Chapter

Crossroad between Obesity and Cancer: A Defective Signaling Function of Heavily Lipid-Laden Adipocytes

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Abstract

Obesity and its comorbidities exhibit a gender-related dimorphism. Obese males tend to accrue more visceral fat leading to abdominal adiposity, which shows a strong correlation with serious obesity-associated comorbidities, cardiovascular diseases and cancers. In contrast, obese females accumulate excessive fatty tissue predominantly subcutaneously enjoying strong protection from the obesity-related diseases. The health advantage of obese women as compared with obese men may be attributed to their higher estrogen production and an increased transactivation of estrogen receptors (ERs). The recently clarified intracrine, paracrine, and endocrine functions of adipose tissue illuminate that concentrations of estrogens and the suitable expression and activity of ERs strongly define all regulatory functions in both men and women. All well-known cancer risk factors are in correlation with defects of estrogen signaling in partnership with glucose intolerance as estrogen regulates all steps of glucose uptake. In central obesity, increased secretions of cytokines and growth factors are not causal factors of developing insulin resistance, and unrestrained cell proliferation, but rather, they are compensatory processes so as to increase estrogen synthesis and ER transactivation. In conclusion, a causal therapy against obesity and obesity-related diseases aims to improve estrogen signaling in both men and women.

Keywords: obesity, insulin resistance, estrogen signaling, cancer risk, cardiovascular disease, estrogen receptor, IGF-1, low-grade inflammation, inflammatory cytokines

1. Introduction

Gender-related differences in the risk for obesity-associated serious diseases, such as type 2 diabetes, cardiovascular lesions, and cancers, are well established [1, 2].

Fat deposition exhibits a strong sexual dimorphism defined by genetic factors [3]. Among healthy lean people, women have a higher body fat content than men. In obesity, males tend to accrue excessive visceral fat leading to abdominal adiposity, which shows a strong correlation with serious obesity-associated comorbidities. In contrast, obese females accumulate excessive fat deposition predominantly subcutaneously in the gluteofemoral region, gaining protection from the obesity-related

diseases. However, after menopause, excessive fat depositions in obese women show a shift to favor the visceral depot in a male-like manner, resulting in an increased risk for obesity and associated comorbidities [4]. Considering the gender and age-related differences in the epidemiology of obesity and obesity-associated diseases, an imbalance of sexual hormone signaling emerges as a crucial player in the dysregulation of adipose tissue in obese patients [5].

Both clinical and experimental results suggest that obesity, particularly a visceral accumulation of fatty tissue, leads to insulin resistance, which is a defect of insulin-assisted cellular glucose uptake [6]. Dysregulation of glucose uptake may induce serious disorders in the gene regulation of cellular metabolism, growth, differentiation, and mitotic activity as glucose is the most important fuel of genomic machinery in mammalian cells [7].

Insulin resistance was the first one among revealed cancer risk factors detrimentally affecting cellular signaling functions [8]. Later on, defective estrogen signaling emerged as a second cancer risk factor, which directly deteriorates the functions of genomic machinery [9]. In the meantime, a central role of sexual steroid synthesis and estrogen signaling emerged as the chief regulator of all extragonadal tissues including adipose tissue [10]. Finally, a fundamental role of estrogen signaling in the regulation of both somatic and reproductive functions of mammalian cells was exposed [11].

The recently clarified intracrine, paracrine, and endocrine functions of adipose tissue illuminate that concentrations of estrogens, and the appropriate expression and activity of their receptors, strongly define the regulatory functions of central adipose tissue in both men and women [12]. Decreased estrogen signaling induces central obesity through an increased lipogenesis and insulin resistance of abdominal adipocytes. The excessive lipid storage strongly inhibits the signaling crosstalk between adipose cells and visceral organs, including intestine, liver, pancreas, kidneys and cardiovascular system. The disturbed inter-tissue crosstalk may cause defects in both metabolic and mitotic activities of parenchymal and stromal cells of different organs and induces serious, life-threatening diseases.

Understanding the pivotal regulatory roles of healthy abdominal fatty tissue in signal transduction may appropriately answer the question: how can abundant visceral fat deposition lead to serious, life-threatening diseases, such as cardiovascular lesions and malignancies in different organs?

2. Weak estrogen signaling in men and postmenopausal women provokes an increased prevalence of abdominal obesity and glucose intolerance

In obese patients, an excessive fat deposition in the intra-abdominal adipose depot is strongly associated with an increased risk for type 2 diabetes, cardiovascular diseases, and cancers developing at different sites [13]. Gender-related dimorphism of adipocyte behavior and fatty tissue accumulation suggests that health advantages of obese women as compared with obese men may be attributed to stronger estrogen signaling and an increased activation of estrogen-regulated genes [14].

In obese men, an excessive abdominal fatty tissue deposition is characteristic. Male-like abdominal obesity is strongly associated with different stages of insulin resistance and an increased risk for obesity-associated comorbidities including cancer [3].

Among obese premenopausal women with regular ovulatory cycles, a female-type gluteofemoral deposition of adipose tissue may be associated with the

maintenance of healthy insulin sensitivity, whereas they have no increased risk for either cardiovascular or neoplastic diseases [15]. Abdominal adipocytes of healthy women exhibit higher insulin sensitivity as compared with those of men [16]. In contrast, in premenopausal obese women with anovulatory infertility or disorders of menstrual cycles, a male-like abdominal obesity and deepening insulin resistance may develop in correlation with the defect of estrogen signaling [17].

In women, menopause is a physiological model revealing how decreased estrogen level may induce adiposity and its comorbidities. In obese, postmenopausal women, an increased inclination to a male-like central obesity and associated insulin resistance may be experienced [4, 5]. Increased prevalence of abdominal obesity and obesity-related diseases in postmenopausal women strongly suggests that decreased estrogen signaling may have pivotal roles in the dysregulation of lipid metabolism, glucose tolerance, and cell proliferation [18, 19]. In contrast, hormone replacement therapy after menopause reduces the accumulation of visceral adipose tissue and improves insulin sensitivity via an activation of estrogen-regulated genes [20].

Inherited serious mutations on estrogen receptor alpha gene (ESR1) or aromatase coding CYP19 gene may result in extreme defects of estrogen signaling and lead to insulin-resistant states and premature cardiovascular diseases in both male and female cases [21–23].

In rodents, estrogen withdrawal via ovariectomy consistently increases adiposity-associated body weight and glucose intolerance, while estrogen treatment results in weight loss and a restoration of insulin sensitivity [24, 25]. Aromatase knock-out (ArKO) transgenic mice with inactivated aromatase enzyme are unable to synthesize estrogen and exhibit increasing obesity and insulin resistance with associated compensatory hyperinsulinemia in males and females [26]. ER-alpha knock-out (ERαKO) male and female mice similarly exhibit metabolic syndrome-like phenotypes, including obesity, glucose intolerance, hyper-insulinemia, and decreased energy expenditure [27].

In ovariectomized obese mice, inoculated T47D tumor cells exhibited an intense proliferation, while estrogen supplementation suppressed the survival of inoculated tumor cells [28]. Ovariectomized female mice were fed diets to induce obesity and were inoculated with mouse mammary cancer cells. Estrogen substitution triggered a loss of body fat, improved insulin sensitivity, and suppressed the proliferation of inoculated tumors [29].

In conclusion, either estrogen deficiency or estrogen receptor (ER) resistance may have a crucial role in the dysregulation of both lipid storage and glucose uptake in adipocytes resulting in obesity and type 2 diabetes as clinical manifestations. Estrogen substitution seems to be a good strategy against obesity and associated chronic diseases including cancer.

3. Obesity-associated failure of estrogen signaling is a stronger cancer risk for males having low baseline estrogen levels

Systematic review and meta-analysis of literary data help to assess the associations between obesity and cancer risk in males and females [30]. Among men, obesity disproportionately increases the prevalence of cancers developing at different sites. These observations strongly suggest that the health advantage in obese women may be attributed to their estrogen predominance supplying defense against failures in DNA replication [31].

In epidemiologic studies, a male predominance was experienced in *esophageal adenocarcinoma* incidence [32]. In a clinical study, *oral cancer* showed a conspicuous male predominance, while from 50 to 52 years of age, oral cancer incidence among

postmenopausal women showed a slow and, later, a steep increase in correlation with the loss of estrogen exposure [33]. Results of meta-analyses do indicate that the association between obesity and an increased risk for *gastric cancer* is stronger in men than in women and the correlation significantly increases with increasing BMI among men [34]. *Colorectal cancer* shows a high prevalence among men, while women are relatively protected against this tumor [35]. Furthermore, hormone replacement therapy provides an additive protective effect against colon tumors in postmenopausal women. Obesity increases the risk for colorectal cancer in both men and women; while in males, associations between excessive adiposity and colon cancer risk seem to be much stronger [30]. Obesity and related metabolic disorders are high risk factors for *primary liver cancer* [36]. The associations are stronger in men, especially in patients with underlying liver disease, such as HCV infection or cirrhosis.

Unexpectedly, the risk for *kidney cancer* is higher in obese women than in men with increasing BMI [37]. Overweight and obese patients were found to have elevated risks of renal cell cancer in a dose-response manner, with an estimated 24% increase for men and a 34% increase for women by every 5 kg/m^2 increase in body mass index (BMI) [30]. Conversely, data from the National Cancer Database during a 10-year period were analyzed and a ratio of 1.65 of renal cell carcinoma risk for males compared to females was established disregarding the impacts of differences in BMI. Nevertheless, the mean age of kidney cancer cases was greater in females (64.3) than in males (60.9) ($p < 0.001$) [38]. In obese women, a long-lasting postmenopausal decrease in estrogen synthesis may be an additional risk for kidney cancer, provoking an inverse gender-related disparity for kidney cancer in an aged population.

Breast cancer in women is the most frequently diagnosed malignant tumor, while in men, it is an extremely rare disease, accounting for less than 1% of all breast cancer cases [39]. Since high estrogen levels are mistakenly regarded as fuels for breast cancer growth, the strong protection of males against breast cancer may be deceivingly attributed to their physiologically lower estrogen levels. The causal factors of male breast cancer are quite similar to those of female breast malignancies—obesity, type 2 diabetes and male infertility [39], which are strongly associated with insulin resistance and deficient estrogen signaling. Healthy female breasts exhibit high estrogen demand attributed to their physiologic cycling activity, and they are highly vulnerable even to slightly defective estrogen signaling. In contrast, in resting male breasts, very serious defects of estrogen signaling may be regarded as dangerous regulatory disorders leading to an increased risk for cancer [31].

Obesity equivocally increases the incidence of breast cancer among males, presumably through similar mechanisms as in case of females [40]. However, among women, an apparently ambiguous interaction can be observed between obesity and breast cancer risk depending on the menopausal status of patients [41]. In young women before menopause, obesity is erroneously regarded to exhibit a protective effect against breast cancer. Conversely, in postmenopausal older cases, there is a strong direct correlation between adiposity and mammary cancer risk. Obesity is associated with dysmetabolism and endangers the healthy equilibrium of sexual hormone production. In reality, among premenopausal women, obesity-associated insulin resistance is moderate, being counteracted by their maintained or increased circulating estrogen levels [15, 42]. In conclusion, it is not obesity but rather the still suitable estrogen level that may be protective against breast cancer in young women. Obese postmenopausal women, who had never used hormone replacement therapy (HRT), exhibit fairly high breast cancer risk in association with their continuously decreasing estrogen levels [43]. In contrast, obese postmenopausal women using hormone replacement therapy (HRT) show a significantly reduced breast cancer risk attributed to the protective effect of estrogen substitution [44, 45].

The higher risk for obesity-associated cancer among men and postmenopausal women as compared with premenopausal cases suggests that the weaker the estrogen signaling in abdominal adipocytes, the stronger is the defect of DNA repair leading to an increased risk for cancer [15, 42].

4. Central adipose tissue is a hub in the signaling network that controls and regulates visceral organs via an inter-tissue crosstalk

Adipose tissue stores excess calories in the form of lipid. In addition, adipose tissue is an endocrine organ regulating the functional activity of both adjacent and remote organs [46].

Adipose tissue is principally deposited in two locations. *Centrally positioned* fatty tissue within the trunk and abdomen closely surrounds the visceral organs, while the *subcutaneously positioned* adipose tissue covers the skeletal muscles [2]. The close vicinity between central fatty tissue and internal organs suggests that adipocyte signaling in this region may regulate vital functions affecting the health of whole body, while subcutaneous adipocytes primarily confer their messages to skeletal muscles and skin. Differences in fatty tissue locations strongly suggest that in pathological situations included obesity, the dysregulation of central adipocytes is a much higher health risk as compared with that of their peripheral counterparts.

In healthy nonobese people, abdominal adipose tissue provides a strong mechanical support for all internal organs [2]. Visceral fat is largely located in the omental and mesenteric adipose tissue in the vicinity of stomach, intestines, liver, and pancreas. Adipose tissue deposition is also characteristic within the visceral pericardium surrounding the myocardium and coronary arteries. Kidneys and the attached adrenal glands are embedded into an abundant fatty tissue capsule. Central adipose tissue is a crucial fat store providing standby energy for physiologic functions and even for the functional activation of visceral organs among various circumstances.

On the other hand, central adipose tissue is a complex and highly active endocrine organ exerting essential regulatory functions through autocrine, paracrine, and endocrine mechanisms [47]. In addition to the mass of adipocytes, adipose tissue contains a connective tissue matrix comprising fibrocytes, nerves, vessels, and immune cells functioning as an integrated unit.

The receptor systems of adipocytes, fibrocytes, and immune cells collect numerous afferent signals arriving from adjacent or remote organs and the central nervous system, while they respond through the secretion of signaling molecules, such as steroid hormones, adipokines, growth factors, and cytokines.

5. Circulating and locally synthesized estrogen hormones regulate the functional activity of adipose tissue

Sex steroids, particularly estrogens, play a pivotal role in the regulation of all tissues in the body [10]. Estrogen-activated ERs are central regulators of the metabolic status, growth, differentiation, and proliferation of cells in mammalians. Estrogen-regulated genes control signaling functions of the whole body via a balanced activation of ERs through liganded and unliganded pathways [48]. Estrogens are the regulators of crosstalks between adipose tissue and adjacent visceral organs via an appropriate expression of signaling molecules in both males and females.

Physiological cellular mechanisms require not only suitable estrogen concentrations but also appropriate expression and activity of ERs in the targeted tissues.

The presence of both isomers, ER-alpha and ER-beta, was confirmed in adipocytes deriving from both subcutaneous and intra-abdominal adipose tissue, suggesting that adipose tissue function is strongly defined by suitable estrogen signaling [49]. Lower prevalence of visceral adiposity in women than in men arises from the high expression and activity of ERs in female abdominal adipocytes being capable of downregulating both adipogenesis and lipid storage [50].

The gonads, ovary, and testis are the primary sites of estrogen synthesis in mammals. Extragonadal estrogen synthesis in adipose tissue was first published in 1974, based on the unexpected observation that androgens were converted to estrogens by aromatase enzyme in adipose tissue [51]. From that time onward, estrogen synthesis and the expression of estrogen receptors have been revealed in several organs [52]. All tissues expressing estrogen receptors are considered to be targets of estrogenic regulation.

Adipose tissue is considered to be a major source of estrogen synthesis among extragonadal sites in both women and men, and it increasingly contributes to the circulating estrogen concentration with aging [12]. In adipose tissue, C19 steroids are essential precursors of estrogen synthesis and the locally synthesized CYP19 aromatase enzyme is able to convert C19 steroids to estrogens [53]. The prerequisite of estrogen synthesis is the local expression of aromatase enzyme, which strongly defines the local estrogen production. In extra-gonadal tissues, the expression level of aromatase enzyme shows strong parallelism with the intensity of estrogen synthesis. Extragonadal sites included adipose tissue are unable to synthesize C19 steroids; hence, their estrogen synthesis is limited by the precursor supply from external sources [53].

Estrogens synthesized in adipose tissue are thought to act locally, in an *autocrine manner*, while they may have sufficient concentration in the adjacent organs too so as to induce ER activation in a *paracrine manner.* The systemic, *endocrine effects* of locally synthesized estrogens are limited [54]. Appropriate local estrogen concentration may exert its biological activity via activation of ERs, which are members of the nuclear receptor superfamily.

Increased estrogen concentrations upregulate estrogen signaling through a DNA stabilizer circuit and lead to a higher expression of ERs, genome stabilizer proteins, and aromatase enzyme [11, 55]. In contrast, estrogen deficiency or a defect of ER activation causes dysregulation in adipocytes and leads to a derangement of their signaling functions.

The noteworthy volume of central adipose tissue and the remarkable estrogen synthesis of adipocytes may support the fact that estrogen signaling has a crucial role in controlling and orchestrating the signaling network of both adjacent organs and the whole body.

6. Estrogen-regulated genes orchestrate the physiological functions of adipose tissue and visceral organs

Estrogen-activated ERs are the chief regulators of somatic and reproductive cellular functions suggesting that a defect in estrogen signaling may produce dysregulation and leads to serious diseases [48]. Current literary data support that activated ERs in adipocytes protect against fat deposition, insulin resistance, inflammation, and fibrosis of adipose tissue [Davis]. Moreover, body fat mass deposition is defined by the level of estrogen signaling in both men and women [56]. Healthy, insulin-sensitive adipose tissue regulates the glucose homeostasis and balanced lipolysis/lipogenesis of adjacent tissues, included liver, skeletal muscles, and further organs via a tissue crosstalk [57].

6.1 Adipose tissue

Estradiol-induced activation of ER-alpha upregulates all steps of cellular glucose uptake increasing the *insulin sensitivity* of adipocytes [58]. In mature adipocytes, estradiol treatment enhances insulin-assisted glucose uptake through liganded and unliganded activations of ER-alpha. Estradiol is capable of stimulating an increased tyrosine phosphorylation of insulin receptor substrate-1 [59]. In vitro, estradiol activates adenosine monophosphate-activated protein kinase (AMPK) and protein kinase B (AKT) inducing unliganded ER signaling even in the absence of insulin [60]. In human adipocytes, GLUT-4 abundance shows high correlation with insulin responsiveness. In 3T3-L1 adipocytes, estradiol treatment facilitated glucose uptake via an increased expression and intracellular translocation of glucose transporters (GLUTs) [61].

In obesity, GLUT-4 content showed a 40% decrease in adipocyte membranes, while in estrogen-deficient adipocytes deriving from either lean or obese PCOS cases, a 36% decrease of GLUT-4 content was experienced [62]. In animal experiments, female, ovariectomized high-fat-fed mice exhibited obesity, and decreased levels of glucose transporter 4 (GLUT4) and ER-alpha protein were found in their abundant visceral fatty tissue coupled with increasing insulin resistance [63].

In women, a higher ER expression in abdominal adipocytes may be associated with higher insulin sensitivity of fatty tissue and a lower susceptibility to inflammation and fibrosis compared to men [56]. Estrogen receptor α gene expression levels are reduced in the adipose tissue of obese women compared to those found in normal weight females [64].

The identification of a mesenteric estrogen-dependent adipose gene (MEDA-4) revealed that estrogen signaling may selectively regulate mesenteric adipocytes in a depot-specific manner [65]. In ovariectomized female mice, an increased MEDA-4 expression in mesenteric adipose tissue was capable of increasing adipose tissue expansion, while estradiol substitution reduced MEDA-4 expression and normalized the balance of lipolysis and lipogenesis in central adipocytes.

In conclusion, estrogen-regulated genes play crucial roles in both lipogenic control and glucose uptake of adipocytes. In contrast, estrogen deficiency-associated insulin resistance and lipogenesis further deteriorate estrogen signaling and strongly decrease the expression of estrogen-regulated genes via a vicious circle [66].

6.2 Liver

In the liver, estrogen-regulated genes control the synthesis of various proteins. Estrogen signaling regulates lipoprotein synthesis, lipogenesis, and lipolysis in hepatocytes. Estradiol controls the synthesis of blood clotting factors, including factors II, VII, IX, X, and plasminogen [67]. Estrogen regulates glucose uptake and glucose homeostasis in hepatocytes, improving insulin sensitivity [68]. In the pathologic conditions of the liver, estradiol treatment exerts anti-inflammatory and antineoplastic impacts through ER-alpha and, predominantly, ER-beta activation [69].
In contrast, a longer duration of estrogen deficiency increases the risk of hepatic fibrosis among postmenopausal women with nonalcoholic fatty liver disease [70].
In female mice, estrogen treatment prevents the development of insulin resistance and low-grade inflammation in adipose tissue [71, 72]. Recent literary data strongly confirm that estrogen hormone protects against the development and progression of hepatocellular carcinoma (HCC) [73]. Estrogen treatment also mediates antitumor effects in intrahepatic cholangiocarcinoma cases via a balance of ER-alpha and ER-beta-regulated pathways [74]. Bilateral oophorectomy in premenopausal women increases the risk of hepatocellular carcinoma via estrogen withdrawal [75].

6.3 Pancreas

In pancreatic islands, the estradiol activation of ER-alpha regulates β cell proliferation during pancreatic development [76]. Estradiol activates the expression of insulin gene and increases insulin synthesis in the β cells [77, 78]. Estradiol activation of ERs inhibits apoptotic death of β cells in case of inflammatory insult [77]. Estradiol promotes β cell recovery after pancreatic injury [80]. In rodent models of type 2 diabetes, estrogen treatment reduced lipid synthesis and prevented β cell failure in pancreatic islets [79]. Correlations between parity and pancreatic cancer risk were studied in a meta-analysis of epidemiologic studies and the findings suggest that higher parity is associated with a decreased risk of pancreatic cancer [80].

6.4 Gut

Local estrogen synthesis and ER expression in the gut are important players in intestinal homeostasis. Estrogen signaling regulates the integrity and function of intestinal epithelium controls intestinal epithelial barriers and reduces intestinal permeability [81]. Estrogen signal provides protection against duodenal ulcer, inflammatory bowel disease, and colon cancer in both animal experiments and clinical studies [82]. Overexpression of ER-beta in healthy human colon coupled with its reduced expression in colon cancer suggests that the activation of ERs, particularly ER-beta, might be particularly involved in the estrogen-mediated protection against colon tumors [35].

The microbes that colonize the human gut (microbiome) may play contributory roles in health and disease. Intestinal microbiome participates in polysaccharide breakdown, nutrient absorption, inflammatory responses, and bile acid metabolism [83]. Gut microbiome is one of the principal regulators of circulating estrogen levels [84]. Microbes in the gut regulate estrogen levels through secretion of β-glucuronidase, an enzyme that converts conjugated estrogens into their biologically active forms. Lower microbial density or a dysbiosis of gut microbiome leads to a decrease in estrogen deconjugation and results in a reduction of both luminal and circulating free estrogen levels.

The low level of luminal estrogens induces gut diseases included inflammation and cancer, while an associated decrease in circulating estrogens may contribute to the development of systemic diseases including obesity and type 2 diabetes.

In medical practice, a fecal microbiome transplant (FMT) from healthy individuals to ill obese patients seems to be a promising way to improve the gut microbiome and for the treatment of obesity and associated metabolic syndrome [85]. Presumably, FMT may provide estrogen hormones and estrogen receptors for recipient patients, which beneficially restore intestinal estrogen signaling besides the re-colonization of microbes capable of increasing free estrogen levels.

In conclusion, alterations in the density and composition of gut microbiome deteriorate the metabolic profile of omental and mesenteric adipose tissues via deficient estrogen signaling and lead to the development of abdominal obesity and metabolic syndrome.

6.5 Kidney

Estrogens have nephroprotective effects. The most important actions of estrogen hormones are represented by the protective effects attenuating glomerulosclerosis and tubulointerstitial fibrosis. Estrogens exert favorable effects on renal osteodystrophy via an improvement of phosphorus-calcium transport equilibrium in renal

tubules [86]. Recently, a meta-analytic study supported that oral contraceptive use may reduce the risk of kidney cancer in women, especially for long-term users [87].

6.6 Cardiovascular system

Premenopausal women have a much lower incidence and prevalence of cardiovascular diseases (CVDs) compared to men of the same age [88]. This sex difference in favor of women suddenly disappears after menopause, suggesting that reduced levels of ovarian hormones constitute a major risk factor for the development of CVD in postmenopausal women.

In central obesity, the associated insulin resistance results in a compensatory high insulin and IGF-1 synthesis stimulating ovarian androgen production at the expense of reduced estrogen synthesis [89]. Hyperinsulinemia promotes adrenal androgen synthesis as well by means of an increased adrenal sensitivity to adrenocorticotropin [90, 91]. Excessive androgen synthesis would provide precursors for an increased estrogen production; however, in insulin-resistant patients, gonads exhibit a decreased capacity to convert androgen to estrogen attributed to a reduction of aromatase enzyme activity [92].

Estrogens are cardioprotective hormones having crucial role in the maintenance of physiologic serum lipid levels. Postmenopausal hormone replacement therapy may reduce the risk of cardiovascular diseases via lowering total cholesterol, LDL cholesterol, and triglyceride levels [93]. Estrogens show antihypertensive activity as well. It is capable of downregulating the components of the renin-angiotensin system (RAS) [94]. Estradiol inhibits the excessive synthesis of vasoconstrictor endothelin and improves endothelial dysfunction [95]. In animal experiments, estrogen receptor-alpha mediated the protective effects of estrogen in response to vascular injury [96].

The risk of mortality for ischemic heart disease is highly increased in patients with left-sided breast cancer as they receive a higher dose of radiation therapy affecting the heart than patients with right-sided tumors [97]. This correlation may be explained by the destructive effect of radiation on the estrogen-synthesizing epicardial fatpad.

7. Secretory functions of abdominal adipose tissue in healthy lean and obese patients

Abdominal adipose tissue has crucial physiological secretory functions [47]. Sex steroids, adipokines, cytokines, and growth factors are important signaling molecules in adipose tissue and their well-regulated activation ensures the health of the whole body.

In central obesity, extreme fat accumulation and a concomitant insulin resistance of abdominal adipose tissue deteriorate all regulatory functions of adipocytes. Dysregulation of adipocyte signaling induces an alarm reaction in all adjacent visceral organs and they inform adipocyte ERs about their functional difficulties via signaling molecules. ERs in adipocytes recognize the emergency situation and may initiate the restoration of ER signaling through increased estrogen synthesis and enhanced liganded and unliganded activations of ERs [98].

7.1 Sexual steroids

In adipose tissue, suitable estrogen signaling regulates the expression of numerous genes and the harmonized synthesis of signaling molecules [67].

In adipocytes, androgen hormones are precursors for the local estrogen synthesis of aromatase enzyme.

7.2 Adipokines

Leptin regulates the energy balance in the hypothalamus exerting anorexinogenic and lipolytic effects. Estrogen treatment increases the expression of leptin receptors amplifying the leptin-sensitivity of various cells [99]. In aromatase knock-out (ARKO) mice, visceral adiposity develops and three times higher levels of circulating leptin were found as compared with control animals [100]. Adiponectin is involved in various inflammatory reactions, modulations of endothelial functions, and is protective against insulin resistance. Oophorectomy increases adiponectin levels in adult mice, while it may be reversed by estradiol substitution [101]. Resistin level increases in parallel with obesity, which may be a compensatory reaction instead of being a causal factor. In subcutaneous adipocytes, an estradiol benzoate injection decreases resistin levels [102].

7.3 Pro-inflammatory cytokines and low-grade inflammation

Pro-inflammatory cytokines are regulatory proteins having great role in the maintenance of genomic stability. In obese patients, strong inflammatory reactions and abundantly expressed signaling molecules occurring in voluminous fatty tissue are mistakenly considered as being causal factors of genomic dysregulation, insulin resistance and its comorbidities [6, 103].

Low-grade inflammation in abundant adipose tissue may be characterized by increased levels of inflammatory cytokines and macrophage and T-cell infiltration [104]. Inflammatory cytokines, including tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), may have not only local effects on adipose tissue but also exert systemic effects on several organs [105]. In adipose tissue, inflammatory cytokines have an important role in the upregulation of estrogen synthesis. Increased pro-inflammatory cytokine level generates an increased expression and activation of aromatase enzyme resulting in higher estrogen concentrations [106].

In ovariectomized mice on high-fat diet, estradiol treatment improved insulin sensitivity and glucose uptake in both adipose tissue and liver and at the same time, decreased the expression of inflammatory cytokines, included TNFα [71]. It was recently found that elevated levels of pro-inflammatory cytokines augment energy expenditure and counteract obesity from animal to human, justifying that pro-inflammatory cytokines have beneficial effects against obesity and obesity-related metabolic disorders [107].

In conclusion, in obesity, deficient estrogen signaling leads to dysregulation of abdominal adipocytes and induces a low-grade inflammatory reaction, while estrogen treatment improves adipocyte signaling function and exerts anti-inflammatory effect.

7.4 Insulin-IGF system

The insulin-like growth factor (IGF) system is involved in regulation and control of physiologic growth and differentiation. Insulin and insulin-like growth factor receptors act as ligand-specific amplitude modulators regulating genes on a common pathway [108]. In obesity, there was a nonlinear relationship of insulin-like growth factor (IGF)-I and IGF-I/IGF-binding protein-3 ratio with indices of adiposity and plasma insulin concentrations [109].

Crosstalks between signaling pathways of ERs and growth factor receptors (IGF-1R, EGFR, VGFR) are well known in both health and disease [110, 111].

Among physiological circumstances, estrogen-activated ERs are capable of either stimulating or silencing cell growth and proliferation, while in tumor cells, an upregulation of ERs is not a proliferative stimulus, but rather, it is an initiator of self-directed death [11].

The IGF system comprises insulin, insulin receptor (IR), IGF-1, IGF-2, each with its receptor (IGF-1R, IGF-2R) as well as the IGF-binding proteins (IGFBPs). Proteins of the IGF system are ubiquitously expressed at different sites included adipose tissue [13]. In the early phases of insulin resistance, an increased IGF-1 level mediates increased insulin synthesis resulting in a compensatory hyperinsulinemia.

Estrogens regulate both insulin-like growth factor 1 (IGF-1) synthesis and the expression of its receptor (IGF-1R) in adipocytes. In turn, an increased synthesis of IGF-1 and its receptor upregulates the AKT and MAPK pathways of growth factor signaling, providing a possibility for an increased unliganded activation of ERs [112]. In an estrogen-deficient milieu, unliganded activation of ERs via IGF-1 receptor signaling pathway exhibits a fundamental role in genome-wide expressions of estrogen-regulated genes [48]. In conclusion, in obesity and insulin resistance, an increased expression and activity of IGF-1 receptors may be a compensatory action against the dysregulation of adipocytes providing a possibility for the restoration of ER signaling.

7.5 Interaction between adipocytes and immune cells

Adipocytes are in signaling crosstalk with immune cells in both healthy and obese adipose tissue. In lean adipose tissue, IL-4 secreted by eosinophil granulocytes and regulatory T (Treg) cells activate M2 type macrophages, which express arginase and anti-inflammatory cytokines such as IL-10. In contrast, in obese adipose tissue, the number of pro-inflammatory immune cells is increased coupled with a decrease in that of anti-inflammatory immune cells [104]. In abundant adipose tissue, neutrophil granulocytes are early responders to inflammatory injuries stimulating both M1 type macrophage infiltration and pro-inflammatory cytokine secretion.

In animal experiments, estrogens are capable of improving metabolic disorders and, at the same time, they exert anti-inflammatory effects [72]. In female mice, estrogen protects from adipocyte hypertrophy and prevents adipose tissue oxidative stress and inflammation. Furthermore, estrogen treatment protected female mice against developing liver steatosis and from becoming insulin resistant.

In conclusion, in obesity, the experienced low-grade inflammation and the increased synthesis of cytokines and growth factors are not causal factors of insulin resistance and cancer development, but rather, they are compensatory efforts so as to restore ER signaling. Estrogen administration seems to be a causal therapy for obesity-related pathologic changes, as the upregulation of ER signaling protects from insulin resistance and decreases inflammatory reactions. Estrogen treatment would provide quite new ways for the prevention and cure of obesity and obesity-related inflammation.

8. Estrogen is protective against cancer

The apparently paradoxical effects of estrogens on both the prevention and promotion of cancers have been debated for over 120 years. However, the pharmaceutical development of endocrine disruptor antiestrogens could not provide appropriate advances in the field of anticancer fight [113].

The blockade of either estrogen-induced (liganded) or unliganded activation of ERs provoked a strong compensatory upregulation on the unaffected domain, while the unbalanced ER activation resulted in modest or even adverse tumor responses

and severe toxic symptoms [114]. In contrast, natural estrogens are capable of restoring DNA surveillance even in tumor cells leading to a self-directed death through a balanced liganded and unliganded transactivation of ERs, whereas they may not provoke genomic instability even in sky-high concentrations [115].

9. Conclusion

Changing concepts concerning the etiology of obesity and obesity-related diseases provide certain new strategies against these diseases.

Since estrogen-activated ERs are the chief regulators of the genomic machinery, a weakening or failure of ER signaling attributed to either genetic or environmental factors induces abundant compensatory actions for the restoration of appropriate estrogen signaling. When the restorative processes may compensate the regulatory failures, patients seem to be healthy. In contrast, when the compensatory reactions are insufficient, a deepening regulatory disorder develops and serious diseases may appear as clinical manifestations.

The causal factor of obesity is deficient estrogen signaling in both men and women; however, there is no direct correlation between obesity and cancer risk. All environmental and genetic cancer risk factors, included smoking, sedentary lifestyle, fat-rich diet, light deficiency, anovulatory infertility, and BRCA mutation strongly deteriorate estrogen signaling; however, they may or may not be associated with the development of obesity.

In certain cases, the weakness of estrogen regulation may induce abdominal fat deposition, and at the same time, the deepening insulin resistance of adipose tissue leads to further irreversible defects in expressions of estrogen-regulated genes. In obese patients, metabolic syndrome and type 2 diabetes are well-known risk factors for the two life-threatening disease groups of humans: cardiovascular lesions and malignancies, while the defect of estrogen signaling frequently remains unknown in the background.

In another group of patients, estrogen deficiency or ER resistance develops without obesity. Defective estrogen signaling exhibits a strong direct correlation with insulin resistance as estrogen regulates all steps of cellular glucose uptake in the whole body. Moreover, the deeper the defect of estrogen surveillance, the stronger is the risk for serious chronic diseases included type 2 diabetes, cardiovascular lesions, and cancers. The strong correlation is well known between anovulatory infertility and an increased cancer risk for female organs, while these associations are quite independent of obesity.

In patients showing central obesity, the increased cytokine secretion and the associated low-grade inflammation in their adipose tissue are not causal factors of the development of insulin resistance, but rather, they are compensatory actions for the activation of aromatase synthesis. Similarly, in abundant adipose tissue, the increased synthesis of growth factors included IGF-1 and the abundant expression of growth factor receptors are not efforts for initiating an unrestrained cell proliferation, but rather they provide unliganded pathways for increased ER activation so as to strengthen estrogen signaling.

In nonobese patients, deficient estrogen signaling is associated with high risk for premature arteriosclerotic complications and cancer development. In these cases, inflammatory reactions at several sites represent compensatory actions against estrogen deficiency via an activation of aromatase enzyme. Moreover, in patients with clinically diagnosed infertility, PCOS, or BRCA mutation, the increased serum estrogen levels are compensatory efforts against ER resistance instead of a harmful induction of pathologic cell proliferation. Patients with ER resistance may exhibit

an increased cancer risk in spite of hyperestrogenism, when the compensatory increased estrogen level is not sufficient for the breakthrough of ER blockade.

In conclusion, in obese patients, the causal therapy is the improvement of estrogen signaling in both men and women via estrogen substitution, changes in lifestyle, or use of natural products upregulating the genomic machinery. These therapies are equally protective against weight gain, metabolic disorders, inflammatory reactions, and obesity-related diseases including cancer. In obesity, medicaments working against the reparative, compensatory processes in the adipose tissue may induce strong counteractions via feedback mechanisms; however, the therapeutic results are transitory, ambiguous, and even dangerous.

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