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GOJAZNOST I KANCER

Sažetak: Gojaznost i maligniteti, tj. kancer, predstavljaju dva multifaktorijalna oboljenja sa progresivno rastućom epidemijskom prevalencijom poslednjih nekoliko decenija. Očekuje se da će kancer, moguće, prevazići kardiovaskularne bolesti kao vodeći uzrok smrti u budućnosti, sa povećanjem prevalence za skoro 50% sledećih 15 godina. Brojne eksperimentalne i epidemiološke studije su ustanovile blisku vezu ove dve bolesti, ali je prava priroda ove veze ostala i dalje nedovoljno razjašnjena. Poznato je da je gojaznost glavni faktor rizika za nastanak nekoliko tipova kancera i da je udružena sa lošijim terapijskim ishodom i povećanim mortalitetom u malignim bolestima.

Opservacione studije su pokazale da smanjivanje težine kod ljudi, kao i kalorijska restrikcija kod eksperimentalnih životinja, smanjuje promovišući uticaj gojaznosti na nastanak i razvoj nekoliko tipova kancera, pre svega kancera dojke i prostate.

Brojni podaci pokazuju da je metabolički milje, koji postoji kod gojaznih osoba, idealan za nastanak i razvoj kancera. Gojaznost karakterišu insulinska rezistencija, aberantni metabolizam glikoze, hronična inflamacija i povećana produkcija ostalih metaboličkih hormona kao što su: IGF-1, leptin i adiponektin, što sve zajedno može učestvovati u modulaciji kancerskog rizika.

Bez obzira što su delimično razjašnjeni neki delovi veze gojaznosti i kancera, ostaje na budućim ispitivanjima da omoguće sklapanje celokupnog mozaika onkogeneze u gojaznosti.

Ključne reči: gojaznost, kancer, insulinski receptor

Gojaznost i malignitet, tj. kancer, predstavljaju dva multifaktorska oboljenja, čija je prevalencija progresivno rasla poslednjih decenija do pandemijskih razmera. Brojne epidemiološke studije su ustanovile blisku povezanost obe dve bolesti, ali je prava priroda ove veze ostala nedovoljno razjašnjena (1, 2). Poznato je da je gojaznost glavni faktor rizika za nastanak nekoliko tipova kancera, da je udružena sa lošijim terapijskim ishodom i povećanim mortalitetom u malignim bolestima, i postala je „surogat“ za druge kancerske faktore rizika kao što su: visokokalorijska ishrana bogata prevashodno mastima, nedovoljna fizička aktivnost, mali unos vlaknaste hrane

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i hronično supkliničko inflamatorno stanje (2, 3). Otprilike oko 14% svih smrti od malignih bolesti kod muškaraca i 20% kod žena pripisuje se prekomernoj telesnoj težini i gojaznosti (1, 4, 5).

Veza između prekomerne težine/gojaznosti i kancera nije uvek čvrsta i pravolinijska. Na primer, postojanje gojaznosti pre menopauze smanjuje rizik od premenopauznog kancera dojke, i postojanje gojaznosti u periodu života između 18–30 godine smanjuje rizik od pre- i postmenopauznog kancera dojke (6). Dalje, sve je više dokaza da stanje prekomerne uhranjenosti može da poveća ukupno preživljavanje posle hirurškog i neoadjuvantnog lečenja kod karcinoma jednjaka, posle imunoterapije kod kancera bubrega, ali i kod kancera kolona. Ovaj paradoks je zato nazvan paradoks gojaznosti i upravo ukazuje da je veza gojaznosti i kancera mnogo kompleksnija i daleko prevazilazi primenu samo indeksa telesne mase u proceni stepena gojaznosti, i zahteva uključivanje i starosti osobe, inflamatornog statusa, hormonskog profila, ali i kvaliteta i distribucije masnog tkiva (6).

Brojne epidemiološke studije su pokazale da su gojaznost, kao i šećerna bolest bitni faktori rizika za različite malignitete i da bi insulinska rezistencija sa hiperinsulinemijom mogla da bude glavni činilac, tj. mehanizam u osnovi uticaja gojaznosti na povećani kancerski rizik (7). Stoga se insulinska-IGF (insulinima slični faktori rasta) hipoteza (7, 8) izdvojila kao centralni molekularni mehanizam. Insulinska rezistencija je normalno ograničena na metabolička dejstva insulina, tj. metabolički deo signalnog puta, dok je mitogeni deo insulinskog signalnog puta očuvan, čak i pojačan, što za posledicu ima insulinsku stimulaciju rasta i proliferacije kancerskih ćelija. Mehanizam koji dovodi do selektivne rezistencije metaboličkog kraka insulinskog signalnog puta ostaje nedovoljno razjašnjen, a mogao bi da uključuje dejstvo neesterifikovanih masnih kiselina i inflamatornih citokina. Dakle, insulinska rezistencija dovodi do poremećaja glikozne homeostaze u insulinskim ciljnim tkivima, dok stimuliše ćelijsku proliferaciju u drugim tkivima (8).

Insulin i faktori rasta slični insulinu (IGF) su sestrinski molekuli sa visokim stepenom homologije, koji imaju zajedničkog pretka, a odvojili su se tokom evolucije sa svojim receptorima da bi zadovoljili različite metaboličke ili trofičke funkcije. Oni čine veoma fleksibilnu i kompleksnu signalnu mrežu molekula, jer u određenim okolnostima insulinski receptor može da prenosi mitogeni signal svojstven IGF, a receptor za IGF da prenosi metabolički signal. Kada ćelija podleže malignoj transformaciji, ona ponovo stiče signalne kapacitete koji su svojstveni samo ćelijama u ranim stadijumima razvoja, tj. embriogeneze (9, 10). To podrazumeva ekspresiju varijante insulinskog receptora, koja je poznata kao A forma receptora, koja je obilno eksprimirana u fetalnim, ali i kancerskim tkivima, a koja je osetljiva i na IGF i insulin (8, 11). Kancerske ćelije, pored preterane ekspresije insulinskih receptora i receptora za IGF, takođe eksprimiraju i hibridne receptore nastale rekombinovanjem receptornih proteina (pola receptora ima strukturu receptora za IGF, a druga polovina za insulin) (8). Dakle, tumorske ćelije stiču aberantne signalne kapacitete i tako,

dejstvom insulina i IGF preko svih ovih receptora, podstiču i ubrzavaju sopstveni rast, proliferaciju i stiču rezistenciju na programiranu smrt, tj. apoptozu. Jedan od mehanizama kojima se telo štiti od kancera je da se početne kancerske ćelije nateraju (indukuju) da izvrše samoubistvo, i to različitim mehanizmima (12, 13). Jedan od tih mehanizama je apoptoza, a insulin i IGF-1 blokiraju apoptozu, tj. štite tumorsku ćeliju od apoptoze.

Inflamacija je dodatni mehanizam koji povezuje gojaznost i kancer (14), jer adipociti proizvode i oslobađaju širok spektar citona (adipokina), uključujući: IL-6 (interleukin 6), TNF-alfa (alfa faktor tumorske nekroze), PAI-1 (inhibitor aktivatora plazminogena 1) i leptin. Svi oni mogu uticati na preživljavanje i rast kancerskih ćelija.

Centralna i najvažnija stvar za lekara-kliničara je briga za pacijenta sa gojaznošću, kod koga bi propisana terapija moguće mogla da modifikuje, tj. poveća rizik od nastanka kancera (3). Na primer, kod gojazne osobe sa šećernom bolešću terapija zasnovana na insulinima mogla bi da promoviše kancer, a primena metformina bi mogla da pruži neku protekciju. No, u svetlu trenutnih dokaza i stečenog znanja svakako da kancerski rizik ne treba da bude glavni činilac u izboru modaliteta lečenja komorbiditeta gojaznosti, uključujući i šećernu bolest kod prosečnog pacijenta . Ali bi se ovo pitanje moglo postaviti kod pacijenta sa visokim rizikom za pojavu ili recidiviranje brojnih kancera.

KANCERSKI ENERGETSKI METABOLIZAM

Različiti podaci pokazuju da kanceri „vole“ metabolički milje koji postoji kod gojaznih osoba, dakle, sredinu veoma sličnu tumorskoj mikrosredini koja je veoma kompleksna i koja, pored samih kancerskih ćelija, sadrži i čitav repertoar regrutovanih prividno „normalnih“ ćelija, a koje takođe učestvuju u stvaranju uslova za progresivni proces sekvencijalnog sticanja bioloških svojstava malignih ćelija (15).

Dakle, da bi kancerske ćelije mogle nekontrolisano da rastu i umnožavaju se neophodno je da prvo sebi obezbede dovoljno energije putem metaboličkog reprogramiranja, dakle, ključan je energetski metabolizam. Jer kancerski metabolizam je dugo smatran primitivnim i neefikasnim, i izjednačavan je sa aerobnom glikolizom, tj. tzv. Varburgovim efektom. Kod normalnih ćelija glikoza se pretvara u piruvat i potom dalje sagoreva u prisustvu kiseonika u mitohondrijama, pri čemu nastaje približno 36 mol ATP (adenozin-trifosfat) po molu glikoze. Kancerske ćelije dramatično menjaju metabolizam u onkogenezi u pravcu krajnje neefikasnog konvertovanja piruvata u laktat u citoplazmi kancerskih ćelija, kao što to čine bakterije u anaerobnim uslovima, iako to kancerske ćelije čine i u prisustvu kiseonika, zbog čega ovaj mehanizam nosi naziv aerobna glikoliza (15, 16). Pri tome od 1 mola glikoze ne nastaje kao kod normalnih ćelija 36 mola ATP već samo 4 mola ATP. I kako ovaj deficit u generisanju

ATP-a maligne ćelije nadoknađuju, tj. kompenzuju? Tako što enormno povećavaju ulazak, tj. „priliv“ glikoze u kancersku ćeliju. Dakle, mora da postoji endokrini milje koji obezbeđuje kancerske ćelije. Tako se stiže do prvog mosta koji jasno povezuje kancer i gojaznost, a to je sistem insulin-IGF, tj. insulinsko-kancerska hipoteza (15). Već pedesetak godina se zna da insulin deluje kao promotor rasta i proliferacije i zdravih i malignih tkiva. Postoji ćelijska linija naročito agresivnog karcinoma dojke, koja je izrazito senzitivna na insulin, a potom ćelije karcinoma dojke ispoljavaju insulinske receptore iako ih ne poseduju normalne ćelije dojke od kojih ovi tumori nastaju. Brojni su karcinomi koji se karakterišu ogromnom ekspresijom insulinskih receptora, kao što su karcinomi prostate, kolone i dojke.

I ovi receptori se tu nalaze očigledno sa određenim razlogom, i to da obezbede značajno veće preuzimanje glikoze putem povećane aktivnosti insulinskog signalnog puta. Sada tumorske ćelije aktivacijom sopstvenih insulinskih receptora povećavaju metabolizam glikoze 10–20 puta, što za posledicu ima i povećano generisanje reaktivnih kiseoničnih radikala koji mogu da indukuju mutacije u genomu (15). Time nastaje „začarani krug“ u kome brže sagorevanje glikoze dovodi do stvaranja veće količine slobodnih radikala koji mogu da oštete genom. I time se dobija maksimalno ubrzanje, tj. progresija kancera. A koja je uloga IGF-1 u celoj priči? Većina gojaznih osoba ima povećane koncentracije ne samo insulina u plazmi već i IGF (insulinu slični faktori rasta). IGF se mogu vezati i aktivirati ne samo insulinske receptore, već i himerične receptore sa istom kaskadom uticaja na metabolizam glikoze.

Ključno pitanje je zašto kancerske ćelije uvode neefikasan način proizvodnje energije oličen u Vartburgovoj aerobnoj glikolizi? Šta time dobijaju? Zašto jednostavno ne zadrže oksidativnu fosforilaciju? Smatra se da je to zato što se aerobnom glikolizom sačuva ugljenično jezgro glikoze koje se preusmerava u pravcu akumuliranja masnih kiselina, tj. triglicerida koji su kancerskoj ćeliji potrebni za pravljenje novih ćelijskih membrana ćelija ćerki, ali i za pravljenje novih molekula DNK i proteina prilikom procesa kancerske replikacije. Dakle, maligne ćelije preuzimaju neefikasan način proizvodnje energije jer njime obezbeđuju gradivni materijal za dobijanje novih kancerskih ćelija. I ovu razmenu mogu da priušte jer se deficit u proizvodnji energije nadoknađuje enormnim povećanjem preuzimanja („priliva“) glikoze od strane tumorskih ćelija (15, 16, 17).

Kako se ova hipoteza može primeniti kod kancera koji ne eksprimuju insulinske receptore? Ovde transdukcija insulinskog signala ne počinje od membranskog receptora na membranama kancerskih ćelija, već je posledica određenih mutacija u samom insulinskom signalnom putu. Pre svega mutacija PI-3K (fosfatidil-inozitol-3 kinaza), ili mutacije koje dovode do konstitutivne aktivacije ovog signalnog puta, dovode do toga da kancerska ćelija više ne zavisi od insulina u njenoj mikrosredini jer on postaje nepotreban. Dakle, insulinska signalizacija je konstitutivno uključena i bez prisustva insulina. Signalni put PI-3K je mesto gde se susreću signalni putevi

određenih faktora rasta sa insulinskim putem, i na nivou PI-3K ispoljava dejstvo i bitan tumor-supresorski gen koji se naziva PTEN (fosfataza i tenzin homolog) (16). Ovaj gen najčešće trpi delecije kod velikog broja različitih uznapredovalih humanih karcinoma. Ako nema mutacije koje pojačavaju aktivnost signalnog puta PI-3K onda će kancer biti zavisan od insulina i IGF u cirkulaciji. Ako postoji mutacija PI-3K onda kancersku ćeliju ne zanima insulinski milje oko tumorskih ćelija.

ZAKLJUČAK

Maligne bolesti su među glavnim komplikacijama gojaznosti i tipa 2 šećerne bolesti (18). Potraga za malignim bolestima treba da bude deo kliničkog ispitivanja kod gojaznih pacijenata. Svakako da je potrebno definisati tipove kancera na koje treba sprovesti skrining.

Što je duže trajanje stanja prekomerne telesne težine i gojaznosti veći je rizik od nastanka različitih tipova kancera. I stepen gojaznosti u odraslom životnom dobu izgleda da ima važnu ulogu u riziku od nastanka kancera. Smanjenje dužine trajanja gojaznosti u odraslom dobu izgleda da redukuje kancerski rizik (19, 20). Otuda prevenciju gojaznosti treba sprovoditi u što ranijem životnom dobu.

I gojaznost i tip 2 šećerne bolesti se karakterišu postojanjem stanja insulinske rezistencije. Smatra se da insulinska rezistencija predstavlja faktor rizika za brojne kancere (12, 13). Pretpostavljena insulin-kancerska hipoteza stoji na stanovištu da hiperinsulinemija i povećan nivo IGF-1, adipokina i drugih faktora rasta kod insulinske rezistencije povećavaju rizik onkogeneze. Malo je verovatno da insulinska rezistencija ima bitnu ulogu u inicijaciji kancera, tj. ranim stadijumima nastanka kancera jer je indukcija kancerske ćelije veoma komplikovan proces. Bez obzira što se naziru delovi veze gojaznosti i kancera, mnogi komadići ove velike zagonetke i dalje ostaju nerazjašnjeni i na budućim je ispitivanjima da omoguće sklapanje celokupnog mozaika onkogeneze u gojaznosti.

LITERATURA

1. Harris HLB, Macaulay MV, David A. Harris AD at al. Obesity: a perfect storm for carcinogenesis. Cancer and Metastasis Reviews (2022)41: 491–515.
2. Cozzo JA, Fuller MA, Makowski L. Contribution of Adipose Tissue to Development of Cancer. Compr Physiol 2018, 8(1): 237–282.
3. Ford AN, Lashinger ML, Allott HE, Hursting DS. Mechanistic targets and phytochemical strategies for breaking the obesity – cancer link. Front Oncol 2013(3): 1–6.
4. Trevellin E, Bettini S, Pilatone A at al. Obesity, the Adipose Organ and Cancer in Humans: Association or Causation? Biomedicines 2023(11): 1–25.

5. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cencer 2004; 4: 579–91.
6. Devericks NE, Carson SM, McCullough EL at al. The obesitybreast cancer link: a multidisciplinary perspective. Cancer and Metastasis Reviews (2022)41: 607–625.
7. Belfiore A, Malaguarnera R. Insulin receptor and cancer. Endocr Relat Cancer 2011, 18: 125–147.
8. Befiore A, Frasca F, Pandini G I sar. Insulin receptor isosofrms and insulin receptor/ insulin growth factors receptor hybrids in physiology and disease. Endocr Rev 2009, 30(6): 586–623.
9. Lashinger ML, Ford AN, Hursting DS. Interacting inflammatory and growth factor signals underlie the obesity-cancer link. J Nutrit 2013: 109–113.
10. Gallagher JE, LeRoith D. Minireview:IGF, insulin and cancer. Endocrinology 2011, 152(7): 2546–51.
11. Renehan GA, Frystyk J, Flyvbjerg A. Obesity and cancer risk: the role of the insulin-IGF axis. Trends Endocrinol Metab 2006, 17(8): 328–336.
12. Allott HE, Hursting DS. Obesity and cancer: mechanistic insights from transdisciplinary studies. Endocr Related Cancer 2015: 365–386.
13. Ye J. Kraegen T. Insulin resistance: central and peropheral mechanisms. The 2007 Sock Conference Report. Obesity Reviews 2007, 9: 30–34.
14. Kolb R, Sutterwala SF, Zhang W. Obesity and cancer: inflammation bridges the two. Current Opinion in Pharmacology 2016, 29: 77–89.
15. Taubes G. Unraveling the obesity-cancer connection.Science 2012, 335: 28–32.
16. Smith U. PTEN-linking metabolism, cell growth and cancer. J Engl J Med 2012, 13: 1061–3.
17. Ward PS. Thompson CB. Metabolic reprogramming: a cancer hallmark even Warburg did not atnicipate. Csncer Cell 2012, 21(3): 297–308.
18. Fagundes Assumpção JA, PasquarellidoNascimento G, Saldanha Viegas Duarte M at al. The ambiguous role of obesity in oncology by promoting cancer but boosting antitumor immunotherapy. Journal of Biomedical Science (2022), 29: 12.
19. Arnold M, Jiang L, Stefanick LM i sar. Duration of adulthood overweight, obesity, and cancer risk in the Women›s Health initiative: SA longitudinal study from the United States. PLOS Medicine 2016: 1–16.
20. Gallagher EJ, LeRoith D. Insulin, insulin resistance, obesity and cancer. Curtr Diab Rep 2010, 10: 93–100.

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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.

LITERATURE

1. Harris HLB, Macaulay MV, David A. Harris AD et al. Obesity: a perfect storm for carcinogenesis. Cancer and Metastasis Reviews (2022) 41:491–515.
2. Cozzo JA, Fuller MA, Makowski L. Contribution of Adipose Tissue to Development of Cancer. Compr Physiol 2018, 8(1):237.282.

3. Ford AN, Lashinger ML, Allott HE, Hursting DS. Mechanistic targets and phytochemical strategies for breaking the obesity-cancer link. Front Oncol 2013(3): 1-6.
4. Trevellin E, Bettini S, Pilatone A, et al. Obesity, the Adipose Organ and Cancer in Humans: Association or Causation? Biomedicines 2023, (11) 1-25. 5. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cencer 2004; 4:579-91.
6. Devericks NE, Carson SM, McCullough EL et al. The obesity breast cancer link: a multidisciplinary perspective. Cancer and Metastasis Reviews (2022) 41: :607–625.
7. Belfiore A, Malaguarnera R. Insulin receptor and cancer. Endocr Relat Cancer 2011, 18:125-147.
8. Befiore A, Frasca F, Pandini G, et al. Insulin receptor isoforms and insulin receptor/ insulin growth factors receptor hybrids in physiology and disease. Endocr Rev 2009, 30(6):586-623.
9. Lashinger ML, Ford AN, Hursting DS. Interacting inflammatory and growth factor signals underlie the obesity-cancer link. J Nutrit 2013:109-113.
10. Gallagher JE, LeRoith D. Minireview: IGF, insulin and cancer. Endocrinology 2011, 152(7):2546-51