Supplement

Supplemental Text

Detailed discussion of the ExprEssence subnetwork

In this section, the interactions defining the subnetwork obtained by ExprEssence will be discussed, except for the ones already featured in the main text. The pioneer transcription factor FOXA1 opens the chromatin and allows estrogen and anti-estrogens to bind the DNA [1]. FOXA1 expression is a signal for proliferation of ER-positive breast cancer and an indicator for good outcome of hormone therapy, as are ESR1 and GATA3 [2]. However, with our data, response to neoadjuvant TFAC treatment was examined. Since patients did not receive anti-estrogens, the proliferative effect of FOXA1 that mediates estrogen binding [3] means that downregulation of the interaction between FOXA1 and ESR1 indicates good response under TFAC therapy. Lower FOXA1 gene expression has also been correlated with lower TFF1 protein levels and prevention of hormone-induced reentry into the cell cycle [4]. Further, the lower activity of the interaction between TFF1 and TFF3 in responders matches the hypothesis that high levels of the Trefoil factors promote both tumor growth and migration [5, 6]. Therefore, the downregulation of the interaction path FOXA1–TFF1–TFF3 indicates good response under TFAC therapy.

Among the interactions that are downregulated in responders to TFAC therapy but are not part of the subnetwork highlighted by the green line in Figure 1, we found GFRA1–ISR1. This interaction is part of a RET oncogene related pathway, which mediates IRS1 activation through GFRA-signalling proteins [7]. The lower activity of this growth-related oncogenetic pathway and lower IRS1 levels in responders may slow down breast cancer progression. IRS1 has also been described to be involved in breast cancer tumorigenesis [8].

In concordance with high expression levels of AGR2 being associated with decreased survival [9], we also observe lower amounts of AGR2 in responders. The interaction between AGR2 and LYPD3 was considered a "viable target for oestrogen-responsive breast cancer intervention" by Fletcher et al. [10]. Moreover, according to Maslon et al. [11], RUVBL2 is "overproduced in a panel of primary breast cancer biopsy specimens" and a validated interactor of AGR2. Thus, we suggest that RUVBL2, AGR2 and LYPD3 are forming a module whose downregulation is beneficial and indicative of good prognosis in case of TFAC therapy. The interaction between PLAT and CPB1 is downregulated in responders, but we have no indication of its role based on the literature.

Next, we will focus on the interactions that are upregulated in responders but are not part of the red box in Figure 1. Among them, we observed lower amounts of S100A1 and S100A7 in responders. Both genes belong to the S100 gene family, which is implicated in breast cancer and melanoma, metastasis, Alzheimer’s disease, cardiomyopathy and other diseases. S100A7 was found to be expressed in high-grade ductal carcinoma in situ (DCIS), a key stage to invasive breast cancer [15]. S100A7 is associated with poor prognostic markers in DCIS and influences progression of breast carcinoma through its interaction with the c-Jun activation domain-binding protein 1 (Jab1) [16], thereby enhancing survival under conditions of cellular stress, such as anoikis [17]. Its downregulation was also shown to inhibit EGF-induced cell migration and invasion in
ER-negative MDA-MB-468 cells [18, 19]. Some recent studies, however, also identified tumor-suppressive effects of S100A7 in ER-positive breast cancer cells [20, 21]. High expression of S100A1, as observed among the group of responders, leads to significant reduction of motility and invasion rates in cells expressing also high levels of metastasis-promoting S100A4 [22]. This observation suggests an antagonistic role of S100A1 against S100A4-mediated metastasis [23]. However, it remains unclear whether S100A1 also counteracts tumorigenic effects mediated by S100A7.
References


