTEN regulates renal extracellular matrix deposit *via* increased CTGF in diabetes mellitus. J Cell Biochem, 2016, 117(5):1187–1198.
[78] McClelland AD, Herman-Edelstein M, Komers R, Jha JC, Winbanks CE, Hagiwara S, Gregorevic P, Kantharidis P, Cooper ME. miR-21 promotes renal fibrosis in diabetic nephropathy by targeting *PTEN* and *SMAD7*. Clin Sci (Lond), 2015, 129(12):1237–1249.
[79] Robinson KN, Teran-Garcia M. From infancy to aging: biological and behavioral modifiers of fetuin-A. Biochimie, 2016, 124:141–149.
[80] Ochieng J, Nangami G, Sakwe A, Moye C, Alvarez J, Whalen D, Thomas P, Lammers P. Impact of fetuin-A (AHSG) on tumor progression and type 2 diabetes. Int J Mol Sci, 2018, 19(8): 2211.
[81] Srinivas PR, Wagner AS, Reddy LV, Deutsch DD, Leon MA, Goustin AS, Grunberger G. Serum alpha 2-HS-glycoprotein

is an inhibitor of the human insulin receptor at the tyrosine kinase level. Mol Endocrinol, 1993, 7(11):1445–1455.
[82] Guo VY, Cao B, Cai C, Cheng KK, Cheung BMY. Fetuin-A levels and risk of type 2 diabetes mellitus: a systematic review and meta-analysis. Acta Diabetol, 2018, 55(1):87–98.
[83] Roshanzamir F, Miraghajani M, Rouhani MH, Mansourian M, Ghiasvand R, Safavi SM. The association between circulating fetuin-A levels and type 2 diabetes mellitus risk: systematic review and meta-analysis of observational studies. J Endocrinol Invest, 2018, 41(1):33–47.
[84] Sujana C, Huth C, Zierer A, Meesters S, Sudduth-Klinger J, Koenig W, Herder C, Peters A, Thorand B. Association of fetuin-A with incident type 2 diabetes: results from the MONICA/KORA Augsburg study and a systematic meta-analysis. Eur J Endocrinol, 2018, 178(4):389–398.
[85] Fernández-Grijalva AL, Aguilar-Lemarroy A, Jave-Suarez LF, Gutiérrez-Ortega A, Godinez-Melgoza PA, Herrera-Rodríguez SE, Mariscal-Ramírez I, Martínez-Velázquez M, Gawinowicz MA, Martínez-Silva MG, Cruz-Ramos JA, Hernández-Gutiérrez R. Alpha 2HS-glycoprotein, a tumor-associated antigen (TAA) detected in Mexican patients with early-stage breast cancer. J Proteomics, 2015, 112:301–312.
[86] Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract, 2014, 105(2): 141–150.
[87] Lucchesi D, Popa SG, Sancho V, Giusti L, Garofolo M, Daniele G, Pucci L, Miccoli R, Penno G, Del Prato S. Influence of high density lipoprotein cholesterol levels on circulating monocytic angiogenic cells functions in individuals with type 2 diabetes mellitus. Cardiovasc Diabetol, 2018, 17(1):78.
[88] Zhou B, Shu B, Yang J, Liu J, Xi T, Xing Y. C-reactive protein, interleukin-6 and the risk of colorectal cancer: a meta-analysis. Cancer Causes Control, 2014, 25(10):1397–1405.
[89] Zwezdaryk K, Sullivan D, Saifudeen Z. The p53/adipose-tissue/cancer nexus. Front Endocrinol (Lausanne), 2018, 9:457.
[90] Shimizu I, Yoshida Y, Katsuno T, Tateno K, Okada S, Moriya J, Yokoyama M, Nojima A, Ito T, Zechner R, Komuro I, Kobayashi Y, Minamino T. p53-induced adipose tissue inflammation is critically involved in the development of insulin resistance in heart failure. Cell Metab, 2012, 15(1):51–64.
[91] Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, Matsuzawa Y, Noguchi S. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res, 2003, 9(15): 5699–5704.
[92] Wei T, Ye P, Peng X, Wu LL, Yu GY. Circulating adiponectin levels in various malignancies: an updated meta-analysis of 107 studies. Oncotarget, 2016, 7(30):48671–48691.
[93] Spyrou N, Avgerinos KI, Mantzoros CS, Dalamaga M. Classic and novel adipocytokines at the intersection of obesity and cancer: diagnostic and therapeutic strategies. Curr Obes Rep, 2018, 7(4):260–275.
[94] Boutari C, Mantzoros CS. Inflammation: a key player linking obesity with malignancies. Metabolism, 2018, 81:A3–A6.
[95] Dinu IR, Popa SG, Moţa M, Moţa E, Stănciulescu C, Ioana M, Cruce M. The association of the *rs1049353* polymorphism of the *CNR1* gene with hypoadiponectinemia. Rom J Morphol Embryol, 2011, 52(3):791–795.
[96] Orrù S, Nigro E, Mandola A, Alfieri A, Buono P, Daniele A, Mancini A, Imperlini E. A functional interplay between IGF-1 and adiponectin. Int J Mol Sci, 2017, 18(10):2145.
[97] Pardina E, Ferrer R, Baena-Fustegueras JA, Lecube A, Fort JM, Vargas V, Catalán R, Peinado-Onsurbe J. The relationships between IGF-1 and CRP, NO, leptin, and adiponectin during weight loss in the morbidly obese. Obes Surg, 2010, 20(5): 623–632.
[98] Mauro L, Naimo GD, Ricchio E, Panno ML, Andò S. Cross-talk between adiponectin and IGF-IR in breast cancer. Front Oncol, 2015, 5:157.
[99] Pan H, Deng LL, Cui JQ, Shi L, Yang YC, Luo JH, Qin D, Wang L. Association between serum leptin levels and breast cancer risk: an updated systematic review and meta-analysis. Medicine (Baltimore), 2018, 97(27):e11345.
[100] Wang C, Wu WK, Liu X, To KF, Chen GG, Yu J, Ng EK. Increased serum chemerin level promotes cellular invasiveness in gastric cancer: a clinical and experimental study. Peptides, 2014, 51:131–138.
[101] Wysocka MB, Pietraszek-Gremplewicz K, Nowak D. The role of apelin in cardiovascular diseases, obesity and cancer. Front Physiol, 2018, 9:557.
[102] Dalamaga M, Christodoulatos GS, Mantzoros CS. The role of extracellular and intracellular nicotinamide phosphoribosyl-transferase in cancer: diagnostic and therapeutic perspectives and challenges. Metabolism, 2018, 82:72–87.
[103] Wang Y, Gao C, Zhang Y, Gao J, Teng F, Tian W, Yang W, Yan Y, Xue F. Visfatin stimulates endometrial cancer cell proliferation *via* activation of PI3K/Akt and MAPK/ERK1/2 signalling pathways. Gynecol Oncol, 2016, 143(1):168–178.
[104] Grolla AA, Travelli C, Genazzani AA, Sethi JK. Extracellular nicotinamide phosphoribosyltransferase, a new cancer metabokine. Br J Pharmacol, 2016, 173(14):2182–2194.
[105] Gallí M, Van Gool F, Rongvaux A, Andris F, Leo O. The nicotinamide phosphoribosyltransferase: a molecular link between metabolism, inflammation, and cancer. Cancer Res, 2010, 70(1):8–11.
[106] Park HJ, Kim SR, Kim SS, Wee HJ, Bae MK, Ryu MH, Bae SK. Visfatin promotes cell and tumor growth by upregulating Notch1 in breast cancer. Oncotarget, 2014, 5(13):5087–5099.
[107] Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, Muruganandan S, Sinal CJ. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem, 2007, 282(38):28175–28188.
[108] Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, Walder K, Segal D. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology, 2007, 148(10):4687–4694.
[109] Booth A, Magnuson A, Fouts J, Foster M. Adipose tissue, obesity and adipokines: role in cancer promotion. Horm Mol Biol Clin Investig, 2015, 21(1):57–74.
[110] Erdogan S, Yilmaz FM, Yazici O, Yozgat A, Sezer S, Ozdemir N, Uysal S, Purnak T, Sendur MA, Ozaslan E. Inflammation and chemerin in colorectal cancer. Tumour Biol, 2016, 37(5):6337–6342.
[111] Zhang J, Jin HC, Zhu AK, Ying RC, Wei W, Zhang FJ. Prognostic significance of plasma chemerin levels in patients with gastric cancer. Peptides, 2014, 61:7–11.
[112] Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. Nature, 2001, 409(6818): 307–312.
[113] Dalamaga M. Resistin as a biomarker linking obesity and inflammation to cancer: potential clinical perspectives. Biomark Med, 2014, 8(1):107–118.
[114] Gong WJ, Zheng W, Xiao L, Tan LM, Song J, Li XP, Xiao D, Cui JJ, Li X, Zhou HH, Yin JY, Liu ZQ. Circulating resistin levels and obesity-related cancer risk: a meta-analysis. Oncotarget, 2016, 7(36):57694–57704.
[115] Buzas R, Rogobete AF, Popovici SE, Mateescu T, Hoinoiu T, Sorop VB, Bratu T, Ticlea M, Popoiu CM, Sandesc D. Nuclear transcription factor kappa B (NF-*κ*B) and molecular damage mechanisms in acute cardiovascular diseases. A review. J Cardiovasc Emerg, 2018, 4(2):65–72.
[116] Bandopadhyay M, Bulbule A, Butti R, Chakraborty G, Ghorpade P, Ghosh P, Gorain M, Kale S, Kumar D, Kumar S, Totakura KV, Roy G, Sharma P, Shetti D, Soundararajan G, Thorat D, Tomar D, Nalukurthi R, Raja R, Mishra R, Yadav AS, Kundu GC. Osteopontin as a therapeutic target for cancer. Expert Opin Ther Targets, 2014, 18(8):883–895.
[117] Rangaswami H, Bulbule A, Kundu GC. Osteopontin: role in cell signaling and cancer progression. Trends Cell Biol, 2006, 16(2):79–87.
[118] Thorat D, Sahu A, Behera R, Lohite K, Deshmukh S, Mane A, Karnik S, Doke S, Kundu GC. Association of osteopontin and cyclooxygenase-2 expression with breast cancer subtypes and their use as potential biomarkers. Oncol Lett, 2013, 6(6):1559–1564.
[119] Weber GF, Lett GS, Haubein NC. Osteopontin is a marker for cancer aggressiveness and patient survival. Br J Cancer, 2010, 103(6):861–869.
[120] Wang Y, Wang Y, Zhang Z. Adipokine RBP4 drives ovarian cancer cell migration. J Ovarian Res, 2018, 11(1):29.

[121] Noy N, Li L, Abola MV, Berger NA. Is retinol binding protein 4 a link between adiposity and cancer? Horm Mol Biol Clin Investig, 2015, 23(2):39–46.
[122] Lapeire L, Hendrix A, Lambein K, Van Bockstal M, Braems G, Van Den Broecke R, Limame R, Mestdagh P, Vandesompele J, Vanhove C, Maynard D, Lehuédé C, Muller C, Valet P, Gespach CP, Bracke M, Cocquyt V, Denys H, De Wever O. Cancer-associated adipose tissue promotes breast cancer progression by paracrine oncostatin M and Jak/STAT3 signaling. Cancer Res, 2014, 74(23):6806–6819.
[123] West NR, Murphy LC, Watson PH. Oncostatin M suppresses oestrogen receptor-*α* expression and is associated with poor outcome in human breast cancer. Endocr Relat Cancer, 2012, 19(2):181–195.
[124] Tawara K, Bolin C, Koncinsky J, Kadaba S, Covert H, Sutherland C, Bond L, Kronz J, Garbow JR, Jorcyk CL. OSM potentiates preintravasation events, increases CTC counts, and promotes breast cancer metastasis to the lung. Breast Cancer Res, 2018, 20(1):53.
[125] Yang RZ, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC, Shuldiner AR, Fried SK, McLenithan JC, Gong DW. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. Am J Physiol Endocrinol Metab, 2006, 290(6): E1253–E1261.
[126] Pleşea IE, Chiuţu L, Bordu SI, Georgescu I, Georgescu EF, Ciobanu D, Mărgăritescu ND, Comănescu V, Nemeş R. Gastrointestinal stromal tumors – a clinical-morphological study on 15 cases. Rom J Morphol Embryol, 2014, 55(2 Suppl): 513–523.
[127] Kawashima K, Maeda K, Saigo C, Kito Y, Yoshida K, Takeuchi T. Adiponectin and intelectin-1: important adipokine players in obesity-related colorectal carcinogenesis. Int J Mol Sci, 2017, 18(4):866.

Corresponding author
Simona Georgiana Popa, Associate Professor, MD, PhD, Department of Diabetes, Nutrition and Metabolic Diseases, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40727–713 051, e-mail: geossim@yahoo.com

Received: May 13, 2019

Accepted: February 27, 2020