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OBESITY AND CANCER

Summary: Obesity and malignancies ie. cancer are two multifactorial diseases with progressively increasing epidemic prevalence over the last few decades. Cancer is expected to possibly overcome cardiovascular disease as the leading cause of death in the future, with prevalence increasing by nearly 50% over the next 15 years. Numerous experimental and epidemiological studies have established a close relationship between these two diseases, but the true nature of this relationship has remained insufficiently elucidated. It is known that obesity is the main risk factor for the occurrence of several types of cancer, and that it is associated with a worse therapeutic outcome and increased mortality in malignant diseases. Observational studies have shown that weight reduction in humans as well as caloric restriction in experimental animals reduces the promoting effect of obesity on the onset and development of several types of cancer, primarily breast and prostate cancer. Numerous data show that the metabolic milieu, which exists in obese people, is ideal for the emergence and development of cancer. Obesity is characterized by insulin resistance, aberrant glucose metabolism, chronic inflammation, and increased production of other metabolic hormones such as: IGF-1, leptin, and adiponectin, which together can participate in the modulation of cancer risk. Regardless of the fact that some parts of the connection between obesity and cancer have been partially clarified, it remains for future investigations to enable the assembly of the entire mosaic of oncogenesis in obesity.

Key words: obesity, cancer, insulin receptor

Obesity and malignancy ie. cancer are two multifactorial diseases whose prevalence has progressively increased in recent decades to pandemic proportions. Numerous epidemiological studies have established a close connection between both diseases, but the true nature of this connection remains insufficiently clarified (1,2). It is known that obesity is a major risk factor for several types of cancer, that it is associated with a worse therapeutic outcome and increased mortality in malignant diseases, and has become a “surrogate” for other cancer risk factors such as a high-calorie diet rich primarily in fats. , insufficient physical activity, low intake of fibrous food, and

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chronic subclinical inflammatory condition (2,3). Approximately 14% of all cancer deaths in men and 20% in women are attributable to overweight and obesity (1,4,5).

The link between overweight/obesity and cancer is not always tight and straight. For example, the presence of obesity before menopause reduces the risk of premenopausal breast cancer, and the presence of obesity in the period of life between 18-30 years, reduces the risk of pre- and postmenopausal breast cancer (6). Furthermore, there is more and more evidence that the state of excessive nutrition can increase the overall survival after surgical and neoadjuvant treatment in esophageal cancer, after immunotherapy in kidney cancer, but also in colon cancer. This paradox is therefore called the paradox of obesity and precisely indicates that the connection between obesity and cancer is much more complex and far exceeds the application of only the body mass index in assessing the degree of obesity, and requires the inclusion of a person's age, inflammatory status, hormonal profile, but also the quality and distribution of fat tissues (6).

Numerous epidemiological studies have shown that obesity as well as diabetes are important risk factors for various malignancies and that insulin resistance with hyperinsulinemia could be the main factor, i.e. the mechanism underlying the effect of obesity on increased cancer risk (7). Therefore, the insulin-IGF (insulin-like growth factor) hypothesis (7,8) emerged as the central molecular mechanism. Insulin resistance is normally limited to the metabolic effects of insulin, ie the metabolic part of the signaling pathway, while the mitogenic part of the insulin signaling pathway is preserved, even enhanced, which results in insulin stimulation of the growth and proliferation of cancer cells. The mechanism leading to selective resistance of the metabolic arm of the insulin signaling pathway remains insufficiently elucidated, and could involve the action of non-esterified fatty acids and inflammatory cytokines. Thus, insulin resistance leads to disruption of glucose homeostasis in insulin target tissues, while stimulating cell proliferation in other tissues (8).

Insulin and insulin-like growth factors (IGFs) are sister molecules with a high degree of homology, which share a common ancestor, and have diverged during evolution with their receptors to fulfill different metabolic or trophic functions. They form a very flexible and complex signaling network of molecules, because in certain circumstances the insulin receptor can transmit the mitogenic signal characteristic of IGF, and the receptor for IGF can transmit the metabolic signal. When a cell undergoes malignant transformation, it regains signaling capacities that are characteristic only of cells in the early stages of development ie. embryogenesis (9,10). This implies the expression of a variant of the insulin receptor known as the A form of the receptor, which is abundantly expressed in fetal but also cancer tissues, and which is sensitive to both IGF and insulin (8,11) . Cancer cells, in addition to excessive expression of insulin receptors and IGF receptors, also express hybrid receptors created by recombining receptor proteins (half of the receptors have the structure of receptors for IGF

and the other half for insulin) (8). Therefore, tumor cells acquire aberrant signaling capacities and thus, through the action of insulin and IGF through all these receptors, they stimulate and accelerate their own growth, proliferation, and acquire resistance to programmed death, i.e. apoptosis.

One of the mechanisms by which the body protects itself from cancer is to force (induce) the initial cancer cells to commit suicide, using different mechanisms (12,13). One of those mechanisms is apoptosis, and insulin and IGF-1 block apoptosis, i.e. they protect the tumor cell from apoptosis. Inflammation is an additional mechanism linking obesity and cancer (14), as adipocytes produce and release a wide range of cytokines (adipokines) including: IL-6 (interleukin 6), TNF-alpha (tumor necrosis factor alpha), PAI-1 (activator inhibitor plasminogen 1), and leptin. All of them can affect the survival and growth of cancer cells.

The central and most important thing for a physician-clinician is the care of a patient with obesity, in whom the prescribed therapy could possibly modify, ie increase, the risk of cancer (3). For example, in an obese person with diabetes, insulin-based therapy might promote cancer, and metformin administration might provide some protection. However, in the light of current evidence and acquired knowledge, cancer risk should not be the main factor in the choice of modality for the treatment of obesity comorbidities, including diabetes in the average patient. But this question could be asked in a patient with a high risk for the occurrence or recurrence of multiple cancers.

CANCER ENERGY METABOLISM

Various data show that cancers “love” the metabolic milieu that exists in obese people, i.e. an environment very similar to the tumor microenvironment, which is very complex, and which, in addition to the cancer cells themselves, also contains a whole repertoire of recruited apparently “normal” cells, which also participate in the creation . conditions for the progressive process of sequential acquisition of biological properties of malignant cells (15).

Therefore, in order for cancer cells to grow and multiply uncontrollably, it is necessary that they first provide themselves with enough energy through metabolic reprogramming, so energy metabolism is key factor. Because cancer metabolism has long been considered primitive and inefficient, and has been equated with aerobic glycolysis, ie the so-called Warburg effect. In normal cells, glucose is converted to pyruvate and then further burned in the presence of oxygen in the mitochondria, producing approximately 36 moles of ATP (adenosine triphosphate) per mole of glucose. Cancer cells dramatically change the metabolism in oncogenesis in the direction of extremely inefficient conversion of pyruvate to lactate in the cytoplasm of cancer cells, as bacteria do in anaerobic conditions, although cancer cells also do it in the presence of oxygen, which is why this mechanism is called aerobic glycolysis

(15,16 ,). In this case, 1 mole of glucose does not produce 36 moles of ATP as in normal cells, but only 4 moles of ATP. And how do malignant cells compensate for this deficit in generating ATP? By enormously increasing the entry or "inflow" of glucose into the cancer cell. So there must be an endocrine milieu that provides cancer cells. This is how we reach the first bridge that clearly connects cancer and obesity, which is the insulin-IGF system, ie the insulin-cancer hypothesis (15). It has been known for about 50 years that insulin acts as a promoter of growth and proliferation of both healthy and malignant tissues. There is a particularly aggressive breast cancer cell line, which is extremely sensitive to insulin, and then the breast cancer cells express insulin receptors even though the normal breast cells from which these tumors arise do not possess them. There are numerous cancers that are characterized by a huge expression of insulin receptors, such as prostate, colon and breast cancers.

And these receptors are apparently there for a reason, namely to ensure a significantly higher uptake of glucose through increased activity of the insulin signaling pathway. Now, by activating their own insulin receptors, tumor cells increase glucose metabolism 10-20 times, which results in increased generation of reactive oxygen radicals that can induce mutations in the genome (15). This creates a "vicious circle" in which the faster burning of glucose leads to the creation of a larger amount of free radicals that can damage the genome. And this results in maximum acceleration, ie cancer progression. And what is the role of IGF-1 in the whole story? Most obese individuals have increased plasma concentrations of not only insulin but also IGF (insulin-like growth factors). IGF can bind and activate not only insulin receptors, but also chimeric receptors with the same cascade of effects on glucose metabolism.

The key question is why cancer cells introduce an inefficient way of energy production presented as Wartburg's aerobic glycolysis? What do they get? Why don't they just keep the oxidative phosphorylation? It is believed that this is because aerobic glycolysis preserves the carbon nucleus of glucose, which is redirected towards the accumulation of fatty acids, i.e. triglycerides, which the cancer cell needs to make new cell membranes of daughter cells, but also to make new DNA and protein molecules during the cancer replication process. . Thus, malignant cells take over an inefficient way of energy production because they provide the building material for obtaining new cancer cells. And this exchange can increase because the deficit in energy production is compensated with an enormous increase in uptake ("inflow") of glucose by tumor cells (15,16,17).

How can this hypothesis be applied to cancers that do not express insulin receptors? Here, the transduction of the insulin signal does not start from the membrane receptor on the membranes of cancer cells, but is a consequence of certain mutations in the insulin signaling pathway itself. First of all PI-3K (phosphatidyl-inositol-3 kinase) mutation or mutations that lead to constitutive activation of this signaling

pathway lead to the fact that the cancer cell no longer depends on insulin in its microenvironment because it becomes unnecessary. Thus, insulin signaling is constitutively switched on even in the absence of insulin. The PI-3K signaling pathway is where certain growth factor signaling pathways meet the insulin pathway, and an important tumor-suppressor gene called PTEN (phosphatase and tensin homolog) also acts at the PI-3K level (16). This gene is most often deleted in a large number of different advanced human cancers. If there are no mutations that enhance the activity of the PI-3K signaling pathway, then the cancer will be dependent on circulating insulin and IGF. If there is a PI3K mutation then the cancer cell is not interested in the insulin milieu around the tumor cells.

CONCLUSION

Malignant diseases are among the main complications of obesity and type 2 diabetes (18). Screening for malignancy should be part of the clinical examination of obese patients. It is certainly necessary to define the types of cancer that should be screened.

The longer the duration of overweight and obesity, the higher the risk of various types of cancer. And the degree of obesity in adulthood seems to play an important role in the risk of cancer. Reducing the duration of obesity in adulthood appears to reduce cancer risk (19,20). Hence, prevention of obesity should be carried out as early as possible.

Both obesity and type 2 diabetes are characterized by the existence of a state of insulin resistance. Insulin resistance is considered to be a risk factor for numerous cancers (12,13). The putative insulin-cancer hypothesis is based on the view that hyperinsulinemia and increased levels of IGF-1, adipokines and other growth factors in insulin resistance increase the risk of oncogenesis. It is unlikely that insulin resistance plays an important role in the initiation of cancer, ie in the early stages of cancer, because the induction of cancer cells is a very complicated process. Although pieces of the obesity-cancer link are emerging, many pieces of this large puzzle still remain unsolved, and it is up to future investigations to enable the assembly of the entire mosaic of oncogenesis in obesity.

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