BIOMOLECULES IN THE RELATIONSHIP OF

CANCER *AND* OBESITY

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Resumo

A obesidade tem sido associada a várias causas principais de morte e morbidade, incluindo neoplasias malignas. Esse aumento da prevalência tem sido acompanhado por um aumento mundial nas taxas de incidência de melanoma cutâneo nas últimas décadas, assim como de gliomas, os tumores cerebrais malignos primários mais comuns em adultos (Almeida et al., 2019). Embora a etiologia da obesidade seja estabelecida, os mecanismos implicados permanecem obscuros (Coelho et al., 2016). O melanoma é refratário às terapias convencionais, e o uso da radioterapia como terapia adjuvante em pacientes com melanoma cutâneo é ineficaz, por isso é extremamente importante entender a modulação antioxidante do melanoma em um ambiente de obesidade (Coelho et al., 2017; Oliveira et al., 2016). Além disso, o potencial metastático de alguns tipos de câncer é reduzido ou inibido pela obesidade, o que gera grandes preocupações sobre o prognóstico de pacientes com metástase (Fonseca et al., 2021). Todos os estudos divulgam modelos interessantes para o estudo da biologia desses tumores em um ambiente obeso, que podem ser explorados na busca de biomarcadores, marcadores de prognóstico e abordagens terapêuticas.

Abstract

Obesity has been associated with various major causes of death and morbidity including malignant neoplasms. This increased prevalence has been accompanied by a worldwide increase in cutaneous melanoma incidence rates during the last decades, as well as gliomas, the most common primary malignant brain tumors in adults (Almeida et al., 2019). Although obesity aetiology is established, the implicated mechanisms remain unclear (Coelho et al., 2016). Melanoma is refractory to conventional therapies, and radiotherapy usage as an adjuvant therapy in cutaneous melanoma patients is ineffective, so it is extremely important to understand the antioxidant modulation of melanoma under an environment of obesity (Coelho et al., 2017; Oliveira et al., 2016). Moreover, the metastatic potential of some types of cancer is reduced or inhibited by obesity, which drives major concerns on the prognosis of metastasized patients (Fonseca et al., 2021). All of the studies disclose interesting models for the study of these tumors' biology under an obese environment, that can be explored for the search of biomarkers, prognostic markers and therapeutic approaches..

Obesity prevalence has significantly increased, leading to a public health concern and worldwide branded as "the modern epidemic". The prevalence of obesity in Europe has increased by approximately 30% over the past 10 years and this phenomenon is corroborated by data from several other countries. It has long been recognized that excess adipose tissue increases the risk of cardiovascular disease, type 2 diabetes and metabolic syndrome, but only in the past few decades it became widely accepted that augmented body adiposity is a risk factor for several types of malignancies. Additionally, obesity can lead to worsened prognosis, poorer treatment outcome, and increased cancer-related deaths. Melanoma arises from the malignant transformation of melanocytes, the pigment-producing cells of the skin, hair and eyes. Its incidence rates have increased in the last decades worldwide from 3% to 7% annually. These statistics suggest a doubling of rates every 10–20 years, raising melanoma to the most rapidly increasing cancer in Caucasians. Several reports showed positive associations between increased body fat and the risk of cutaneous melanoma

later in life, suggesting that the increasing incidence of melanoma may be related to the enlarged obesity prevalence. In vivo adiposity-related stimulation of melanoma growth has been demonstrated. Tumour-associated macrophages and endothelial cells have been pointed out as possible mediators in the growth-promoter effect of adipose tissue towards melanomas. In fact, tumour stroma comprises many different cell types, including fibroblasts, adipocytes, immune, and endothelial cells that, along with the extracellular matrix, are key players in cancer development and progression. However, we hypothesize that adiposity might also exert a direct effect over melanocytes without the involvement of stromal cells in a paracrine or endocrine manner. In the paper entitled "Effect of Adipocyte Secretome in Melanoma Progression and Vasculogenic Mimicry", it is explored the biological role of adipocytes secretome in B16-F10 and MeWo melanoma cell survival and plasticity (Coelho et al., 2016).

Moreover, and considering malignant melanoma, lungs are main target organs for metastization and their immune response is a key modulator of this mechanism. The concept that the metastatic potential of some types of cancer is reduced or inhibited by obesity, known as the obesity paradox, drives major concerns on the prognosis of metastasized patients. The aim of the study "Lower melanoma pulmonary metastatic burden in obese mice: role of FGF-21" was to investigate how high-fat diet (HFD)-induced obesity affects melanoma metastization. C57Bl6/J mice were fedwith HFD or standard diet for 180 days and inoculated intravenously with B16F10 melanoma cells. Upon 21 days of inoculation, lung tissue of overweight and lean mice was assessed for histology and immunohistochemistry assays. Adipokine antibody arrays were performed in mice serum. In vitro RAW 264.7 macrophage cultures were established and incubated with FGF-21 and/or lipopolysaccharide (LPS). Conditioned media was added to B16F10 cells for viability quantification. HFD-fed mice presented a reduced number of metastases with lower proliferative rates. The high content of inflammatory foci observed in noninoculated obese mice was significantly decreased upon B16F10 inoculation, concurrent with a slight fibrosis reduction. Plasma levels of fibroblast growth factor-21 (FGF-21), an endocrine regulator, were elevated in noninoculated HFD mice and the expression of FGF receptor 1 (FGFR-1) was significantly upregulated after inoculation. FGF-21 reduced melanoma viability in LPS-stimulated macrophages. Altogether, these findings suggest that higher amounts of FGF-21 are able to counterbalance the proinflammatory eff¬ects associated with obesity, protecting the lungs from melanoma metastization.

Melanoma has poor prognosis with a median survival rate between 6 and 9 months. Currently it remains one of the most challenging cancers due to its

refractory behavior to conventional therapies. While early-stage melanoma can be detected and effectively removed through surgery, melanoma with high metastatic potential is difficult to treat and more prone to develop resistance to available therapies, such as chemotherapy and radiation. Although the diagnosis of melanoma is straightforward, there are many disagreements regarding treatment and surveillance In order to surpass some of the limitations addressed to melanoma treatment, preventive or adjuvant methods like dietary factors are nowadays a relevant field of research. Despite the knowledge about melanoma biology, pathogenesis and developed therapies, is extremely important to understand the effect of these dietary compounds in redox modulation of melanoma under an obesity environment, especially the effect of antioxidant vitamins A, C and E or the effect micronutrient such as selenium salts. These antioxidant compounds are hypothesized to reduce the risk of developing melanoma because of their properties. Thus, in the review "Melanoma and obesity: Should antioxidant vitamins be addressed?" it is provided a systematic and up-to-date scientific discussion for the better understanding of the contribution of antioxidant compounds like vitamins A, C, E and selenium salts and their potential role against melanoma (Oliveira et al., 2016). Nowadays micronutrients are a trendy field of research. These dietary factors, such as vitamins may be useful on melanoma prevention, acting as anti-cancer agents possibly by suppressing the reaction/ light-induced erythema of human skin, preventing the development or progression of melanoma in general, inhibiting growth, proliferation, inducing apoptosis and differentiation of human and murine melanoma cell lines population, decreasing inflammatory environment associated with melanoma development in an obesity context and by restraining toxic effects of ROS released during inflammation. Despite all the research and investigation some data still remain controversial, and more studies are needed in order to understand dietary factors in particular these antioxidant vitamins and their potential role in melanoma therapy.

Radiotherapy is frequently used to treat the majority of malignancies and has a direct impact in the proliferative phenotype of both normal and cancer cells. Radiation induced ionization of regulatory proteins and DNA might render the cells unviable and culminate in cellular death. Ionizing radiation can also indirectly cause cellular damage. The formation of highly reactive oxygen and nitrogen radicals increases the intracellular oxidative stress, depleting the antioxidant defenses, which subsequently react with many cellular components (DNA, proteins, lipids) leading to unrecoverable damage. However, melanoma is known to be radioresistant, which discourages the use of ionizing radiation as an adjuvant therapy in melanoma patients. Recently, the use of radiation in higher

delivered doses, hypofractionated and in combination with immunotherapy has led to some positive outcomes in melanoma metastasis treatment and palliation. Nonetheless, obesity, particularly high visceral adiposity, presents a problem in treatment planning and delivery of radiation to internal metastases. Generally, higher body adiposity is associated with both cancer initiation and progression. Obesity itself is a risk factor for several types of neoplasms, including melanomas. High adiposity can be a contraindication for (and may limit the extent of) cancer surgery since it contributes to the inadequate dosing of chemotherapeutic drugs and complicates the planning and delivery of radiation. Adipocytes secrete a ariety of factors that exert effects at both local and systemic levels. The grand majority of these factors are cytokines, chemokines and inflammatory mediators, but a role in growth regulation as a new aspect of adipokines has been revealed by novel adipocyte-released molecules. Fat-derived molecules stimulate melanoma progression and aggressiveness and act as mediators of proliferation in melanoma cells. Resistance to oxidative stress appears to be a key mechanism of tumor radioresistance. Obesity is linked to a more pro-oxidative status, with a concomitant systemic increase in reactive oxygen species (ROS), acting as an additional source of oxidants. For the current study, we hypothesized that adipocytes might lead to two antagonistic outcomes towards melanocyte radiosensitivity. Although the fat-derived growth factors might protect melanocytes from radiation-induced loss of survival by stimulating their overall proliferation, the adipocyte-generated oxidants can further increase the oxidative burden, aggravating the radiation-induced damages. In the study entitled "Adipocyte Secretome Increases Radioresistance of Malignant Melanocytes by Improving Cell Survival and Decreasing Oxidative Status" cell cultures were irradiated at standard doses to investigate the action of the adipocyte secretome in melanoma radioresistance (Coelho et al., 2017).

Gliomas, a wide term which comprises all tumors arising from the supportive tissue of the brain, represent 30% of all brain tumors and 80% of all malignant brain tumors. They are the most common primary malignant brain tumors in adults. Prognosis is extremely poor, with a median survival time of approximately 12 to 15 months and is almost invariably fatal. This tumor represents about 12–15% of all primary brain tumors and about 60–75% of all astrocytomas. Gliomas increase in frequency with age and affect, preferentially, men. Genetic factors in glioma etiology are poorly understood; less than 5% of glioma cases are familial in origin, with only a few described by rare genetic syndromes. In 2001, different studies from the International Agency for Research into Cancer (IARC) and the World Cancer Research Fund (WCRF)

have reported a relationship and established a link between obesity and cancer risk. Excess adiposity is related with an increase the incidence and/or death rates from a wide variety of human cancers, being the most common colon, rectum, esophagus, kidney, pancreas, gallbladder, ovary, cervix, liver, prostate and certain hematopoietic cancers. Overweight and obesity are important risk factors for developing cancer and also for cancer related mortality. It is important to understand the pathophysiological mechanisms involved in the link between obesity and cancer, in order to target future preventive and therapeutic strategies for cancer in obese people. Despite its high morbidity, the etiology of glioma remains largely unknown. Among several risk factors, lifestyle was also recently identified as a major risk factor for the development of primary glioma. Consequently, there might be a relationship between the increase and dysfunction of adipose tissue. Obesity, favored by the modern lifestyle, acquired epidemic proportions nowadays, and accelerated weight gain, in adults, is associated with increasing incidence of all central nervous system tumors, mostly glioma. At the present time, it is not clear which factors might be involved in this relation. Genes that influence obesity are highly expressed in the brain and could also mediate glioma susceptibility. Some studies analyzed body weight in relation to survival in glioma demonstrating higher death rates in patients with an excess body weight. Obesity, and in particular visceral obesity, plays a major role in the pathogenesis of several metabolic disorders. Recently two large sample studies have established that obesity has no clear relationship with the occurrence of glioma. The study presented in "Adipocyte proteome and secretome influence inflammatory and hormone pathways in glioma" aimed to develop an in vitro rodent model for the study of the influence of adipokines secreted by adipose tissue in glioma biology (Almeida et al., 2019). We propose a model in which GL261 cells, a mouse glioma cell line, is cultured in the presence or absence of 3T3-L1 mature adipocytes conditioned medium. The 3T3-L1 pre-adipocytes were differentiated under controlled experiments and the adipokines and inflammation chemokines pattern expression were examined by proteome microarrays in the mature adipocytes conditioned medium were grown.

Our studies disclose some paradoxical relationship between obesity and cancer. They have also been able to develop an interesting in vitro and in vivo models for the study of melanoma and glioma biology under an obese environment, that can be explored for the understanding of cancer cells biology, for the search of biomarkers, prognostic markers and therapeutic approaches.

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