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EDITORIAL COMMENTARY

Editorial: Listen to your belly, fat is not your foe!

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At the beginning of oncological PET imaging, FDG uptake in cervical, supra- and infraclavicular, axillary, and paravertebral regions following chemotherapy, particularly in the cold season and in young women, was recognized as a typical (false positive) pitfall in patients with Hodgkin's lymphoma. It could be prevented by warming or medication for muscle relaxation. Lately, integrated PET/CT imaging clarified that this FDG accumulations are caused by brown adipose tissue (BAT). Furthermore, this new approach allowed systematic whole body studies to capture BAT distribution, as well as its activation state. Several groups were encouraged to study the function and stimulation of BAT by coldness and different medications in healthy and obese adults in detail [1–3]. And there is a persistent interest in the compound of adipose tissue, its genetic determination, its participation in cardiovascular disease as well as in diabetes mellitus and obesity and generally in its thermogenic capacity as a target tissue for inducing weight loss and adjusting energy homeostasis [4].

Visualization of hormonal regulation and paraneoplastic syndromes

Apart from FDG several radiotracers can address BAT and visualize its distribution and its innervation state including Tc-99m-MIBI, I-123-MIBG, C-11- and F-18-choline, and methionine. The BAT thermogenesis is dependent on the ß-adrenergically mediated activation of lipolysis and subsequent degradation of fatty acids via uncoupling protein 1 (Ucp-1), which dissipates large amounts of chemical energy into heat. The adrenergic stimulation is also leading to the transport of glucose into brown adipocytes for combustion into the mitochondria which is responsible for the FDG uptake in BAT [5]. Anesthesia (e.g. ketamine) can stimulate thermogenesis and ß-blocker can interrupt the metabolic flux [6]. The latter effect can be clinically used to increase specificity in tumor imaging. Stimulation of BAT is also known from hormonally active, secreting pheochromocytomas [5]. Tumors can be detected by direct addressing the malignant cells but also indirect in case of secretion of humoral substances and paraneoplastic syndromes. Well known examples are paraneoplastic hypertrophic osteoarthropathy (Pierre Marie-Bamberger syndrome) from lung cancer or various neurological impairments [7]. At the moment, there are hints that tumor cachexia is mediated by a paraneoplastic syndrome, too [8].

Metabolic switch

Heart metabolism depends on fuel supply: A hallmark of fetal metabolism is the predominance of carbohydrates as substrates for energy provision in a relatively hypoxic environment [9]. When the normal heart is exposed to an oxygen rich environment after birth, energy substrate metabolism is rapidly switched to oxidation of fatty acids. However, the heart retains the ability to return to the "fetal" gene program. High glucose load will force cardiac metabolism to glycolysis which can be used for imaging of hibernating myocardium. This is possible vice versa, since cardiac metabolism can be directed to lipids for investigation of cardial tumors or inflammation of heart valves. Tumor metabolism depends on genetic changes, too. The "Warburg effect" addresses the switch of

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tumor metabolism from multi-fuel preferential to the ineffective glycolysis which stimulates glucose transporters and hexokinase activity resulting in an increased glucose and FDG uptake what is the base of PET tumor imaging. Even 90 years after its description the Warburg effect is not understood in every detail [10]. However, it is important to look not only at changes of glucose metabolism in tumors, but also in the opposite direction: the fatty acid metabolism in tumors and the balance (or imbalance) between both pathways.

Adipose tissue as a secretory organ

Brown adipose tissue is the main site of non-shivering thermogenesis in mammals, whereas white adipose tissue (WAT) is the main depot where metabolic energy is stored in the form of triglycerides [11]. The activity of BAT is associated with the protection against obesity and metabolic alterations such as insulin resistance. BAT has systemic effects by secreting regulatory molecules in addition to its role in thermogenesis. Both BAT and WAT are secreting multiple autocrine and paracrine factors controlling the expansion and activity of BAT and the extent of WAT browning. BAT releases endocrine factors that can target peripheral tissues such as liver, pancreas, heart, and bone, as well as affect systemic metabolism by interacting with the central nervous system [11]. Fukuwa et al. [12] investigated the regulation of cachexia in vitro and in a mouse model. They identified a human cancer cell line that induced pronounced weight loss after engraftment into the mice. They determined that the cancer cell line secreted multiple factors which have been previously implicated to contribute to cachexia or induce it by itself. They cultured myotubes in conditioned media from the cachexia-inducing and non-inducing cancer cell lines and observed a response only in the first one including a reduction of muscle growth as well as pronounced changes in the expression of gene levels associated with glycolytic and fatty acid metabolism. Most recently, Rohm et al. [13] could demonstrate that tumor cell exposure and tumor growth in mice triggered the futile energy-wasting cycle in cultured white adipocytes. They identified inactivated AMP-activated protein kinase (Ampk) as a mediator, which is normally activated in peripheral tissues during states of low cellular energy. Both groups reported first success to ameliorate or even prevent this fatal energy-wasting syndrome [12, 13].

There are several reports available that assess impact of obesity and body fat distribution on survival and prognosis of various cancer entities. However, the report of Van de Wiele et al. is the first one demonstrating not only morphology for this purpose but also glucose metabolism estimated by FDG PET/CT [14]. Based on metabolic imaging they describe a different metabolism of visceral and subcutaneous fat tissue. The clinical value of this observation has to be investigated in further detail. However, differences of glucose uptake and metabolism in visceral and subcutaneous fat tissues have been reported in healthy and obese persons before but now in cancer patients, too. The one-stop-shop FDG PET/CT not only provides a highly sensitive and specific tumor staging, but offers additional information on risk factors for cachexia when images are carefully read and reported [15].

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