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DANCE ROUND

We dance round in a ring and suppose,
But the Secret sits in the middle and knows.
Robert Frost

ADIPOPARACRINOLOGY: PERIPROSTATIC ADIPOSE TISSUE AS AN EXAMPLE

Nikolai Evtimov[1], Alexander I. Hinev[2], Deyan Anakievski[2], Marin Zhelezov[3,4], Peter I. Ghenev[3], and George N. Chaldakov[4*]

[1]Clinic of Urology, St Anna University Hospital, Varna, Bulgaria, [2]Clinic of Urology, St Marina University Hospital, Varna, Bulgaria, [3]Department of General and Clinical Pathology, Medical University, Varna, Bulgaria, and [4]Laboratory of Cell Biology, Medical University, Varna, Bulgaria

Abstract

The global epidemic of obesity (globesity) and related cardiometabolic and cancer diseases has focused attention on adipose tissue biology and the role played by adipose-secreted bioactive molecules (adipokines, neurotrophic factors, fatty acids, prostaglandins, steroid hormones, vitamin D3, NO, H2S) in the regulation of a wide array of physiological and pathological processes. Until recently, physicians have looked upon obesity as an accumulation of external adipose tissue (subcutaneous and abdominal). This was routinely evaluated by anthropometric measurements including body mass index and waist, hip and, recently, neck circumference. However, recent data using non-invasive imaging methods (echography, computed tomography, magnetic resonance imaging, and positron emission tomography), reveal a novel picture of adipotopography (fat mapping). Together with secretory functions, such a topography has been conceptualized as two major subfields of adipobiology, adipoendocrinology and adipoparacrinology. Here we introduce periprostatic adipose tissue as an example of adipoparacrinology of prostate cancer; its implication in the therapy is also outlined.

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Correspondence: Dr George N. Chaldakov, Laboratory of Cell Biology, Medical University, BG-9002 Varna, Bulgaria. Tel.: 359 052 754 394; E-mail: chaldakov@yahoo.com

Introduction

Recently, the prevalence of obesity and related cardiometabolic and cancer diseases is increasing dramatically and globally. Arguably, more has been learned about the molecular control of food intake, particularly the role played by adipose tissue in the pathogenesis of these diseases, studying the structure and function of both white adipose tissue (1-15) and brown adipose tissue ("thermogenic tissue", a term suggested by Caroline Pond, personal communication).

Human adipose tissue is partitioned into two large depots (subcutaneous and visceral), and many small depots associated with internal organs, e.g. heart, blood vessels, major lymph nodes, pancreas, kidneys, prostate gland and ovaries. Since the discovery of leptin in 1994, the adipose tissue has been perceived not merely as a lipid store, but as a secretory – endocrine and paracrine – organ. Evidence for paracrine interactions between adipose tissue and other tissues was presented in the 1990s by

Pond and Mattacks (1), but the secretory function of adipose tissue was not conceptualized until the early 2000s when two major subfields of adipobiology - adipoendocrinology and adipoparacrinology - have emerged (2,3, reviewed in 7,12-14).

Inflammation, immunity, endothelial dysfunction, insulin resistance, vascular tone, hemostasis, reproduction, cell growth, memory/learning, and vitamin D_3 and bone metabolism (see Trayhurn *et al*, Bełtowski, Kanazawa, and Gualillo, this volume of *Adipobiology*) have been implicated in the effects of adiposity on human health and disease.

Adipoparacrinology of prostate cancer

Obesity is associated with larger size of prostate cancer and higher Gleason scores. However, the mechanisms by which obesity promotes prostate cancer remain unknown. We hypothesize that the prostate may be the target of various pro-cancerogenic adipokines (8-11), at paracrine level focusing on the potential role of periprostatic adipose tissue. This tissue was neglected until recently when few publications had been released (16-18). In one of these latter studies (16), periprostatic adipose tissue has been harvested from patients undergoing radical prostatectomy, and interleukin-6 in periprostatic adipose tissue conditioned medium was approximately 375 times greater than that in patient matched serum; this correlated with higher pathological Gleason score in 45 patients. These findings suggest that periprostatic adipose tissue may have a role in modulating prostate cancer aggressiveness by serving as a source of pro-cancerogenic adipokines. Likewise, the presence of periprostatic adipose tissue measured by computed tomography correlates with prostate cancer aggressiveness (18).

Adipopharmacology of prostate cancer

To date, no effective therapeutic treatment prevents prostate cancer progression to more advanced and invasive disease forms. The prostate is an abundant source of nerve growth factor (NGF) that is secreted by malignant epithelial cells and utilized as an important autocrine factor for growth and metastasis. Recently, the possible "oncotrophic" role of this "classical" neurotrophin, which is also produced by adipose tissue (6 and references therein), in the pathogenesis of prostate cancer has been reported (19-23). In our ongoing study, we are collecting samples of periprostatic and anterior perirectal adipose tissue from prostate cancer patients undergoing radical prostatectomy, aimed at studying the immunohistochemical expression of NGF receptors, $p75^{NTR}$ and TrkA, and of BDNF receptor, TrkB. Noteworthy, CEP-701 (Lestaurtinib), a pan tyrosine kinase receptor (Trk) inhibitor that causes cell death in prostate cancer models (24), is in clinical trials (25,26). In the same vein, tamoxifen, a drug traditionally applied in breast cancer therapy (27), might also be considered in the therapy of prostate cancer. Further, adiponectin receptor agonists (28,29) and/or leptin receptor antagonists (30) may also be of therapeutic value. Last but not least, new adipokines, semaphorins, and their receptors, neuropilins and plexins (31), were implicated in the pathogenesis of prostate cancer (32).

Coda

Many routes may lead to the transition from healthy to diseased phenotype. However, there are not so many routes to travel the opposite direction, that is, to treat obesity and related diseases, and thus extend human life expectancy. The principle questions thus remain: which are the pathogenic routes, and how would be they counteracted for therapeutic purposes?

Here, we have *Danced Round* the dysfunctional periprostatic adipose tissue paracrine secretion of adipokines as implicated in the pathogenesis of prostate cancer and, possibly, benign prostatic hyperplasia. Mechanistically, each step of the intracellular secretory pathway of these adipokines might be a potential target for drug development. Although a significant amount of work is still required to uncover the multiplex biology of both adipose secretion and prostate cancer, the present *Dance Round* proposes that a detailed molecular understanding of paracrine secretion may open new avenues for discovering drugs for prostate cancer as well as other, adipose tissue-related diseases (Table 1). Thus, the present challenge is to cultivate an adipocentric thinking about how we can make the adipose tissue secretion work for the benefit of human's health.

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Table 1. Examples (n = 16) of adipoparacrinology of diseases*

• Epicardial adipose tissue/pericoronary adipose tissue and cardiometabolic diseases
• Periadventitial adipose tissue (*tunica adiposa*) and peripheral atherosclerosis
• Intramyocardial adipose tissue and arrhythmogenic right ventricular dysplasia
• Mesenteric adipose tissue and Crohn's disease and ulcerative colitis
• Mammary gland-associated adipose tissue and breast cancer
• Periprostatic (and anterior perirectal) adipose tissue and prostate cancer
• Lymph node-associated (perinodal) adipose tissue and Crohn's disease and HIV-associated adipose redistribution syndrome (HARS)
• Infrapatellar fat pad (Hoffa's fat pad) and osteoarthrosis
• Retromalleolar adipose tissue and Achilles tendon disorders
• Orbital adipose tissue and thyroid-associated (Graves') ophthalmopathy
• Peripancreatic adipose tissue and type 2 diabetes mellitus
• Periovarian adipose tissue and ovary gland disorders
• Epidural adipose tissue and spinal cord disorders
• Subcutaneous adipose tissue and skin diseases
• Epididymal adipose tissue and sexual disorders (?)
• Parasellar region (cavernous sinus)-associated adipose body and brain disorders (?)

* For references (see also 33-50).

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