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Are the estrogen receptor and SIRT3 axes of the mitochondrial UPR key regulators of breast cancer sub-type determination according to age?

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Abstract

Aging is a major risk factor of developing breast cancer. Despite the fact that post-menopausal women have lower levels of estrogen, older women have a higher rate of estrogen receptor alpha (ERα) positive breast cancer. Conversely, young women who have elevated levels of estrogen tend to develop ERα negative disease that is associated with higher rate of metastasis. This perspective proposes a unifying model centered around the importance of mitochondrial biology in cancer and aging to explain these observations. Mitochondria are essential for the survival of cancer cells and therefore pathways that maintain the functionality of the mitochondrial network in cancer cells fulfill a critical role in the survival of cancer cells. The ERα and the mitochondrial sirtuin-3 (SIRT3) have been reported to be key players of the mitochondrial unfolded protein response (UPR^{mt}) [1–5]. The UPR^{mt} is a complex retrograde signaling cascade that regulates the communication between the mitochondria and the nucleus to restore mitochondrial fitness in response to oxidative stress [5–7]. SIRT3 is a major regulator of aging [8]. Its level decreases with age and single nucleotide polymorphisms (SNPs) that preserve its expression at higher levels are observed in centenarians [9,10]. We propose a model whereby the ERα axis of the UPR^{mt} acts to compensate for the loss of SIRT3 observed with age, and becomes the dominant axis of the UPR^{mt} to maintain the integrity of the mitochondria during transformation, thus explaining the selective advantage of ERα positive luminal cells in breast cancer arising from older women.

Graphical Abstract:

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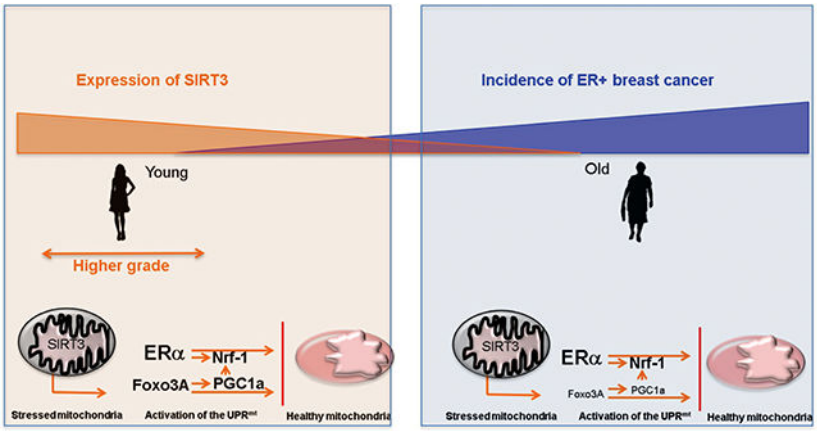

Aging is a major risk factor of developing breast cancer. Despite the fact that post-menopausal women have lower levels of estrogen, older women have a higher rate of estrogen receptor alpha (ERα) positive breast cancer. Conversely, young women who have elevated levels of estrogen tend to develop ERα negative disease that is associated with higher rate of metastasis. This perspective proposes a unifying model centered around the switch between the SIRT3 and estrogen receptor axes of the mitochondrial unfolded protein response with age to explain these observations.

Keywords

Breast cancer; SIRT3; estrogen receptor alpha; mitochondria; mitochondrial unfolded protein response; aged breast; aging

The association between age and the development of breast cancer is clearly indicated by the fact that 80% of breast cancers occur in women that are 50 years old or older [11–15]. This observation suggests that post-menopausal involution of the breast and/or cessation of ovarian function impose changes to the breast that create a more favorable environment for transformation. Curiously, while the levels of estrogen decrease drastically after menopause, breast cancers in women aged more than 75 years old tend to be positive for the estrogen receptor alpha (ERα). This observation suggests that the activation of the ERα in these women may be mainly driven by estrogen-independent or by other events that cooperate with low level of estrogen for its activation. In order to gain a better understanding of the mechanism by which the ERα can be activated in presence of low concentration of estrogen, the modes of activation of the transcriptional activity of the ERα must be considered.

Phosphorylation of the ERα by Akt leads to its activation

The ERα is composed of one DNA binding domain and two activation function (AF) domains. The AF2 contains the ligand-binding domain and is activated through binding of estrogen [16,17]. The AF1 domain however is activated through phosphorylation by AKT in an estrogen-independent fashion. Several studies have now shown that the ERα binds to several hundred binding sites across the genome [17]. A follow up study from this original report described that approximately 300 genes are activated when cells are treated with estrogen in presence of constitutively active AKT but not by estrogen alone [18]. Further the

phosphorylation of the ERα by AKT was shown to prolong the binding of the ERα to certain promoters [18]. These observations raise the possibility that the synergy between AKT and estrogen may be a mechanism to explain not only the activation of the ERα despite low levels of estrogen in post-menopausal women but also that the transcriptional programs that are turned on vary whether the ERα is activated through the AF1 and/or AF2 functions (Fig. 1). As described in this perspective, some of the ERα target genes that are activated upon mitochondrial stress are only transcribed upon phosphorylation of the ERα by AKT.

However, mutations in PI3K are frequent in breast cancer but they tend to affect ERα negative breast cancer [19,20]. Therefore, this observation argues that activation of AKT in ERα positive cancer cells is mediated through another mechanism.

One possibility for such alternative mechanism arises from the observation that AKT can be activated by reactive oxygen species (ROS). PI3K/AKT pathway is negatively regulated by the phosphatase PTEN. While mutations in PTEN are less frequent, PTEN can be inactivated by ROS. ROS have been shown to oxidize the active site cysteine on PTEN (Cys124) resulting in a disulfide formation to another intra-protein cysteine (Cys71) [21–23]. This results in inactivation of PTEN and constitutive activation of AKT. The activation of AKT by ROS is therefore a potential mechanism that would contribute to the activation of the ERα in presence of low level of estrogen in post-menopausal women.

The main source of cellular ROS is the mitochondria and therefore pathways that link increased mitochondrial ROS and the activation of the ERα are potentially key regulators of the increased incidence of ERα positive breast cancer in older women. Mitochondrial ROS is regulated by the sirtuin SIRT3, a deacetylase that localizes to the matrix of the mitochondria [24,25]. SIRT3 deacetylates several key regulators of metabolism and DNA repair [24–26]. However, one of the best characterized substrate of SIRT3 is the dismutase SOD2, which is implicated in the conversion of superoxide (O2) into hydrogen peroxide (H2O2) [27,28].

SIRT3 was identified as a longevity gene in several experimental models [8–10]. These findings are supported by the observations that SNPs leading to increased expression of SIRT3 were identified in centenarians and life-style interventions known to affect aging and longevity such as calorie restriction, exercise, and high fat diet all affect SIRT3 levels with calorie restriction and exercise increasing SIRT3 and high fat diet reducing SIRT3 [29–31]. Therefore, reduction in SIRT3 in aging directly contributes to an elevation in mitochondrial ROS.

This observation raises the possibility that the reduction of SIRT3 during aging and the resulting increase in ROS levels, leads to activation of AKT, which in turn promotes the activation of the ERα despite low level of estrogen in older women.

Additionally, the functions of SIRT3 and the ERα are intimately interconnected through their common role in the maintenance of the mitochondrial fitness. This interconnection arises from their implication in the mitochondrial unfolded protein response (UPR^{mt}).

The ERα and SIRT3 play important roles in the mitochondrial UPR.

The first unfolded protein response (UPR) to have been identified refers to the signaling cascade that is activated upon accumulation of misfolded proteins in the lumen of the endoplasmic reticulum. This cascade activates three parallel axes, the ATF6, PERK and IRE axes which collectively leads to the activation of a large nuclear transcriptional program that culminates in the reduction of stress in the lumen of the endoplasmic reticulum [32,33].

In the last few years, it has become abundantly clear that a similar signaling cascade orchestrates the communication between the mitochondria and the nucleus upon stress in the mitochondria [3,4]. However, the players of the mitochondrial UPR (UPR^{mt}) are distinct from those of the endoplasmic reticulum UPR (UPR^{ER}).

Our current understanding of the UPR^{mt} is that it also involves three axes (Fig. 2). The original axis was identified by the Hoogenraad group in mammalian cells and implicates the transcription factor CHOP, which results in the transcription of mitochondrial chaperones and proteases [34–38]. CHOP regulates the transcription of ATF5, which was recently found to be the mammalian homolog of ATFS-1 in C. elegans [39,40]. Our group identified two additional axes; the ERα axis and the SIRT3 axis.

The ER axis the UPR^{mt}: coordinated regulation of mitochondrial metabolism and cytosolic proteostasis

In addition to the CHOP axis of the UPR^{mt}, the ERα is activated upon accumulation of misfolded proteins and ROS in the mitochondria [1]. ROS was found to be essential in the activation of the ERα under mitochondrial stress conditions, as treatment of cells with N-acetyl-cysteine (NAC) abolished the activation of the ERα [1]. Further, ROS was necessary for the activation of AKT and in turn, AKT was necessary for the activation of the ERα [1]. Down-stream of the activation of the ERα, as first reported by the Klinge group [41], the transcription factor NRF1 is up-regulated upon mitochondria stress [1]. NRF1 is a key transcription factor implicated in mitochondrial biogenesis and metabolism [42,43]. Further, the activity of the proteasome was also found to be up-regulated [1]. The link between the proteasome and the ERα is intriguing but is entirely consistent with numerous reports that inhibition of the proteasome adversely affects the mitochondria [44–46]. Therefore, in addition to the large number of genes regulated by the ERα that are implicated in cell cycle progression and proliferation, the transcriptional program regulated by the ERα includes genes implicated in mitochondrial biogenesis and cytosolic proteastasis. This latter set of genes appears to be transcribed however only when the ERα is phosphorylated by AKT.

The ERα axis of the UPR^{mt} was found to be a distinct axis from the CHOP axis of the UPR^{mt} based on the findings that despite both axes being activated by the same mitochondria stress, inhibition of the ERα by shRNA did not affect the up-regulation of CHOP or its down-stream targets upon mitochondrial stress conditions [1]. Conversely, inhibition of CHOP did not abolish the activation of the ERα and its down-stream targets [1].

The SIRT3 axis of the UPR^{mt}: coordinated regulation of mitophagy, mitochondrial biogenesis as well as the anti-oxidant machinery.

Since luminal cells but not basal cells of the breast express the ERα, following the discovery of the ERα axis of the UPR^{mt}, one pending question that arose was the mechanism by which ERα negative breast cancer cells survive elevated ROS in response to mitochondrial stress. This line of investigation led to the discovery of the SIRT3 axis [2,47]. SIRT3 was found to regulate a distinct axis from the CHOP and ERα axes of the UPR^{mt}, based on the observation that inhibition of either did not affect SIRT3 and its down-stream targets and vice versa [2].

The SIRT3 axis of the UPR^{mt} orchestrates a multi-functional response aimed at reducing mitochondrial stress, which includes the activation of anti-oxidant SOD2 at the mRNA level through transcription by FOXO3A and also at the protein level through its deacetylation by SIRT3 [2]. The SIRT3 axis also regulates mitophagy of irreversibly damaged mitochondria as well as NRF1 indicating that both the ERα and the SIRT3 axes regulate mitochondrial biogenesis [2].

Importantly for the hypothesis presented in this perspective, inhibiting SIRT3 expression in basal cells that do not express the ERα leads to excessive ROS and cell death [2]. In contrast, inhibition of SIRT3 in luminal ERα positive cells had limited effect on the survival of these cells under mitochondrial stress conditions [2].

The importance of this later observation arises from its potential impact on the fact that older women, who have lower level of SIRT3, tend to develop ERα positive breast cancer. In support of this possibility, the SIRT3 knockout mice develop exclusively ERα positive mammary tumors [27].

The integral view of the UPR^{mt} and its potential role in defining breast cancer sub-type with age

These observations support the hypothesis that upon transformation and elevation in ROS in epithelial cells of the breast that lack SIRT3, the maintenance of the integrity of the mitochondria becomes dependent of the ERα axis of the UPR^{mt}.

As the mitochondria are essential to produce metabolites to generate the building blocks of cellular mass: amino acids, lipids and nucleotides, despite the fact that the mitochondria of cancer cells are less efficient at producing ATP, their integrity must be preserved in order for a cancer cell to grow and proliferate. It is in this setting that the essential housekeeping function of the UPR^{mt} may become mandatory. Further, by being composed of parallel axes, such multi-axes pathway allows for compensatory mechanism to maintain mitochondrial integrity despite the failure of one of the axis.

While the role of the CHOP axis is not clear in relation to breast cancer in elderly women, this axis appears to be activated very early during transformation and remains activated at all stages of tumor progression [48]. Therefore, the CHOP axis may also play a general role in maintenance of the mitochondrial network without being specific for luminal or basal cells in the ductal tree of the breast.

The SIRT3 axis and metastasis: a potential mechanism that contributes to the more aggressive breast cancers in young women?.

In cancer, SIRT3 has been reported both as an oncogene [49–53] and as a tumor suppressor [27,54–58], therefore creating confusion regarding its role in cancer. For instance, SIRT3 was reported to be decreased or absent in 87% of breast cancers and deleted in 20% of all human cancers and 40% of breast cancer [59]. This reduction in SIRT3 leads to increase in ROS and the stabilization of HIF1α, which promotes a switch to glycolysis and contribute to the Warburg [59]. Subsequently, our group also found that SOD2 levels are decreased in breast cancer upon activation of the oncogene Ras [2]. Taken together, these results suggest that a moderate increase in ROS levels may be necessary for tumor initiation. Importantly however, deletion of SIRT3 gene was reported to be heterozygous suggesting that a selective pressure is taking place to maintain one copy of SIRT3 intact. Since the SIRT3 axis of the UPR^{mt} induces NRF1, the antioxidant machinery and mitophagy to maintain mitochondrial integrity [2], the retention of one wild type copy of SIRT3 in cancer cells may be necessary for the activation of this axis of the UPR^{mt} upon mitochondrial proteotoxic stress.

Therefore, the oncogenic function and tumor suppressor functions of SIRT3 may be reconcile by acting as a rheostat of ROS levels in cancer cells. Initially, SIRT3 and SOD2 levels decrease to up-regulate ROS and mediate the Warburg effect. However, under increased stress conditions, to avoid ROS levels to raise to excessive levels and induce cell death, the SIRT3 axis of the UPR^{mt} would be activated to reduce ROS levels below a threshold that is compatible with mitochondrial function and maintain cell viability. In support of this idea, it has been reported that SIRT3 is overexpressed in highly metabolic tissues such as the heart [60,61], and in lymph node-positive breast cancer suggesting a need for SIRT3 during stress conditions in disease progression such as metastatic dissemination [62].

The idea that ROS levels in a cancer cells must be elevated but not to excess, a goldilocks-like phenomenon, is not without precedent. This proposed model is reminiscent of mitochondrial hormesis and the dual effect of ROS during aging. In the setting of aging, moderate levels of ROS are protective by activating cytoprotective responses however excessive ROS levels accelerate aging and decrease cell viability.

Importantly for this perspective however, age has never been considered in these studies. A diagram of the hypothetical dual role of SIRT3 is shown in figure 3. On one hand, SIRT3 is down regulated in older women and as stated above this decline may impose a selective pressure for the transformation of luminal cells due to their ability to rely on the ERα axis of the UPR^{mt} to maintain mitochondrial fitness and cancer cell survival.

On the other hand, SIRT3 levels are high in both basal and luminal cells in young women. However, basal cells are more proliferative and invasive such that upon transformation of both cell types, over time basal cells overgrow the luminal cells resulting in a mainly basal cancer. In support of this possibility, we recently found using a gene signature of the SIRT3 axis of the UPR^{mt} to inquire a large dataset of over 1800 breast cancer patients that the SIRT3 axis is significantly higher in triple negative breast cancer sub-type and inversely correlates with ERα status [63,64]. Further, the SIRT3 axis signature was associated

with increased rate of metastasis [63,64]. Therefore, we hypothesize that these findings may contribute to the observation that young women tend to develop ERα negative breast cancers that are more aggressive (Fig. 3).

Concluding remarks:

The counterintuitive trend for older women to develop ERα positive breast cancers and younger women to develop ERα negative breast cancers remains a mystery. In this perspective, we propose a hypothesis that is centered on the critical importance to maintain mitochondrial function in cancer cells. One key pathway involved in the maintenance of the mitochondria is the UPR^{mt} and both the ERα and SIRT3 have been shown to play key roles in this signaling cascade. Since SIRT3 declines with age and the gene signature of the SIRT3 axis of the UPR^{mt} is associated with metastasis, higher level of SIRT3 may explain why younger women develop more aggressive tumors.

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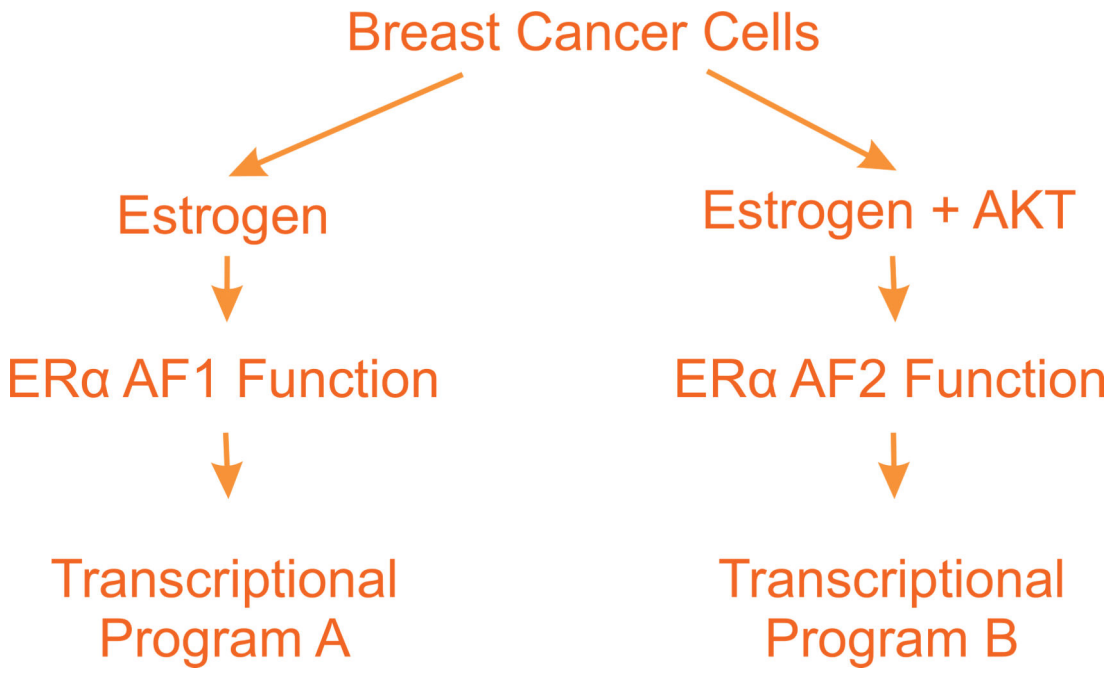

Figure 1:

Activation of the ERα can be mediated either by elevated level of estrogen or low levels of estrogen in combination with phosphorylation of the ERα by AKT. These modes of activation result in the activation of distinct transcriptional programs.

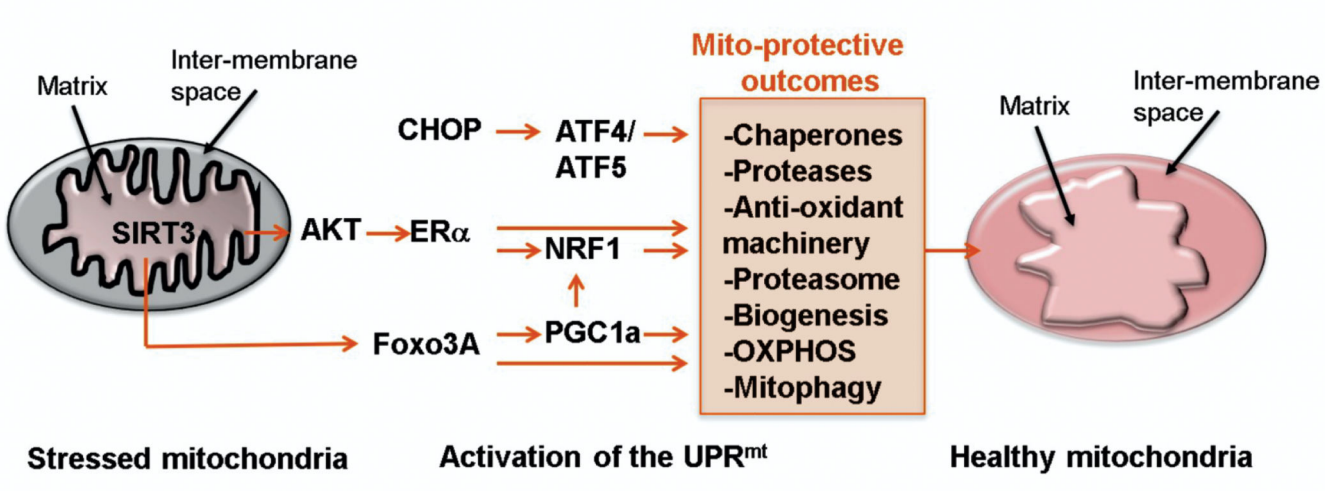

Figure 2:

Diagram of the three axes of the mitochondrial unfolded protein response (UPR^{mt}) that are activated upon stress (illustrated by orange star shapes) on the left side and resulting in several mitochondrial protective outcomes leading to restoration of healthy mitochondria (right).

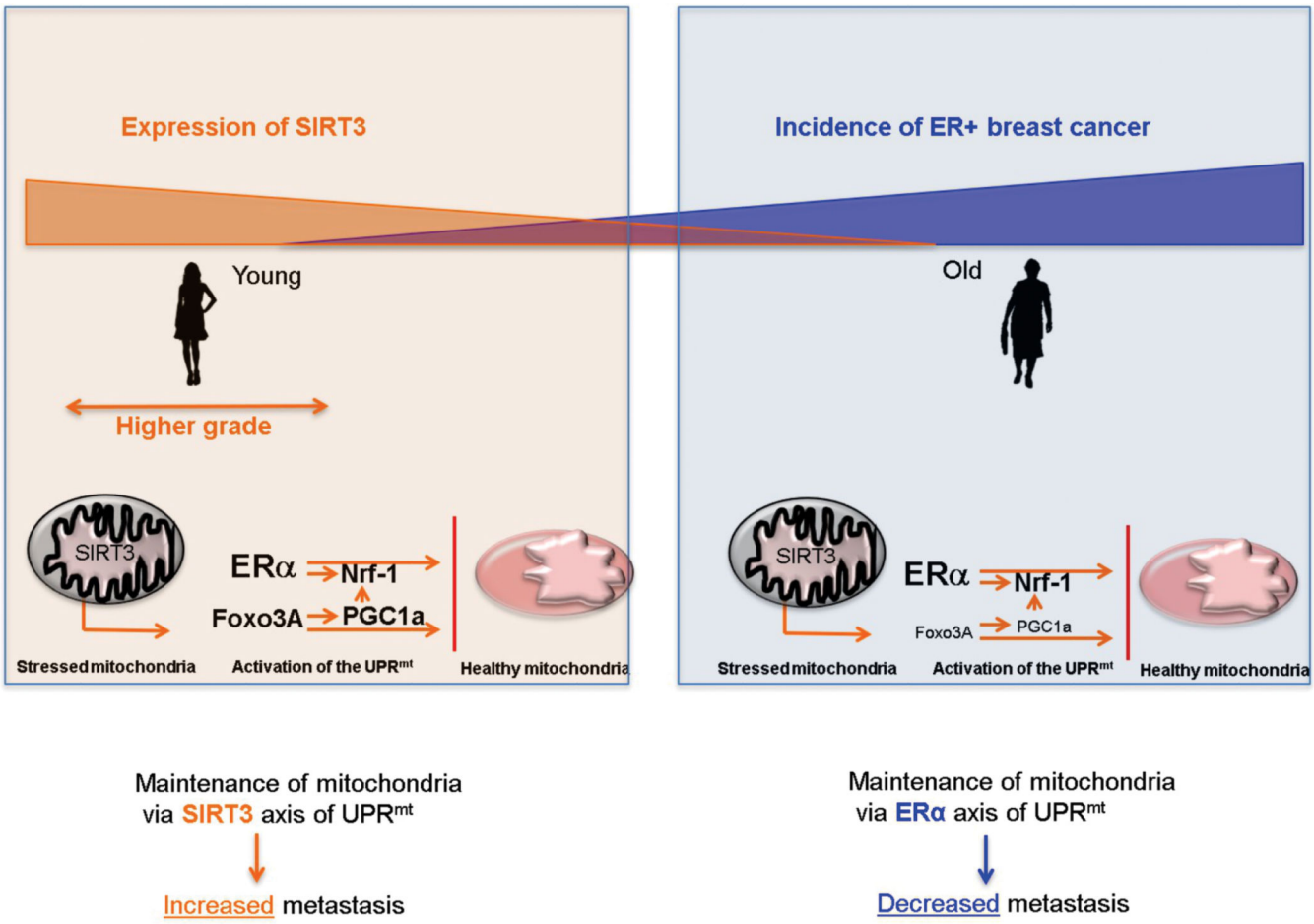

Figure 3.

Hypothetical model of how young women (orange box) with high level of SIRT3 may maintain mitochondrial fitness through the SIRT3 axis of the UPR^{mt,} and develop more aggressive tumors, while older women (blue box) rely on the ERα axis of the UPR^{mt} and therefore develop mainly luminal and less aggressive breast cancers.