Human Cancers Deriving from Either Genetic or Lifestyle Factors, Are Initiated by the Damage of Estrogen Signaling

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Review

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Abstract

Background. Genetic studies justified that germline *BRCA1* gene mutation is the origin of highly increased cancer risk. Clinical studies suggested that increased cancer risk in type-2 diabetes maybe attributed to unhealthy lifestyle factors and bad habits. **Purpose.** Patients with either *BRCA1* gene mutation or type-2 diabetes similarly exhibit increased cancer risk, insulin resistance and fertility disorders. It was suggested that these three alterations derive from a common genomic failure and its recognition may shed light on the unsolved secret of cancer. **Results**. 1. Germline mutations on *ESR1, BRCA1, and CYP19A* genes encoding estrogen receptor alpha (ERα), genome safeguarding BRCA1 protein and CYP19 aromatase enzyme, cause genomic instability. *BRCA1* and *ESR1* gene mutations cause particularly breast cancer, while the error of *CYP19A* gene leads to cancers in the endometrium, ovaries and thyroid. 2. ERα, BRCA1 and CYP19 aromatase proteins are transcription factors creating the crucial DNA stabilizer circuit driven by estrogen regulation. Liganded ERα drives a second regulatory circuit for controlling cell proliferation as well, in partnership with various growth factors. In a third regulatory circuit, liganded ERα drives cellular glucose supply in close interplay with insulin, IGF-1 and glucose transporters. 3. Weakening expression or activation of each transcription factor of the triad, leads to defective estrogen signaling and endangers regular cell proliferation, insulin sensitivity and fertility. 4. Weakening estrogen signaling caused by either genetic or lifestyle factor, is alarming for the hypothalamus and it sends neural and hormonal commands throughout the body so as to restoring estrogen signaling. 5. When the compensatory actions cannot restore estrogen guideline, the breakdown of genomic regulation leads to cancer initiation. 6. Lifestyle factors upregulating estrogen signaling, decrease, while downregulating estrogen signaling increases the risk for cancer. **Conclusion.** Increased cancer risk, insulin resistance and infertility all are originating from defective estrogen signaling.

Keywords: alcohol consumption; DNA damage; DNA repair; endocrine disruptor; estrogen; estrogen receptor; growth factor receptor; immune reaction; lifestyle factors; mutation; smoking

1. Introduction

Cancer is a major challenge globally, attributed to its rapidly increasing morbidity and mortality rates worldwide [1]. The mechanism of cancer initiation and progression is not exactly clarified until now and the results of enormous therapeutic efforts are fairly questionable.

According to the reigning opinion, cancer initiation derives from the incidence of oncogenic mutations that maybe either inherited, increasing the susceptibility, or acquired arising under harmful environmental exposure [2]. An accumulation of mutations in crucial genes presumably disrupt normal genomic regulation leading to unrestrained cell proliferation. The majority of cancers may develop through an unfortunate interaction between genetic predispositions and environmental influences [3]. Since only a small percentage of cancers exhibit solely inherited origin, small genetic

differences among individuals may define the response to environmental exposures leading to increased or decreased risk for cancer.

Analysis of a huge number of cancer genomes resulted in around 300 genes that were mutated in at least one type of cancers [4]. Thoroughly examining the features of oncogenic mutations, their accurate roles in cancer development were not clarified. Increased prevalence of certain somatic mutations in the genes of various cancers cannot justify their oncogenic impact, but rather a genome repairing effort maybe supposed [5].

Historically, the first causal factor for cancer affecting the female breast in particular was introduced at the end of the 19th century. The clinically observed pulsation of tumors parallel with the menstrual cycle mistakenly suggested that breast cancer growth maybe associated with the ovulatory peak of serum estrogen level. High concentration of estrogen hormone emerged as being a unique causal factor for premenopausal breast cancer. Surgical oophorectomy was applied as a causal therapy of breast cancer targeting ovarian estrogen synthesis [6]. Nevertheless, the regression of breast tumors via surgical estrogen withdrawal was modest and transient [7].

The absurdity of estrogen induced breast cancer and the therapeutic blockade of estrogen signaling has remained a gold standard for breast cancer care through centuries until today. The concept of estrogen induced breast cancer yielded further mistakes in cancer research and fairly held back the understanding of the key to human health and the development of cancer therapy [8].

In 1988, a causal factor for human diseases (and later for cancer) was introduced into the scientific world. Gerald Reaven established and popularized his concept in his Banting Lecture that a defect of insulin assisted glucose uptake, nominated as insulin resistance is the source of human diseases [9]. Insulin resistance was linked with a cluster of metabolic disorders and they were summarized as Metabolic Syndrome or Syndrome X. Metabolic syndrome is characterized by impaired glucose metabolism, high blood pressure, central obesity, and low HDL-cholesterol coupled with increased triglyceride levels [10].

In the early stage of insulin resistance, compensatory hyperinsulinemia maintains the blood glucose levels within the physiological range via stimulating the insulin secretion of pancreatic β-cells [11]. Advanced insulin resistance leads to metabolic syndrome, obesity and nonalcoholic fatty liver disease [12]. Type-2 diabetes develops, when the compensatory insulin synthesis cannot keep up with the insulin demand of insulin resistant target cells leading to hyperglycemia [13]. Thorough investigations equivocally revealed that insulin resistance is the underlying disorder for developing cardiovascular diseases and cancers, which are the leading causes of human mortality [14,15]. Since insulin resistance leads to various, quite different chronic human conditions, clarifying its origin seemed to be crucial for the recognition of the principal regulator of human genome.

Insulin resistant status shows gender related differences as men exhibit a fairly higher prevalence of metabolic diseases as compared to women. In addition, among women, premenopausal cases are protected from the defect of glucose uptake via their active hormonal cycles, whilst postmenopausal cases exhibit a quite similar incidence rate of insulin resistance like age matched man [16]. These gender and menopause related differences in the prevalence of insulin resistant cases led to putting forward that estrogen hormone has crucial role in glucose homeostasis and energy balance [17]. Moreover, estrogen deficiency or impaired estrogen receptor activation seemed to be a causal factor for insulin resistance and the development of metabolic diseases [18,19].

Gender related differences are conspicuous in the prevalence of cardiovascular diseases as well [20]. Healthy premenopausal women are typically protected from cardiovascular diseases and hypertension compared to age matched men suggesting protective effects of cycling estrogen hormone levels [21]. Estrogen plays a crucial regulatory role in the health of cardiovascular system [22]. After menopause, decreasing estrogen levels and the associated insulin resistance are important causal factors in the pathogenesis of atherosclerosis, myocardial dysfunction, cardiac hypertrophy, heart failure, and myocardial ischemia.

Pan-cancer analyses support that men in general show a higher cancer incidence and worse survival than women across most cancer types [23]. These sex-based differences in cancer incidence

are likely due to a combination of biological, environmental, and behavioral factors; however, a robust estrogen signaling in women seems to be protective against cancer. Oral cancer incidence shows conspicuous gender related differences [24]. Premenopausal women are highly protected from this tumor, while after menopause, estrogen loss is associated with a steeply increasing prevalence of the disease even in non smoker, non drinker cases.

Breast cancer incidence is significantly higher in postmenopausal women as compared with premenopausal cases showing increasing risk with age after menopause [25]. In postmenopausal women, the loss of estrogen increases the risk for type-2 diabetes and obesity and these chronic conditions are high risks for breast cancer.

During the fight against insulin resistance, clinical investigations revealed that certain lifestyle factors and bad habits may induce and worsen insulin resistance [26]. At the same time, positive life-style changes of patients and abandoning their bad habits are associated with surprising improvement in metabolic diseases and decreasing risk for cancer development [27].

Parallel with thorough investigations on the origin and progression of insulin resistance, there was a continuous fight against excessive estrogen signaling in breast cancer cases. Antiestrogens including estrogen receptor blockers and aromatase inhibitors were introduced against estrogen receptor positive (ER+) breast cancers [28]. Breast cancer therapy has remained a challenge until now as the half of targeted ER-positive breast cancers proved to be primarily non responsive to antiestrogen therapy. In addition, the earlier responsive tumors lost their responsiveness during the therapy [29]. This behavior of breast cancers was evaluated as primary and secondary therapy resistance. In reality, ER-positive tumors that are not responsive to the inhibitory therapy are not antiestrogen resistant. They are incapable of counteraction or exhausted in the fight against the genomic damage caused by the inadequate therapy [30].

The mechanism of insulin resistance induced oncogenesis has remained highly debated. Investigators follow the old erroneous theory suggesting that an increased concentration of certain molecular players and somatic mutations of their genes are causal factors for cancer initiation and progression. During the past decades, hyperinsulinemia [15], hyperglycemia [31], overexpression of proinflammatory cytokines [32] and increased growth factor signaling [33] were supposed as cancer initiators in insulin resistant cases. Although, the presence of these alterations is characteristic for insulin resistance, they may be regarded as compensatory efforts for restoring genomic functions, rather than facilitating cancer development [8].

This work introduces the defective estrogen signaling as the causal factor of cancer initiation and presents the wonderful genome-repairing efforts of healthy cells, tumor cells and the whole body in humans. These facts recommend that natural biotherapies are highly superior over the inhibition of genomic pathways and the blockade of immune responses.

2. Hyperinsulinemia Is Not the Predecessor of Insulin Resistance

There has been a continuous debate on the cause-effect relationship between insulin resistance and hyperinsulinemia; however, it can equivocally be established that their coexistence leads to serious chronic conditions and increasing mortality [34].

Until the beginning of the 21th century, insulin resistance itself was regarded as the origin of disorders leading to metabolic syndrome and type-2 diabetes, while the associated excessive insulin synthesis seemed to be a compensatory action helping cellular glucose uptake [35]. The origin of insulin resistance seemed to be variable, and the relative importance of each presumed causal factor has been under thorough investigation [36]. Searching for the causal factors of insulin resistance, authors focused on the role of inflammation, altered lipid metabolism, and the dysbiosis of gastrointestinal microbiota. Nevertheless, these factors are counteractions to insulin resistance, rather than being its initiators.

Recent studies established that hyperinsulinemia equivocally precedes insulin resistance becoming a causal factor for the defective glucose uptake, obesity, type-2 diabetes, cardiovascular diseases and cancer [37–39]. In PCOS (polycystic ovary syndrome) cases, hyperinsulinemia seemed

to be the predecessor of insulin resistance creating a self-generating circuit for worsening the reproductive and metabolic defects [40]. Nevertheless, the initiator of either insulin resistance or hyperinsulinemia remained quite obscure.

Recently, genetic background together with over-nutrition seems to be responsible for inducing hyperinsulinemia that shows primacy over insulin resistance. Hyperinsulinemia is regarded as a major driver for obesity, type-2 diabetes and the associated chronic conditions [41,42]. Presumably, energy rich food intake drives the increased insulin synthesis of pancreatic β-cells. Over time, β-cells become exhausted and high insulin levels cannot keep up with the insulin demand of resistant cells resulting in elevated blood sugar level and type-2 diabetes. It was supposed that hyperinsulinemia deregulates the balance of insulin-GH-IGF axis promoting lipid deposition coupled with low energy expenditure.

Development of type-2 diabetes via hyperinsulinemia is explained by a supposed interplay among insulin, GH and IGF-I [43]. Type-2 diabetes develops attributed to increased insulin levels of portal vein that increases liver sensitivity for growth hormone (GH). Liver increases insulin-like growth factor-1 (IGF-1) levels, which means a negative feedback on the hypothalamus decreasing significantly the GH levels. The low GH/insulin ratio stimulates lipogenesis and increases the body weight. Nevertheless, the limited regulatory axis of three molecular players is erroneously picked out from the whole regulatory network.

In clinical practice, diabetes treatment using insulin with high affinity for IGF-I receptors, improves the lipid profile, increases insulin sensitivity and helps glucose metabolism. [44]. IGF-I shows cardioprotective effects and improvement of insulin sensitivity in patients being after a myocardial infarct [45]. These results suggest that insulin and GH-IGF-I axis improve endocrine regulation and metabolic balance instead of disrupting them.

3. The Origin of Insulin Resistance Is a Defect of Estrogen Signaling, While Hyperinsulinemia Is a Compensatory Effort for Improving Estrogen Regulation

Since glucose supply is the prerequisite of cellular health being the fuel for all cellular functions, glucose deprival seriously affects the continuous work of the main regulatory circuits of ER alpha. These circuits control genome stabilization, cell growth/proliferation as well as glucose supply [46]. Insulin and IGF-I together are important players in the regulatory circuit of ERs controlling glucose supply and metabolic balance. A weakening ER expression/activation or low estrogen level upregulates compensatory insulin secretion leading to hyperinsulinemia that is an effort for the restoration of estrogen signaling, even when it is not successful.

Weakening estrogen signaling poses an emergency situation for mammalian cells by disrupting glucose and lipid metabolism and at the same time endangering DNA stability. The hypothalamus-hypophysis unit then sends neuro-endocrine signalings to the adipose tissue as commands for the upregulation of estrogen synthesis and ER activation. Restoration of estrogen signaling improves glucose uptake, metabolic homeostasis and energy expenditure in insulin resistant patients [47,48].

Insulin and estrogen (specifically 17β-estradiol) signalings work in synergism on the activation of glucose transporter 4 (GLUT4) by promoting its translocation to the plasma membrane [49]. Incorporation of GLUT4 into the plasma membrane allows the entrance of glucose into the cell. In estrogen deficiency, increased insulin level may exert a complementary effect on GLUT4 translocation facilitating cellular glucose uptake.

Insulin-like growth factor-1 (IGF-1) has a direct role on glucose uptake, working in partnership with insulin, particularly in peripheral sites like adipose tissue and muscles [50]. IGF-I promotes glucose uptake by activating its own IGF-I receptors and hybrid receptors reacting to both IGF-I and insulin receptors (IRs). Amplified insulin levels facilitate IGF-I signaling and at the same time IGF-I activation increases the unliganded activation of membrane associated ERs closing the regulatory circuit [30].

Low grade inflammation is a characteristic finding in insulin resistant adipose tissue. Insulin and IGF-1 signaling have complex regulatory effects on the development of inflammation. In healthy adipose tissue, they are acting as anti-inflammatory agents. Conversely, in insulin resistance, including obesity and ageing, paralelly increased insulin and IGF-1 signalings promote inflammation [51]. In insulin resistance, macrophages and immune competent cells recruit for increasing pro-inflammatory cytokine expression, facilitating aromatase enzyme concentration and estrogen synthesis [52]. When estrogen concentration can reach an appropriate level, estrogen signaling improves cellular glucose uptake. Restored glucose uptake silences the inflammation and lowers estrogen concentration [8]. In insulin resistant adipose tissue, the inflammation continuously remains low grade as estrogen level cannot achieve suitably high concentration for the improvement of glucose uptake.

Estrogen and insulin show a close interplay in regulating the balance of lipolysis/lipogenesis. In insulin resistance, the defect of estrogen signaling liberates free fatty acids (FFAs), while hyperinsulinemia cannot exert its powerful anti-lipolytic effect [53]. In obesity, abundant FFAs in the circulation are pathologically deposited in non adipose organs and tissues; such as liver, pancreas, skeletal muscles and heart [54].

In postmenopausal women, estrogen deficiency decreases the body's ability to oxidize (burn) lipids, leading to insulin resistance and fat accumulation. In obesity, weak estrogen signaling in the background leads to a dysregulation of fatty acid metabolism and visceral lipid deposition [55]. Phosphodiesterase 3B (PDE3B) is an enzymatic hydrolyser of cAMP and cGMP pathways in partnership with estrogen. They are co-regulating the key metabolic actions of estrogen: lipolysis, energy homeostasis and insulin secretion. Using a pharmacological blockade of AKT phosphorylation and PDE3B expression promoted lipolysis even in the presence of insulin [56]. These findings support that in insulin resistance, an estrogen deficiency induced damage of AKT and PDE3B pathways inhibit the antilipolytic action of insulin in spite of its high concentrations.

Takeuchi et al. published in Nature that in humans, increased carbohydrate metabolism by the gut microbiota contributes to the development of insulin resistance [57]. In insulin resistant patients, increased fecal carbohydrate content associated with microbial metabolism and the inflammatory cytokines of patients showed strong correlations. Recently, it was established that gut bacteria associated with insulin sensitivity and insulin resistance, exhibit different patterns of carbohydrate metabolism [58]. Bacteria associated with insulin sensitivity, improved the insulin resistance in a mouse model.

Unique bacterial components of the gut microbiome nominated as estrobolome, play a crucial role in the reactivation of inactive, bound estrogens helping the maintenance of insulin synthesis in the pancreatic β cells [59]. Inactive, conjugated estrogens are arriving from the liver via bile secretion and bacteria of the estrobolome showing high β-glucuronidase activity, may reactivate them in the gut. In conclusion, the accumulation of gut bacteria with high β-glucuronidase activity improves insulin sensitivity via increasing the levels of bioactive estrogens. In postmenopausal women, a partnership was observed between estrogen deficiency and dysbiosis of gut bacteria leading to the development of type-2 diabetes [60].

Recently, gut bacterial sequences were found in healthy brain samples suggesting that there is a microbiome in the brain [61]. Considering the importance of high β-glucuronidase activity in the gut, it can be presumed that intestinal bacteria reactivate conjugated estrogens in the brain as well, increasing the levels of bioactive estrogen.

Mitochondrial dysfunction is important finding in insulin resistance. Dysfunction of mitochondria leads to decreased β-oxidation, low ATP creation and increased ROS production [62]. Estrogen maintains mitochondrial function by affecting mitochondrial respiration, mitochondrial biogenesis, and mitochondrial quality control [63]. Insulin and estrogen signaling come together on Sirt1, mTOR, and PI3K signaling pathways in the joint regulation of autophagy and mitochondrial metabolism [64]. In insulin resistance, hyperinsulinemia is an effort for compensating the lack of estrogen regulation on mitochondria.

In conclusion, estrogen signaling as the chief regulator of metabolic processes shows strong interplay with insulin and IGF-I and with other molecular players participating in the control of glucose uptake. Weakening estrogen signaling leads to a failure of glucose uptake, while recruits insulin and IGF-1 for restoring the regulation of glucose and lipid metabolism. In crisis situations, growth factor receptors including IGF-1 receptor are capable of the unliganded activation of ERs.

4. The Defect of Estrogen Signaling Is the Origin of Genomic Instability and Insulin Resistance in BRCA Gene Mutation Carriers

The identifications of *BRCA1* and *BRCA2* genes were enormous steps in cancer research [65,66]. The products of these genes, BRCA1 and BRCA2 proteins proved to be safeguards of genomic integrity controlling transcriptional processes, DNA replication and recombination as well as the repair of DNA damages [67].

Inheritable mutations of *BRCA1* and *BRCA2* genes led to an increased risk of hereditary cancers via genomic instability particularly in the female breasts and ovaries [68,69]. Well functioning BRCA proteins exhibit pivotal role in the genomic stability of all cell types in men and women. Nevertheless, the specific risk for breast cancer development in *BRCA1* mutation carriers, mistakenly suggested an excessive estrogen signaling in the background.

The receptor landscape of *BRCA1* mutant breast cancers show typically ER-alpha negativity and histologically they are poorly differentiated, while clinically they exhibit a rapid growth and poor prognosis [70]. The vast majority of *BRCA1* mutant cancers are ER-alpha negative and ER-PR-HER2 negative (triple negative), being apparently independent of estrogen regulation [71,72]. In non familial, sporadically occurring ER-alpha negative breast cancers, a decreased expression of BRCA1 protein and reduced ER-alpha mRNA level reflect a defective interplay between the two regulatory proteins [73]. These findings reveal that *BRCA1* gene mutation inhibits the transcriptional activity of ER-alpha via weakening its liganded activation. In *BRCA1* mutation carriers, weakening estrogen signaling causes increased risk for cancer development, metabolic diseases and sex hormone imbalance with infertility [46].

In *BRCA1* mutation carriers, decreased estrogen signaling may be the origin of ER-negative and TNBC type tumors, instead of excessive estrogen activation [74]. The conspicuous prevalence of breast cancers among *BRCA1* mutation carrier women may be explained by the unique demand of female breast for the balanced liganded and unliganded ER activation. In postmenopausal women with type-2 diabetes and obesity, estrogen loss increases the metabolic and hormonal imbalances leading to increased risk for TNBC development.

Molecular investigations tried to reveal the key to interactions between ER alpha and BRCA1 proteins. Wild type BRCA1 protein could suppress the transcriptional activity of ER alpha [75] inhibiting near all genes that are regulated by estrogen [76]. BRCA1 could inhibit ER acetylation conferred by p300 that is crucial for ER transactivation [77]. Conversely, BRCA1 protein could induce an upregulation of p300, which is a coactivator of ER alpha [78]. Similarly, BRCA1 was capable of facilitating Cyclin D binding to ER alpha that upregulated the transcriptional activity of ERs [79]. These ambiguous findings suggest a complex interplay between BRCA1 and ER alpha signalings.

BRCA and ER proteins are also capable of direct binding for regulation of each other's activation [80]. In reality, a decreased expression or inactivation of either ER alpha or BRCA1 protein deregulates their interaction, jeopardizing both estrogen signaling and genomic stability [46]. Healthy BRCA1 upregulates ER alpha activation via amino-terminus binding; however, its carboxyl-terminus binding confers repressive effect on ER alpha.

In healthy breast cells with *BRCA1* gene mutation, BRCA1 protein synthesis is low together with decreased expression of ER alpha mRNA and ER alpha protein [81]. In *BRCA1* gene mutation carrier breast cancer cells, the liganded activation of ERs was decreased [75] and ER alpha also showed a decreased expression [82].

Molecular investigations revealed that both healthy and tumor cells carrying *BRCA* mutation, are intelligent and respond to the danger of estrogen defect via driving the regulatory circuits of ERs

through different pathways [5]. *BRCA1* mutation promotes an increased expression of epidermal growth factor receptors (IGFs) in healthy epithelial breast cells [83]. In *BRCA* mutation carrier cells, increased growth factor receptor signaling and P13K/Akt cascade activated ERs via an unliganded manner [84]. In fibrous adipocytes of the breast, BRCA protein defect facilitates increased estrogen synthesis choosing the PII promoter region on aromatase gene [85]. In mammary luminal progenitor cells with BRCA protein deficiency, a further coactivator of ER alpha, nuclear factor kappaB (NF-κB) showed persistent activation [86] as a compensatory effort for the improvement of estrogen signaling.

In ovarian tumor cells with BRCA protein deficiency, ER alpha showed an unusual, conspicuously high unliganded transcriptional activity [87]. In a *BRCA* mutation carrier tumor cell line, increased activation of p300 (an ER coactivator) facilitated the transcriptional activity of ERs [78]. In breast cancer cells having *BRCA* gene mutation, Cyclin D1, another activator of ER transcription was highly expressed [88].

Mutant variants of p53 (genome safeguarding protein) were observed in the luminal cells of healthy breasts in *BRCA* mutation carriers [89]. Mutant *TP53* gene was found in both familial and sporadic TNBC type tumors. These findings support that in germline *BRCA* mutation carriers, somatic mutation of *TP53* maybe an effort for replacing the lost genome safeguarding function of BRCA protein.

In *BRCA* gene mutation carrier women, anovulatory infertility frequently occurs [90] attributed to the weakness of liganded estrogen signaling. Early menopause caused by ovarian failure is a feature finding in *BRCA* mutation carriers [91]. In the majority of women with *BRCA1* mutation, the lack of functional BRCA1 protein was associated with compensatory increased aromatase levels and abundant estrogen synthesis [92]. In *BRCA* gene mutation carriers, defective ER signaling promotes insulin resistance; however, compensatory high levels of insulin and IGF-1 are not successful in the improvement of glucose uptake [74].

Development of central obesity and metabolic syndrome are markers of insulin resistance that correlate with a higher penetrance of *BRCA* mutation [93]. *BRCA* mutation associated damage of estrogen signaling disturbs not only genomic stability but also further regulatory circuits of ERs including those for glucose and lipid metabolism [46].

In conclusion, genomic instability is originated from the defect of liganded ER activation, rather than from an excessive estrogen concentration. In addition, both healthy and tumor cells have protective efforts against genomic damages through rising estrogen signaling via gene amplification and activating mutations. In *BRCA* mutation carrier women, the defect of liganded ER activation explains metabolic and fertility disorders and the increased risk of breast cancer.

5. Polycystic Ovary Syndrome Originates from the Disruption of Estrogen Signaling via CYP19A Gene Mutation

In premenopausal women, having functioning ovaries, polycystic ovary syndrome (PCOS) is the manifestation of insulin resistance syndrome. PCOS presents in adolescent girls with multiple ovarian cysts, menstrual disorders, anovulatory infertility and hirsutism besides metabolic syndrome and obesity [94]. These findings suggest a failure of genomic estrogen regulation. In young men with insulin resistance, a damage of semen quality and infertility may be found in the background of the predominant metabolic alterations attributed to the defect of estrogen signaling [95].

In PCOS, the defect of neuro-hormonal signaling along hypothalamic-pituitary-gonadal axis deregulates the whole hormonal system [96]. In PCOS cases, the glucose uptake of cells is defective, and insulin resistance leads to compensatory hyperinsulinemia as an effort for improving the glucose supply of cells [97]. In vitro studies revealed that high insulin level may augment both basal and LH stimulated androgen synthesis in ovarian theca cells leading to hyperandrogenism in women with PCOS [98].

Development of cystic ovaries is a characteristic symptom in women with genetically defined serious defects of estrogen signaling, caused by a mutation of *CYP19* aromatase or *ESR1* gene [99,100]. In aromatase deficient girls with *CYP19* aromatase gene mutation, cystic ovaries and delayed bone

maturation develop during childhood. At puberty, primary amenorrhea, failure of breast development, virilization, and hypergonadotrophic hypogonadism may be experienced [99]. In women with PCOS, the increased androgen synthesis of ovaries and adrenal glands is a compensatory answer to low estrogen levels; however, there is no conversion from androgen to estrogen attributed to aromatase deficiency [100].

The germline mutation of *ESR1* gene, encoding ER alpha, resulted in deep estrogen resistance, delayed puberty and polycystic ovaries in a young girl [101]. Despite the compensatory sky-high serum levels of estrogen, the absence of breast development, small uterus and enlarged polycystic ovaries revealed missing estrogen signaling. ER resistance repressed the insulin assisted uptake of glucose and hyperinsulinemia was observed as a counteraction to deepening insulin resistance.

Women with PCOS clearly exhibit a higher risk for early cardiovascular diseases, attributed to their metabolic dysfunction and abnormal hormonal pattern [102]. In PCOS cases, increased risk for clotting disorders and low fibrinolytic activity is a characteristic feature promoting the development of thrombotic complications [103]. In women with PCOS, immune responses are dysregulated. Insulin resistance and hyperandrogenism are associated with immune cell dysfunction and cytokine imbalance leading to long term inflammatory environment [104]. In PCOS cases, all these complications and co-morbidities are associated with the defect of aromatase synthesis and decreased estrogen signaling.

In women with PCOS, an increased risk maybe observed for gynecological tumors. Increased prevalence of endometrial, ovarian and thyroid cancers was found in PCOS cases [105]. Endocrine disorders with anovulatory infertility including PCOS are associated with highly increased risk for endometrial cancer [106].

Recently, PCOS studies in humans and rodents revealed that a disruption of estrogen signaling is highly associated with the development of the syndrome [107]. These experiences led paradoxically to the therapeutic targeting of estrogen by using antiestrogen clomiphene or aromatase inhibitor letrozole therapy so as to induce ovulation [108]. Fortunately, the inhibition of an earlier defective estrogen signaling provokes extreme counteractions abruptly upregulating both estrogen synthesis and ER activation, which explains the achievement of good pregnancy outcomes.

6. Estrogen Is the Principal Regulator of All Cellular Functions in Mammalians

Estrogens (estrone, estriol, and estradiol) are unique hormones, as they have no harmfully high concentrations like other hormones [46]. Activated estrogen receptors (ERs) can choose from several genes for expression and activation and at the same time they may facilitate or silence the regulatory processes using their coactivators or corepressors. Enormous upregulation of estrogen signaling is necessary for ovulation and during pregnancy for the growth of the uterus and for embryonic development. Conversely, the low level of estrogen or the defect of ER activation is an emergency situation as it leads to genomic deregulation throughout the body in men and women.

ERs have possibilities for liganded (estrogen bound) activation through their activation function-2 (AF2) domain and for unliganded activation by transduction molecules, such as growth factor receptors (GFRs) through the ancient activation function-1 (AF1) domain [109] (Figure 1). In estrogen deficient periods, increased growth factor receptor (GFR) expression and activation may transiently maintain the appropriate ER activation via unliganded pathway [110,111]. Balanced liganded and unliganded activation of ERs stimulates estrogen synthesis and ER expression ensuring DNA stabilization and upregulation of the whole genomic machinery [112]. Artificial inhibition of either liganded or unliganded activation of ERs induces a strong compensatory upregulation of the unaffected domain, while the failure of restorative efforts may lead to a breakdown of the whole genomic regulation.

The genomic machinery is driven by estradiol (E_2) activated ERs via stimulating and silencing all physiological pathways through regulatory circuits [113]. The main regulatory circuits of ERs control DNA stabilization, cell proliferation and cellular glucose supply. Activated ERs harmonize all physiological actions via balanced upregulation or downregulation of its regulatory circuits. The

upregulation of estrogen signaling is always reparative effort aiming the restoration of defective genomic functions
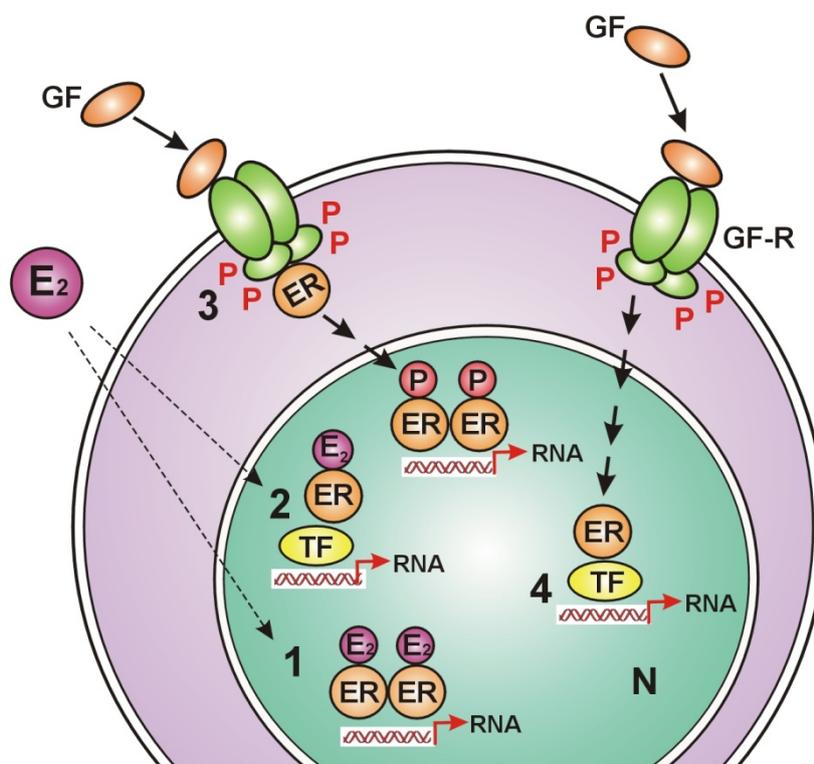
Figure 1. Liganded and unliganded activation possibilities for estrogen receptors. 1. Liganded estradiol (E_2) activated estrogen receptors (ERs) bind directly to the gene promoter region. 2. E_2 activated ERs bind indirectly to the gene promoter region, through transcription factor (TF). 3. Growth factor (GF) activated growth factor receptors (GF-Rs) activate membrane associated ERs that can further activate nuclear ERs, bound to the gene promoter region. 4. GF activated GF-Rs activate nuclear ERs through TF, bound to the gene promoter region. P: phosphorylation, RNA: ribonucleic acid, N: nucleus.

The principal regulatory round of ERs is the *circuit of DNA stabilization* [46]. It initiates with the estrogen activation of ER alpha and then inducing upregulation of further ER expression. Abundant activated ERs work via upregulation of genome safeguarding protein, such as BRCA1. The transcription proteins, ER alpha and BRCA1 are in close interplay via direct binding and they are capable of either rising or silencing each other's activation. BRCA1 is responsible for the balance between ER alpha expression and aromatase enzyme activation. When ER alpha expression or its activation is weakening, BRCA protein facilitates aromatase enzyme expression and activation leading to compensatory increased estrogen synthesis [114]. In conclusion, the ^{E_2}ER – BRCA – aromatase – E2 – ^{E_2}ER circuit ensures the continuous maintenance of both genome stabilization and estrogen signaling.

In the *regulatory circuit of cell proliferation* estrogen activated ERs drive and control the cell growth and proliferation at all sites of the body in strong interplay with growth factor receptors: epidermal growth factor receptors (EGFRs) and insulin-like growth factor-1 receptors (IGF-1Rs) [111]. Estrogen activated ERs control the expression and activation of growth factors (GFs) and growth factor receptors (GFRs). Transduction of growth factor signal (GFS) induces kinase cascade pathways sending further unliganded activation to nuclear ERs [30]. Low estrogen level is an emergency state leading to increased expression/activation of GFRs and compensatory unliganded activation of ERs.

In tumors, a therapeutic inhibition of estrogen signaling activates growth factor kinase cascades providing a compensatory stimulation of ER activation through unliganded pathway.

In the *regulatory circuits of glucose supply,* estrogen drives and controls all steps of cellular glucose uptake and glucose homeostasis [115]. Estrogen safeguards the vitality of pancreatic islet cells protecting them from lipid deposition [116]. Estrogen controls insulin expression, activation and secretion [117]. Estrogen controls insulin assisted glucose uptake through helping the expression and translocation of intracellular glucose transporters (GLUTs) [118]. Defects of glucose uptake always reflect the failure of estrogen signaling in the background [100].

7. Adipose Tissue Ensures Metabolic Balance and Energy Homeostasis via Estrogen Regulation

Circulating estrogen regulates body fat distribution, remodeling, and the maintenance of adipose tissue health [119]. Males tend to accumulate adipose tissue in visceral location promoting metabolic disorders and increasing the risk for chronic conditions like cardiovascular diseases and cancers. In contrast, females show inclination to the deposition of subcutaneous fatty tissue in the gluteofemoral region that is not associated with metabolic disorders. After menopause, estrogen loss is associated with male-like abdominal deposition of fatty tissue in women, becoming similarly endangered by metabolic disorders like men [120].

Adipose tissue mass is an estrogen regulated endocrine organ that exhibits the highest activity of estrogen synthesis among extragonadal sites [121]. Circulating and locally produced estrogens exert their regulatory effects locally on growth, metabolism and estrogen signal of adipocytes in an intracrine manner. In addition the hormonal regulation and energy supply is extended to the adjacent organs and tissues in a paracrine manner [122]. Adipose tissue health maintenance is regulated chiefly by estrogen in partnership with other hormonal and neural signalings [123].

Estrogen exerts its regulatory effects on estrogen responsive adipocytes depending on the intensity of their receptor expression [124]. Estrogen signaling regulates glucose metabolism, lipolysis/lipogenesis [48] and energy balance [125,126] in the whole body. In adipose tissue, defects of estrogen signaling result in deregulation in all regulatory functions of adipocytes leading to metabolic disorders, obesity and chronic conditions in the fat regulated organs and tissues [18].

Subcutaneously positioned fatty tissue supplies energy and estrogen regulation for the skeletal muscles and skin. The abdominally located visceral adipose tissue surrounds and nurses the visceral organs, gonads and cardiovascular structures [127]. Female breasts and the bone marrow enjoy extremely good energy supply as breast lobules and bone marrow cell populations are closely intermingled with abundant adipose tissue. Female breasts require strict hormonal regulation and high energy supply parallel with the hormonal changes of menstrual cycles [128]. In the bone marrow, adipocytes are actively influencing the proliferation and functional activity of hemopoietic and immune competent cells via their estrogen signaling and hormonal secretome [129]. Bone marrow fat supplies energy and regulatory command for the bones as well.

Abdominal adipose tissue has crucial physiological secretory functions [130]. The secretory activities of adipose tissue are defined by its estrogen supply and estrogen sensitivity [119]. Suitable estrogen signaling ensures the health and functional activity of adipocytes. Visceral fat as a central endocrine organ regulates metabolic balance, vascular health, appetite, body weight, and immune system among many others [131].

Sexual hormones, adipokines, cytokines and growth factors are important signaling molecules in the adipose tissue and their estrogen regulated activation ensures the health of the whole body. In postmenopausal women and men, the vast majority of estrogens are produced from circulating adrenal androgens via conversion by aromatase enzyme [132]. In addition, adipose tissue is capable of synthesizing sexual steroids locally, de novo from cholesterol. In adipose tissue, estrogen synthesis and appropriate estrogen signaling regulates the expression of numerous genes and the harmonized synthesis of various signaling molecules [123].

Adipokines are regulatory hormones secreted by the adipose tissue in health and disease. Circulating leptin ensures the energy balance in the hypothalamus through anorexinogenic and lipolytic effects. Estrogen increases the expression and activation of leptin receptors increasing the leptin-sensitivity of different cells [133]. Adiponectin improves insulin sensitivity silencing inflammatory reactions, and restoring endothelial functions. In adult mice, oophorectomy facilitates adiponectin synthesis, while estradiol substitution restores the normal levels [134]. Resistin is an anti-obesity hormone showing paralelly increased levels with weight gain. Estradiol benzoate treatment decreased resistin levels in subcutaneous adipose tissue [135].

Ghrelin is a multifaceted hormone secreted by gastric and intestinal cells showing endocrine function. Ghrelin is known as the hunger hormone, increasing growth hormone release, food intake and fat storage, when the stomach is empty [136]. Estrogen regulates ghrelin secretion and ghrelin receptor activation controlling ghrelin effect on appetite, energy balance, and metabolic changes [137].

In conclusion, estrogen signaling controls all hormones regulating appetite, hunger, food intake and fat deposition. Weakening ER activation or estrogen deficiency obviously disturbs the balance of food intake and energy expenditure promoting weight gain and the development of obesity. .

Estrogen deficiency and/or ER resistance deregulates all signaling functions of adipocytes. Adipocytes, losing their ER expression and estrogen synthesizing capacity, exhibit an excessive lipid deposition, parallel with becoming insulin resistant [138]. Considering that weakening estrogen signaling endangers DNA stability as well, abdominal obesity is not the origin of cancer development in visceral organs, but rather defects of estrogen function is the common initiator of both obesity and cancer.

In obese adipocytes, lipogenesis become predominant over lipolysis and deepening estrogen deficiency strengthens this imbalance. In thin stromal adipose cells, increased insulin levels stimulate aromatase expression and estrogen synthesis [139]. This observation justifies that in obesity, increased insulin and IGF-1 levels exert anti-obesity effects via facilitation of estrogen synthesis. Regulatory defect of obese adipose tissue promotes further disorders in the adjacent insulin resistant organs, resulting in serious co-morbidities, such as metabolic disorders, fatty degeneration and malignancies [140,141].

In health and disease, adipose tissue produces inflammation regulating cytokines that are regulatory proteins having great role in either anti-inflammatory or pro-inflammatory activities. Cytokines are secreted by adipocytes, fibroblasts and immune competent cells within the adipose tissue influencing systemic metabolic and immune functions [142].

In obesity, adipose tissue mass exhibits low grade inflammation with abundant macrophages and T-cells [143] targeting the improvement of glucose uptake. Macrophages produce proinflammatory cytokines, including tumor necrosis factor alpha *(TNF-α)* and interleukin-6 (IL-6). Proinflammatory cytokines drive increased expression and activation of aromatase enzyme leading to augmented estrogen synthesis [144]. In obese adipose tissue, overexpression of ER alpha increases estrogen sensitivity of fat adipocytes, silences inflammation, rapidly promotes lipolysis and improves the signaling function [145].

Estrogens have pivotal roles in the improvement of metabolic dysfunctions via orchestrating inflammatory changes and immune responses [131]. Low grade inflammation in obese, insulin resistant fatty tissue is a compensatory process for improving the regulatory capacity of adipocytes via increasing aromatase expression and estrogen concentration [5].

Dense inflammatory reaction in the vicinity of HER2-rich and TNBC type breast tumors is an effort for facilitating aromatase expression and estrogen synthesis helping the regulatory improvement of these poorly differentiated cancers [8]. In case of ER positive, highly differentiated breast cancers, immune competent cells are not recruited as the adjacent adipocytes increase their estrogen synthesis, helping the genomic repair of tumors. Conversely, the tamoxifen blockade of ER positive tumors activates a neighboring inflammation, which is a compensatory response to the sudden inhibition of estrogen signaling.

Adipocytes synthesize insulin like growth factor 1 (IGF-1) as well and they exhibit IGF-1 receptor expression (IGF-1R). IGF-1 signaling works within the growth hormone (GH)–IGF-I axis regulating growth, development, and metabolism in mammals, particularly during childhood [146]. GH, produced by the pituitary gland, stimulates the adipose tissue, liver and skeletal muscles for IGF-1 secretion. IGF-1 then acts directly on various tissues, including bone, muscle, and cartilage, to regulate protein synthesis, cellular growth and cell division.

IGF-1 shows regulatory functions on glucose and lipid metabolism in partnership with insulin and estrogen. IGF-1 regulates glucose and fatty acid uptake, improving insulin sensitivity and reducing body weight as it shares similar signaling pathways with insulin [147]. Increased IGF-1 levels paralelly augment insulin synthesis leading to compensatory hyperinsulinemia, in the early phase of insulin resistance [148]. IGF-1 is important player in the regulatory circuits of estrogen for controlling cell proliferation and glucose uptake [113].

In adipose tissue, estrogens regulate both IGF-1 synthesis and IGF-1R expression of adipocytes. Estrogen stimulated IGF-1 synthesis and IGF-1 receptor activation upregulate the AKT and MAPK pathways facilitating an increased unliganded activation of ERs [149]. In the absence of estrogen, IGF-1 receptor signaling maintains the unliganded activation of ERs ensuring a transient, genome wide expression of estrogen regulated genes [109]. In conclusion, in insulin resistance and obesity, an upregulation of IGF-1 signaling improves glucose uptake and helps the loss of body weight via increasing the unliganded activation of ERs.

Adipose tissue is a crucial organ in the regulation of immune reactions and immune defense [150]. It actively participates in host defense against pathogens and regulates the quality and intensity of inflammatory processes. In the adipose tissue, inflammation is a means for the improvement of genomic stability in metabolic diseases as well and provides help for tumors in their fight to achieve a self-directed apoptotic death [8].

Estrogen acts as a major regulator of the immune system, influencing the development, function, and activity of various immune cells, including lymphocytes, monocytes, macrophages, as well as T and B lymphocytes. Estrogen exerts these effects by binding to its specific receptors, which activate gene expression and signaling pathways modulating both innate and adaptive immunity [151].

There is a thorough interaction between adipocytes and immune competent cells, such as macrophages, T cells, and B cells in both healthy and obese adipose tissue [152]. In lean adipose tissue, eosinophil granulocytes show IL-4 cytokine secretion and regulatory T cells activate M2 type macrophages promoting the expression of arginase and anti-inflammatory cytokines including IL-10. Conversely, in obese adipose tissue, increased number of M1 type macrophages and abundant secretion of pro-inflammatory cytokines including TNFα and IL-6 may be observed [143]. In obese female mice, estrogen treatment improved insulin sensitivity, silenced the inflammation and reduced obesity [153].

In conclusion, insulin resistance and obesity equally originate from the defect of estrogen signaling. Estrogen loss inhibits glucose uptake and increases the lipid deposition of adipocytes weakening their regulatory functions. Heavily lipid laden deregulated adipocytes cannot control DNA surveillance, increasing the risk for cancer development in visceral organs.

8. Skeletal Muscle Contraction Improves Insulin Sensitivity via Rapid Unliganded Activation of ERs by IGF-1 Receptor

Physical activity is in strong correlation with human health. The skeletal muscle mass accounts for about 40% of the total body, and the regulation of its glucose metabolism has a crucial role in the glucose homeostasis of the whole body [154]. Regular exercise improves mental health, enhances the quality of life, and it is capable of improving existing chronic conditions including obesity and type 2 diabetes [155].

In skeletal muscles, glucose uptake is mainly insulin dependent at rest, while during exercise, glucose uptake is stimulated by muscle contraction and increased blood flow via insulin-independent pathways [156]. In resting muscle, insulin binding to its membrane receptor, triggers a cascade of

intracellular signalings culminating in the activation of GLUT4 that migrates to the plasma membrane and allows the entry of glucose. By contrast, muscle contraction induces changes in levels of intracellular molecules such as ATP and calcium, regulating GLUT4 translocation and glucose uptake, even in the absence of insulin.

Estrogen is the principal regulator of cellular glucose uptake and metabolism. Estrogens regulate pancreatic β-cell survival [116] and activate insulin biosynthesis and release [157]. Estradiol treatment facilitates GLUT4 expression and intracellular translocation to the plasma membrane [118]. Weakening estrogen signaling is an emergency state and requires compensatory efforts for the improvement of glucose supply.

Under estrogen regulation, IGF-1 signaling pathway is strongly linked to insulin signaling, working synergistically on muscle insulin sensitivity, growth, metabolism and overall health [158]. Insulin and IGF-1 signaling initiate a cascade activating IRS-1 and IRS-2 signaling proteins initiating downstream pathways of PI3-kinase and MAPK.

Estrogen treatment may stimulate a rapid cellular response within seconds to minutes through the activation of cell membrane associated ERs [159]. This rapid response avoids the time consuming transcription and translation processes that can take several hours or even one day. These membrane-located rapid ER responses work through the activation of kinases, calcium mobilization, and G protein cascades, promptly realizing different cellular functions.

The technique of rapid ER response to estrogen was studied on muscle cells and adipocytes [49,118]. Following estradiol treatment, a prompt translocation of ER alpha was observed from the nucleus to the cell membrane so as to interacting with membrane associated growth factors and fulfilling a rapid, non genomic signaling. The rapid response to estradiol facilitated GLUT4 expression and translocation to the plasma membrane improving glucose uptake in both muscle cells and adipocytes.

Facilitating the glucose uptake through a rapid response to estrogen may have a great importance in the physiology of mammalians as glucose shortage highly endangers the integrity and function of cells. In addition, a rapid activation of non-nuclear estrogen receptor signaling was observed conferring protection against vascular injury [160].

Contraction in muscles requires high energy utilization evoking a rapid translocation of ER alpha from the nucleus to the cell membrane, similarly, like under estrogen treatment. Along the cell membrane, IGF-1 receptors are accumulated waiting for unliganded estrogen receptors in an estrogen deficient milieu. ER alpha, arriving to the cell membrane gains rapid, non genomic activation from the IGF-1 receptor. Activated ERs induce increased expression and activation of GLUT4 vesicles and promote their migration to and incorporation into the cell membrane of muscle cells. Increased glucose entrance into the muscle cells explains the improvement of insulin resistance attributed to contraction. Membrane associated ERs activated by IGF-1 receptor exhibit further possibilities for the activation of nuclear ERs as well [Figure 2].
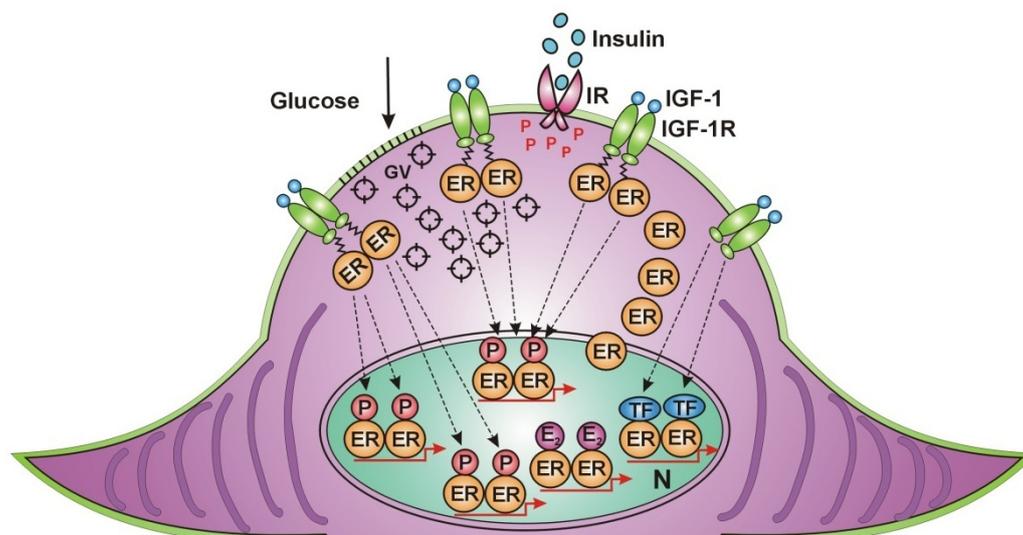
Figure 2. Skeletal muscle cell in contraction. 1. Estrogen receptors (ERs) are migrating from the nucleus to the cell membrane. 2. Insulin like growth factor 1 (IGF-1) activated receptors (IGF-1Rs) carry out rapid, unliganded activation on the arriving ERs. 3. Activated ERs induce GLUT4 expression and rapid translocation of GLUT4 vesicles (GVs) to the cell membrane. 4. The incorporation of GLUT4s into the cell membrane allows glucose entry into the cytoplasm. 5. Membrane associated, IGF-1R activated ERs may transfer their activation for the nuclear ERs. IR: insulin receptor, P: phosphorylation, E_2: estradiol, TF: transcription factor, N: nucleus.

The activation of the ER network in the huge mass of skeletal muscles explains the improvement of glucose uptake in the whole body in correlation with physical exercise.

9. Estrogen Regulation of Multitude Functions of the Liver

Liver development, integrity and functional activity are regulated by the neuro-hormonal signalings of hypothalamus-hypophysis system. GH/IGF-1 axis is one of the major regulators of liver as liver has a primacy in IGF-1 synthesis [161]. Moreover, estrogen hormones also are acting on the liver centrally, controlling the pituitary GH secretion and peripherally, by modulating GHR-JAK2-STAT5 signaling pathway [162]. Estrogens and GHs show thorough interplay in liver physiology, while a disruption of either GH or estrogen signaling leads to dramatic changes in the function of liver both during development and in adulthood.

Estrogen regulates directly the functions of liver as it expresses abundant ERα. Estrogen controls liver development, growth and regeneration [163] and regulates hepatic lipid and glucose metabolism [164].

In addition to the maintenance of hepatic health, estrogen signaling controls multitude functions of the liver influencing the regulation of the whole body. The liver is the major secretor of IGF-1, producing approximately 75% of circulating IGF-1, highly surpassing the IGF-1 synthesis of other tissues like adipose tissue and skeletal muscle [165]. This liver-derived IGF-1 behaves as an endocrine hormone, participating in the regulation of further tissues via distribution in the circulation. Conversely, in other tissues, locally secreted IGF-1 may function via paracrine and autocrine mechanisms.

Estrogen controls IGF-1 signaling pathways interacting in a complex manner in the regulation of glucose supply [166]. In turn, IGF-1 receptor is capable of unliganded activation of ERs via growth factor kinase cascades. This interplay between ER and IGF-1 receptor involves multiple levels, including their direct binding. Moreover, ER may modulate IGF-1 binding protein levels leading to increasing or decreasing bioavailability of IGF-1.

ER and IGF-1 receptor signaling interact in the protection of cardiovascular health. IGF-1 regulates cardiac development and improves the output, stroke volume, contractility, and ejection

fraction of heart [45]. In human studies, IGF-1 stimulates contractility and tissue remodeling improving heart function after myocardial infarction. Low serum levels of free or total IGF-1 lead to an increased risk of cardiovascular and cerebro-vascular diseases.

Endogenous estrogen is the chief regulator of the liver in balanced production of clotting and fibrinolytic factors. The liver synthesizes coagulation factors, anticoagulants, proteins involved in fibrinolysis and the platelet production regulator, thrombopoeitin, deriving from megakaryocytes [167]. In cirrhotic patients, hepatic dysfunction perturbs the clotting process [168]. The risk for thrombosis in patients treated with synthetic estrogen and/or progestin derives from pharmaceutical mistakes [112]. The production of chemically modified hormones, such as ethinylestradiol, and medroxyprogesterone results in a blockade of unliganded ER activation on AF1 domain and compensatory activation on AF2 domain. This regulatory imbalance leads to unforeseeable toxic effects of synthetic hormones in human practice.

Liver also have crucial roles in immune responses [169]. Hepatocytes exhibit immune functions via expressing pattern-recognition receptors (PPRs), secreting complement components and cytokines. Hepatocytes also show immunoglobulin secretory capacity.

In the liver, estrogen controls insulin sensitivity and glucose uptake via a balanced activation of glycogen synthesis and glycolysis. In animal experiment, ER alpha knockout mice showed insulin resistance parallely in the liver and skeletal muscles [170]. The hepatic lipid metabolism is regulated by estrogens. Estradiol treatment showed antidiabetic and antiobesity effects in mice kept on high fat diet. Estrogen decreased the expression of lipogenic genes in adipose tissue and liver, and suppressed the expression of hepatic G-6-Pase. Estradiol treatment in aged rats decreased the lipid peroxidation and improved the functional parameters of the liver [171].

In humans, estrogen has pivotal role in the hepatic regulation of serum lipid levels. In postmenopausal women, estrogen loss resulted in higher total and LDL cholesterol levels, and increased triglyceride levels compared to premenopausal women [172]. Menopausal estrogen therapy decreases the risk of cardiovascular diseases and this result maybe conferred by the advantageous changes of plasma lipid profile [173].

Insulin resistance in hepatocytes deregulates glucose metabolism, particularly the control of glucose output into the circulation. In insulin resistance, hepatic fatty acid synthesis becomes stimulated leading to hepatic steatosis. Type-2 diabetes is a significant risk factor for progressive hepatic steatosis, from non alcoholic fatty liver to hepatic cirrhosis [174]. Recent data show that type-2 diabetes and obesity are risk factors for hepatocellular carcinoma [175].

10. Hypothalamic Estrogen Signaling Is the Central Regulator of Somatic, Reproductive and Mental Health

The hypothalamus is situated in the ventral brain above the pituitary gland creating a central regulatory entity with it [176]. The hypothalamus exhibits integrative role in linking mental and somatic functions for well-being and adaptability. The hypothalamus continuously receives outer, environmental and internal stimuli from the body and answers by regulatory commands so as to maintain the internal balance.

Light signals arriving through the eye play a crucial role in visual perception but also evoke a non-image-forming vision by stimulating hypothalamic nuclei. The light-eye-body axis is a neuro-hormonal signaling network thoroughly influencing the genomic regulation of the entire body [177]. The hypothalamus regulates the hormone production of hypophysis and sends neural impulses through the autonomic nervous system. In the hypothalamus, estrogen is the chief coordinator between circadian system and gene expression/activation adapting all mental, somatic and reproductive functions to the changes of light and darkness in mammals [178].

Estrogen is the master regulator of bio-energetic systems in the brain and the body via hypothalamic activation [179]. Hypothalamus-pituitary unit exhibits interplay with sex steroids, modulating all neuro-hormonal signalings deriving from the central nervous system. Estrogen regulates cognitive functions by acting on the hypothalamus and other brain regions, promoting

synaptic plasticity and neuron survival through both genomic and non-genomic ER activation [180]. HPG axis driven regulation shows various links with stress signaling and their somatic impacts [181]. HPG axis regulates the immune system showing strong correlations between sex steroid activation and immune responses [182].

Hypothalamic estrogen signaling regulates adipose tissue metabolism and energy homeostasis via hypothalamus-pituitary adipose tissue (HPA) axis [183]. There is a gender-specific protection for females against metabolic diseases and increased disease susceptibility for males. Adipose tissue regulation is driven by the activation of estrogen receptor alpha (ERα) through neuro-hormonal interactions together with other hormones, particularly insulin and adipokines [119].

Hormonal and neural signalings arrive from all regions of the adipose tissue to the hypothalamus conferring their own energy homeostasis and those of various adjacent organs and tissues [184]. In certain hypothalamic regions, the loss of ER alpha positive cells results in obesity and fertility disorders. The hypothalamic arcuate nucleus (ARC) is widely recognized as a central regulator of appetite [185]. The complex hormonal network regulating appetite, hunger and food intake is under estrogen control [186].

Disrupted estrogen regulation of HPA axis contributes to the development of insulin resistance, metabolic syndrome, obesity and type-2 diabetes, as estrogen plays pivotal role in the regulation of metabolism and energy homeostasis of fatty tissue.

11. The Origin of Cancer Development by Unhealthy Lifestyle Factors and Bad Habits: A Defect of Estrogen Signaling and the Associated Insulin Resistance

Much of the burden of cancer may be associated with modifiable lifestyle factors that increase one's risk for the disease [187]. There are epidemiological evidences on the contributions of major risk factors to cancer incidence and mortality: tobacco use, alcohol consumption, unhealthy dietary patterns and physical inactivity.

Smoking habit. Tobacco use is the major cause of cancer among harmful lifestyle factors affecting several regions, such as oral cavity, digestive tract, upper respiratory tract, lung, urinary tract, cervix uteri and ovaries [188].

Smoking is linked with insulin resistance in a dose-dependent manner [189]. Smoking increases the risk for insulin resistance, mainly via deregulation of hormones participating in glucose uptake, and causing a shift to lipogenesis and lipid deposition promoting abdominal obesity [190]. Studies have demonstrated that in animal models and in human tissues, nicotine and its metabolites inhibit aromatase enzyme in a dose-dependent manner decreasing androstenedione conversion to estrogen [191] In smokers, nicotine inhibits aromatase enzyme expression and activity in the brain, negatively influencing some basic psychological activities, such as cognition, libido and appetite [192].

Summarizing the smoking associated insulin resistance and the aromatase inhibition of nicotine, the defect of estrogen signaling and the associated failure of glucose uptake may explain the strong cancer inducing capacity of tobacco use at several sites.

Alcohol consumption. Chronic, heavy alcohol consumption deregulates the glucose homeostasis and is associated with the development of insulin resistance [193]. Excessive alcohol consumption is an independent risk factor for type-2 diabetes [194]. Alcohol drinking is in close correlation with cancer development of oral cavity, pharynx, larynx, esophagus, [squamous cell carcinoma only], colorectum, liver [hepatocellular carcinoma only], and female breast [188].

Multiple molecular mechanisms contribute to cancer development mediated by drinking [195]. Acetaldehyde, deriving from ethanol metabolism is a potent carcinogen capable of inducing DNA damage and mutations. During alcohol metabolism, oxidative stress can damage cellular components, including DNA, proteins, and lipids, contributing to genetic mutations and genomic instability [196].

Alcohol abuse disrupts the hypothalamic regulation of endocrine system, affecting various hormones that regulate growth, metabolism, stress and reproduction leading to metabolic disorders, cognitive decline and infertility [197]. Alcohol upregulates aromatase activity and increases estrogen

levels in heavy drinker women that are presumably causal factors for their increased risk for breast and ovarian cancers [198]. In reality, increased aromatase activity and estrogen synthesis are compensatory actions in drinkers, against the inhibition of ERs and the developing insulin resistance.

The toxic, antiestrogenic effects of ethanol were studied on osteoblasts in female rats and on cultured osteoblasts in vitro [199]. Ethanol inhibited estrogen receptor signaling via the blockade of both ER alpha and ER beta activation, while estradiol treatment restored the health of osteoblasts. These results explain that in highly alcohol-exposed females, bone loss develops, while estrogen treatment exhibits protective effects.

The alcohol induced blockade of ER activation deregulates all genomic functions and increases the risk for several cancers in both men and women, in spite of the increased compensatory estrogen concentration, The aromatase inhibition of smoking and the ER blockade of drinking clearly explains the amplification of cancer risk in patients having smoking and drinking habits together

Unhealthy Dietary Patterns. Overeating and excess body weights are associated with increased risk for cancer in esophagus (adenocarcinoma only), gastric cardia, colorectum, liver, pancreas, endometrium, ovary, kidney, thyroid and female breast (postmenopausal cancers only) [200]. Interestingly, among premenopausal women, consistent inverse associations have been observed between obesity and breast cancer risk [201]. Overeating in premenopausal women with healthy hormonal balance, leads to gluteofemoral adiposity that is independent of metabolic disorders. It is not obesity but rather cycling estrogen levels and insulin sensitivity of abdominal adipocytes that protects obese young women from metabolic diseases and breast cancer [202].

The quality of diet is a significant factor in the development of insulin resistance. Studies show that a high-energy, high-fat, high-carbohydrate, and low-fiber diet as well as taking ultra-processed foods can increase the risk for type-2 diabetes [203]. Diet and nutrition seem to be modifiable risk factors for the development of several cancers, but the associations may be faulty due to inherent bias of investigations. [204]. It was established that only few single food or nutrient proved to be strongly or suggestively associated with cancer risk as tumor development is influenced by multitude genetic and environmental factors beyond the quality of diet.

Sedentary lifestyle. Sedentary behaviors have wide-ranging adverse impacts on the human body including high risks of metabolic disorders such as diabetes mellitus, and obesity, musculoskeletal disorders such as sarcopenia and osteoporosis, as well as depression and cognitive impairment [205]. Lack of physical activity increases the risk for cardiovascular diseases and cancers and raises the all-cause mortality in populations.

Physical activity is strongly linked to a lower risk of developing several types of cancer, including bladder, breast, colon, and lung cancer [206]. Regular exercise decreases cancer risk by maintaining a healthy weight, regulating hormonal balance particularly that of estrogen and insulin, and strengthening the immune system. Experimental studies show that physical activity improves insulin sensitivity through skeletal muscle contraction both immediately during exercise and for up to 48 hours afterward [207]. Muscle contraction is capable of increasing glucose uptake by a coordinated increase in microvascular perfusion and at the level of glycogen synthase.

Considering the crucial role of estrogen signaling in glucose uptake, muscle contraction may be associated with a rapid, non genomic ER activation facilitating glucose uptake. Muscle contraction improves insulin sensitivity via rapid, unliganded ER activation and regular exercise decreases the risk for cancer.

12. Conclusion

Oncogenic mutations are regarded as initiators of cancer development. Cancers with a strong family history may develop by inherited germline mutations, while bad habits and unhealthy lifestyle factors may presumably induce cancers conferred by somatic mutations.

Patients exhibiting either germline mutation or clinically diagnosed type-2 diabetes, similarly exhibit insulin resistance, fertility disorder and increased cancer risk. According to a new idea, it was

suggested that these strongly associated three alterations derive from a common genomic failure and its recognition may shed light on the unsolved secret of cancer.

Germline mutations on *ESR1, BRCA1, and CYP19A* genes encoding estrogen receptor alpha (ERα), genome safeguarding BRCA1 protein and CYP19 aromatase enzyme, similarly cause genomic instability and increased cancer risk. *BRCA1* and *ESR1* gene mutations cause particularly breast cancer, while the error of *CYP19A* gene leads to cancers in the endometrium, ovaries and thyroid.

ERα, BRCA1 and CYP19 aromatase proteins are transcription factors creating the crucial DNA stabilizer circuit driven by the estrogen activation of ERα. Estrogen bound ERα drives a second regulatory circuit as well, for controlling cell proliferation in partnership with various growth factors and kinase cascades. In a third regulatory circuit, liganded ERα drives cellular glucose supply in close interplay with insulin, IGF-1 and glucose transporters. In the DNA stabilizer circuit, aromatase produced estrogen completes the round via a liganded activation of ERα. In the second and third circuit, growth factor signalings complete the round via an unliganded activation of ERα.

Weakening expression or activation of each transcription factor of the triad; ERα, BRCA1 or CYP19 aromatase, leads to defective estrogen synthesis or estrogen refractory receptors. Any defect of estrogen signaling endangers together the regular cell proliferation, cellular glucose supply and reproduction. Estrogen regulated hypothalamus gathers the neuro-endocrine signals of the body and the environmental influences so as to ensure adaptive answers to the internal and external changes. Weakening estrogen signaling caused by either endogenous or environmental factor is alarming for the hypothalamus and it sends neural and hormonal commands for the whole body aiming the restoration of estrogen signaling.

In the first, compensated phase of defective estrogen signaling, patients are apparently healthy. Hyperinsulinemia is a whisper of the genome notifying about the successful restoration of estrogen signaling and glucose uptake at the expense of excessive insulin synthesis. Later, the strengthening defect of estrogen signaling and impaired glucose uptake result in metabolic syndrome with various symptoms: hypertension, obesity and laboratory findings showing defects in lipid metabolism. The compensatory low grade inflammation with pro-inflammatory cytokine expression and high levels of insulin and IGF-1 are warnings from the endangered genome having difficulties in the restoration of estrogen signaling and DNA stability. The deepening defect of estrogen signaling leads to type-2 diabetes. Serum glucose levels are increasing in spite of high insulin and IGF-1 levels and other compensatory actions. At the same time organs are suffering of the lack of glucose and excessive lipid deposition. The complete breakdown of estrogen signaling results in DNA damage and uncontrolled cell proliferation leading to cancer initiation in the affected organ. Cancer development is a cry of the genome asking for help that supports its combat against deregulation.

Human body maintains its integrity and functional activity via appropriate estrogen signaling. Advantageous lifestyle factors drive genomic machinery via the upregulation of estrogen signaling ensuring the maintenance of human health. Conversely, bad habits and unhealthy lifestyle slow down estrogen synthesis or inhibit ER activation endangering all genomic functions and leading to metabolic diseases, reproductive failures and increased cancer risk.

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