Intratumoural inflammation and endocrine resistance in breast cancer

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Abstract

It is becoming clear that inflammation-associated mechanisms can affect progression of breast cancer and modulate responses to treatment. Estrogen receptor alpha (ER α (ESR1)) is the principal biomarker and therapeutic target for endocrine therapies in breast cancer. Over 70% of patients are ESR1-positive at diagnosis and are candidates for endocrine therapy. However, ESR1-positive tumours can become resistant to endocrine therapy. Multiple mechanisms of endocrine resistance have been proposed, including suppression of ESR1. This review discusses the relationship between intratumoural inflammation and endocrine resistance with a particular focus on inflammation-mediated suppression of ESR1.

Key Words

- breast
- estrogen receptor
- endocrine therapy resistance
- molecular immunology
- biomarker

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Introduction

The association between inflammation and cancer has long been established. Inflammatory cells are commonly found in tumour tissues and chronic inflammation is associated with many cancers, including breast cancer, and is capable of affecting tumour progression and differentiation of tumor cells (Coussens & Werb 2002, Balkwill *et al.* 2005, Reiman *et al.* 2007, Pages *et al.* 2010, Hanahan & Weinberg 2011, Balkwill & Mantovani 2012). The immune system can exert both pro- and anti- tumour effects in breast cancer. For example, multiple studies have shown that CD8⁺ tumor-infiltrating lymphocytes (TIL) are associated with improved outcome in breast cancer (Mahmoud *et al.* 2011, Liu *et al.* 2012), particularly in estrogen-receptor-negative breast cancer where TILs are often present in higher numbers (Teschendorff *et al.* 2007*a,b*). However, it is increasingly clear that inflammation-associated tumour-promoting mechanisms can

also be a factor in breast cancer progression (Baumgarten & Frasor 2012, Coussens *et al.* 2013, Jiang & Shapiro 2014). Perhaps more significant are the results of studies that have indicated that inflammation mediates or modifies the response to treatment (Desmedt *et al.* 2008, DeNardo *et al.* 2011, West *et al.* 2011, Andre *et al.* 2013, Zitvogel *et al.* 2013). However, intratumoural inflammation, like the neoplastic process that stimulates it, is a complex process and we know relatively little of the specific pathways that connect them.

In breast cancer, the estrogen receptor alpha (ER α (ESR1)) is an important target for a group of therapies collectively known as endocrine therapies. The ESR1 is a nuclear transcription factor that not only guides and serves as a target for endocrine therapies, but also occupies a central position in subtype classification and role in breast cancer biology. Nevertheless, the mechanisms that

regulate the expression and activity of ESR1 in breast cancer are not well understood (Zwart *et al.* 2011). ESR1-positive tumours account for approximately 70% of cases at diagnosis and are candidates for endocrine therapies. However, ESR1-positive tumours can manifest resistance at the outset or become resistant to endocrine therapy over time. There have been many reviews describing the clinical problem of endocrine therapy resistance in breast cancer as well as advances in understanding the mechanisms underlying this resistance (Musgrove & Sutherland 2009, Osborne & Schiff 2011, Baumgarten & Frasor 2012, Sas *et al.* 2012, Patani & Martin 2014). Much attention has been focused on mechanisms that short-circuit the ESR1 pathway downstream of the receptor and those arising from altered activities of intracellular kinase pathways. Yet factors and mechanisms that change the expression of the ESR1 itself are clearly present in some instances and may also be important (Lapidus *et al.* 1998, Stearns *et al.* 2007). We consider here the possibility that inflammation-derived-cytokine signalling plays an important and hitherto under-explored role in the suppression of ESR1 levels. This possibility is supported by strong correlations between intratumoural inflammation and ESR1-low or ESR1-negative status of breast tumours, which are readily observed in clinical practice. However, a specific mechanism to explain this observation and to connect it with acquired resistance to endocrine therapy and increased invasive properties has been lacking. In other words, how does the immune system, and the intratumoural inflammatory response that it directs, affect the level of ESR1 in breast cancer? Also, does chronic inflammation affect response to endocrine therapy?

ESR1 is a predictive biomarker in breast cancer

Advances in knowledge regarding breast cancer over several decades have resulted in therapies, such as those targeting the ER and the epidermal growth factor receptor 2 (HER2), that specifically benefit the subsets of patients defined by these biomarkers. ESR1 in particular is now well established as a central biomarker for prescribing treatment programmes, and targeted inhibitors of ER signalling have been the mainstay of breast cancer therapy for over 30 years. However, development of resistance curtails the effectiveness of such therapies (Gee *et al.* 2005, Osborne & Schiff 2011). ESR1 is a transcription factor that is routinely measured by immunohistochemical (IHC) assays to determine clinical ER status (ER-positive or ER-negative) and to guide endocrine therapy (Murphy & Watson 2002). Endocrine therapy is often deployed when primary

tumours are classified as ER-positive and mostly revolves around the use of drugs that either block the estrogen growth stimulus directly at the level of ER (selective ER modulators/downregulators (SERMs/SERDs)) or indirectly by inhibition of estrogen production (aromatase inhibitors (AIs); Lewis & Jordan 2005, Cheang *et al.* 2008).

The clinical designation, 'ER status' is based on assays that assess expression levels of only one ER, the classical ESR1. However, it is now recognised that the definition of clinical ER status is more complex, and that many tumour cells express a second type of ER, ER β (ESR2; Hartman *et al.* 2009) that may differentially affect ER signalling in distinct cellular contexts (discussed in more detail in a later section). Multiple isoforms of both ERs and their phosphorylation status also complicate the picture (Skiris *et al.* 2008, 2010, Murphy *et al.* 2011, Murphy & Leygue 2012). It is becoming evident that the measurement of additional indicators such as phosphorylation of ESR1 and ESR2 may also be needed to fine-tune the predictive value of ER status (Hartman *et al.* 2009, Murphy & Leygue 2012). It is also well known that there can be heterogeneous expression of ESR1 across tumours that are clinically ER-positive. Homogeneous and 'strongly' ER-positive tumours generally have better response rates to endocrine therapy in comparison with heterogeneous and 'weakly' ER-positive tumours (Goldhirsch *et al.* 2009). However, tumours with as few as 1% of the tumour cells staining positive by IHC are considered ER-positive for the purpose of clinical decisions and can be responsive to endocrine therapy (Hammond *et al.* 2010).

Mechanisms of resistance to endocrine therapy

At clinical presentation, approximately 70% of primary tumours are categorised as ER-positive and approximately 30% as ER-negative. The former are regarded as potentially responsive to endocrine therapy (Musgrove & Sutherland 2009), while the latter are regarded as intrinsically resistant and not eligible. However, it is now recognised that hormone-receptor-positive tumours are very heterogeneous at both the clinical (Lim *et al.* 2012, Nagaraj *et al.* 2012) and molecular levels (Curtis *et al.* 2012, Ellis *et al.* 2012) and that ER-positive tumours often exhibit a spectrum of response at the outset. Many eventually develop acquired resistance that leads to tumour recurrence despite continued therapy (Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005). Furthermore, metastasis dormancy is problematic in ER-positive cancer (Zhang *et al.* 2013) and predicting resistance remains a major challenge.

Endocrine resistance may have many underlying causes that differ between intrinsic and acquired circumstances (Gee *et al.* 2005, Osborne & Schiff 2011). In general, resistance may be considered to reflect three possible mechanisms: i) overactivity of coregulators and/or kinase pathways that alter signalling downstream of ER; ii) the emergence and dominance of a minor ER-negative cell population harboured within a heterogeneously ER-positive tumour (Stearns *et al.* 2007, Brinkman & El-Ashry 2009) and iii) plasticity and partial conversion from ER-positive to ER-negative tumour cell differentiation (Doane *et al.* 2006, Massarweh *et al.* 2006).

When resistance occurs despite ER-positive status at diagnosis or persistence of ESR1 expression at recurrence, it is likely to be attributable to mechanisms that lie downstream of ESR1, such as overactivity of kinase pathways or altered expression of ESR1 coregulators (Murphy *et al.* 2002, Schiff *et al.* 2004, Gee *et al.* 2005). This can occur at the level of systemic growth factors (e.g. EGF, heregulin and amphiregulin) that stimulate signalling, at the level of receptor kinases themselves (e.g. EGFR, ERBB2 and IGF1R/IR) and at the level of signalling pathways downstream of receptor tyrosine kinases (e.g. PI3K, AKT, MAPK and MTOR). Increases in growth factor receptor expression levels (e.g. ERBB2) can lead to ligand-independent ESR1 activation and tamoxifen resistance (Shou *et al.* 2004). Activation of EGFR and ERBB2 can also stimulate MAPK14 (p38) and MAPK1/MAPK3 (ERK1/2) MAPK signalling, leading to altered crosstalk with ESR1 signalling and endocrine resistance (Gutierrez *et al.* 2005, Arpino *et al.* 2008, Patani & Martin 2014). PI3K and AKT signalling, downstream of growth factor receptor tyrosine kinases, contributes to tamoxifen resistance by modulating phosphorylation and activation of ESR1, co-activator activity and progesterone receptor levels (Bunone *et al.* 1996, Cui *et al.* 2003, 2005, Faridi *et al.* 2003, deGraffenried *et al.* 2004, Miller *et al.* 2011). Phosphorylation and amplification of co-activators, such as NCOA3, can also lead to increased ligand-independent activity and endocrine resistance (Osborne *et al.* 2003, Antoon *et al.* 2012).

Loss of ESR1 in breast cancer

When resistance occurs in conjunction with reduction and/or loss of ESR1 in the tumour (as occurs in 25–30% of cases with acquired resistance (Johnston *et al.* 1995, Kuukasjarvi *et al.* 1996, Broom *et al.* 2009)), it is likely to be attributable to changes in overall cell phenotype or to a more focused alteration in ESR1 regulation.

Overall change in cell phenotype, or ‘tumour cell plasticity’, with respect to the evolution of molecular subtypes is one possibility (Doane *et al.* 2006, Massarweh *et al.* 2006). It is known that the molecular phenotype can be altered through the actions of single master regulators such as *FOXA1* and *ELF5* (Bernardo *et al.* 2010, 2013, Kalyuga *et al.* 2012), and that approximately 10% of triple-negative tumours (clinically negative for ESR1, progesterone receptor (PGR) and ERBB2) manifest luminal-like gene expression profiles (Creighton *et al.* 2006, Bertucci *et al.* 2012). Downregulation of the transcription factor and chromatin remodelling factor *FOXA1* results in downregulation of ESR1 in MCF7 cells (Bernardo *et al.* 2010). *FOXA1* represses basal gene expression patterns in luminal cell lines, and silencing *FOXA1* can shift the transcriptional balance away from a luminal gene expression profile and towards a basal-like state (Bernardo *et al.* 2013). Forced expression of the transcription factor *ELF5* was also shown to reduce ER and estrogen responsiveness and induce a gene expression signature associated with ER-negative status, thus potentially contributing to endocrine resistance (Kalyuga *et al.* 2012, Frend & Watson 2013). As yet another mechanism, it has been suggested that an ER-negative phenotype with luminal and basal features can emerge from ER-positive luminal tumours during endocrine therapy through a notch-dependent process (Haughian *et al.* 2012).

Specific alteration at the level of the ER is another possibility. At diagnosis, it is possible that some clinically ER-positive breast tumours that have low levels of ESR1 expression, or some ER-negative status tumours with overall gene expression profiles akin to luminal subtype tumours (e.g. the ‘LAR’ subtype; Lehmann *et al.* 2011, Nagaraj *et al.* 2012, Peddi *et al.* 2012), may in fact represent ‘ER suppressed’ tumours. This is supported by expression array analysis that identified subsets of ER-negative tumours (comprising approximately 25% of ER-negative tumours) that share overall gene expression profiles with subsets of ER-positive tumours but lack apparent ER expression (Creighton *et al.* 2006, Lehmann *et al.* 2011, Nagaraj *et al.* 2012). Although this may be in part due to the expression of androgen receptor and its binding to and regulating ESR1 *cis*-regulatory elements in apocrine tumour subsets (Robinson *et al.* 2011), this cannot explain all cases.

Downregulation or suppression of ESR1 in the breast tumour cell can be caused by both internal and external factors. The former include factors associated with epithelial-to-mesenchymal transition (EMT) and related signalling. The EMT-related transcription factor Twist has been shown to down-regulate the expression of ESR1 expression

by recruiting DNA methyltransferase 3B and histone deacetylase 1 to the ER promoter region, resulting in endocrine resistance (Vesuna *et al.* 2012). Another prominent EMT-related transcription factor, Snail, has also been implicated in ER suppression and endocrine resistance (Dhasarathy *et al.* 2007). Other internal cellular factors include acquired intracellular alterations in kinase signalling pathways (Brodie *et al.* 2005, Massarweh *et al.* 2006, Creighton *et al.* 2010, Giamas *et al.* 2011), trans-repression through upregulation of NF κ B (Pradhan *et al.* 2012, Sas *et al.* 2012), effects of proteasome targeting factors (Man & Zhang 2011, Pan *et al.* 2011) or microRNA expression (Guttilla *et al.* 2012). Finally, suppression of ESR1 can also be caused by various extracellular factors including growth factors and cytokines (to be discussed below).

Intriguingly, results from multiple studies have established that ER suppression and endocrine resistance can be reversible processes and that inhibition of MAPK signalling leads to restoration of ESR1 expression, ER function and tamoxifen responsiveness (Oh *et al.* 2001, Bayliss *et al.* 2007, Riggins *et al.* 2007, Antoon *et al.* 2013). El-Ashry and colleagues have shown that hyperactivity of MAPK signalling downregulates ESR1 and causes features of endocrine resistance. Briefly, EGFR receptor tyrosine kinase signalling in breast cancer cell lines led to activated RAS and downstream MAPK1/MAPK3 (ERK1/2) MAPK signalling affecting ER at both the mRNA and protein levels. Re-expression of ER in ER-negative breast cancer cell lines was achieved by intracellular inhibition of MAPK1/MAPK3 (ERK1/2) MAPK signalling (with the small-molecule inhibitor U0126) or by blocking extracellular growth factor signalling to the cell with Iressa (EGFR) or Herceptin (ERBB2) (Bayliss *et al.* 2007). Of note, not all ER-negative cell lines tested re-expressed ESR1 upon MAPK inhibition. The authors observed that two basal-like cell lines did not re-express ESR1 and attributed this to hypermethylation of the ER promoter (Bayliss *et al.* 2007). Increased ERBB2 signalling via the PI3K/AKT pathway has also been implicated in ER suppression. Sonenshein and colleagues have observed that forced AKT activity in breast cancer cell lines can result in the inactivation of FOXO3, an ER-modulating transcription factor, and subsequent suppression of ER levels (Guo & Sonenshein 2004). They further showed that inhibition of PI3K/AKT signalling leads to increased levels of ER expression in breast cancer cell lines (Guo & Sonenshein 2004).

Whatever the mechanism, plasticity of tumour phenotypes indicates an opportunity for interventions that re-direct ER-negative basal tumours towards more ER-positive, luminal phenotypes and potentially the

better outcomes associated with luminal tumours. Therefore, elucidating the spectrum of mechanisms by which ESR1 expression is altered, particularly those that are reversible, will illuminate tangible targets for agents to be used in combination with existing modalities that may enhance initial responsiveness and/or restore responsiveness to endocrine therapy in resistant disease.

Intratumoural inflammation in breast cancer

A growing body of evidence has revealed that the host immune system can influence tumour cell differentiation and tumour progression through the intra- or peri-tumoural inflammatory response (Reiman *et al.* 2007, 2010). Infiltrating leukocytes, a feature of many tumours including those of the breast, can secrete factors such as cytokines, chemokines and proteases that promote tumour angiogenesis, tissue remodelling and pro-tumourigenic signalling in both neoplastic and stromal cells (Balkwill *et al.* 2005). Cancers can directly sculpt inflammatory responses through the production of cytokines that influence the composition and activities of the inflammatory and immune cell compartment within the tumour (Schreiber *et al.* 2011).

In general terms, robust antigen-driven immune responses can drive tumour rejection and are dominated by Th1 CD4⁺ T-cells, cytotoxic CD8⁺ T cells, pro-inflammatory M1 macrophages and Th1 cytokines such as IFN γ (Coussens & Werb 2002, Dunn *et al.* 2004; see Fig. 1). Ideally, cytotoxic killer CD8⁺ T cells, with help from Th1 CD4⁺ T cells, can recognise tumour antigens and kill cancer-cell targets via perforin and granzyme or FAS-ligand-mediated pathways. Indeed, results from multiple studies have indicated that high levels of CD8⁺ T cells are associated with improved outcomes in breast cancer (Mahmoud *et al.* 2011, Liu *et al.* 2012). Th1 CD4⁺ T cells also polarise macrophages to an anti-tumour M1 phenotype by secreting IFN γ (Biswas *et al.* 2013).

Unfortunately, tumours can adapt to such immune pressure through various mechanisms. These include exploitation of the properties of immune-derived cytokines and diversion of the immune response towards pro-tumourigenic smoldering inflammation featuring Th2 CD4⁺ T cells, regulatory T cells (Tregs) and M2 macrophages (Balkwill *et al.* 2005, DeNardo & Coussens 2007, De Palma & Lewis 2013; Fig. 1). Th2 CD4⁺ T cells secrete cytokines such as interleukin 6 (IL6) and tumour necrosis factor alpha (TNF), to promote tumour cell survival and invasion, as well as IL4 and IL13, promoting activation of M2 type macrophages (or alternatively activated macrophages). Tumour-associated macrophages

Figure 1

Cellular sources and major functions of selected cytokines in breast cancer. The breast tumour microenvironment harbours a complex milieu of immune cells and leukocyte-derived products. Shown here are common cytokines and other secreted immune factors found in breast tumours, their primary haematopoietic sources and, based on the available literature, their key tumour-modulatory effects and associations with clinical outcome. Pink represents factors that exert generally pro-tumourigenic effects; blue, factors with host-protective roles and yellow, factors with mixed pro- and anti-tumourigenic effects. Actual effects of the indicated cytokines are likely to be highly context-dependent, with tumour molecular subtype and histological grade being particularly important

variables. Nevertheless, the balance of evidence indicates that inflammatory cytokines such as *OSM*, *TNF α* , *IL6*, *IL1 β* and *CXCL8* promote tumour progression by enhancing cancer cell survival, metastatic capacity and tumour stem cell features. In contrast, *IFN γ* , *GZMB* and *PRF1* impair tumour progression by acting as primary effectors of cell-mediated anti-tumour immunity. *IL10* and *TGF β* , produced in abundance by Tregs, have potent immune-suppressive roles and can thus impair both protective immunity and pro-tumourigenic inflammation. In addition, *TGF β* can act directly on tumour cells to promote EMT. Depending on tumour phenotype, results from different studies have revealed both positive and negative associations between Tregs and clinical outcome of breast cancer.

are associated with poor prognosis in breast cancer (discussed in greater detail below) and have been shown to promote pro-tumourigenic processes such as tissue remodelling, tumour angiogenesis and tumour cell invasiveness and metastasis in mouse models (Biswas *et al.* 2013). In a study of the complex role of the tumour microenvironment in breast cancer, DeNardo *et al.* (2011) found that a CD68 $^{\text{high}}$, CD4 $^{\text{high}}$, CD8 $^{\text{low}}$ phenotype (i.e. high levels of tumour-associated macrophages and CD4 $^+$ T cells in the absence of cytotoxic CD8 $^+$ T cells) correlated with poor survival in breast cancer. Additional tumour-associated stromal cells, including endothelial cells,

cancer-associated fibroblasts (CAF) and adipocytes, secrete cytokines, proteases and inflammatory factors promoting tumour cell survival and tumour progression (Hanahan & Coussens 2012, Gilbert & Slingerland 2013). Infiltration of macrophages into breast adipose tissue results in increased prostaglandin (PGE $_2$) and cytokine (TNF and IL1B) signalling (Howe *et al.* 2013, Vona-Davis & Rose 2013). Secreted PGE $_2$ and TNF stimulate aromatase expression, resulting in increased estrogen levels and increased ER signalling in ER-positive breast cancer (Howe *et al.* 2013, Vona-Davis & Rose 2013). Thus, the breast tumour microenvironment is rich in a variety of secreted

cytokines, chemokines and proteases that have multiple effects on tumour biology and tumour cell gene regulation, and ultimately tumour progression and response to therapy (Fig. 1). Results from gene-profiling studies have revealed inflammation-related gene clusters that predict recurrence in breast cancer patients receiving tamoxifen (Loi *et al.* 2008) and anastrozole (Ignatiadis *et al.* 2012). It is therefore important to decipher the key cytokines and cellular factors that determine the balance between beneficial and deleterious ‘types’ of inflammation within the tumour. Likewise, understanding the specific mechanisms whereby inflammation drives tumour progression and response to therapy is critical.

Mechanisms of inflammation-mediated ER suppression

Generally, ER-negative-status tumours have higher numbers of infiltrating leukocytes and inflammatory cytokines (Chavey *et al.* 2007, Teschendorff *et al.* 2007a). Teschendorff *et al.* (2007a) studied four major microarray gene expression datasets using unsupervised independent component analysis and observed a significant association between upregulation of immune response pathways (e.g. *IL2RB*, *HLA-C*, *CD69*, *CD48*, *CD8A*, *CD19*, *CD14*) and ER-negative status. Results from a study of cytokine expression in breast cancer have revealed high levels of multiple cytokines in breast carcinomas compared with normal breast (Chavey *et al.* 2007). In this study, the levels of expression of several cytokines (including *IL2*, *IL6*, *IL8*, *IFN γ* , *CCL2*, *CCL4* and *TNF*) were inversely correlated with ER status and a subset (*IL8*, *MCP1* and *MIP1 β*) correlated with leukocyte infiltration (Chavey *et al.* 2007). Inflammation has been shown to instigate and promote aggressive features

in ER-positive breast cancer through the actions of cytokines on the interplay between ESR1 and NF κ B, two key molecular switches within the breast tumour cell (recently reviewed by Baumgarten & Frasor (2012) and Sas *et al.* (2012)). Activation of NF κ B has been shown to cause acquired resistance and suppression of ESR1 in an MCF7 cell line model (Oida *et al.* 2014), and downstream of NF κ B signalling, the transcriptional repressor Blimp1 has been shown to suppress transcription of ESR1 by acting directly on the ESR1 promoter (Wang *et al.* 2009). These examples are part of an increasing body of evidence that chronic inflammation can lead to aberrant tumour cell signalling affecting the levels or activity of ESR1. More specific support for a mechanism of inflammation-mediated modulation of ESR1 comes from more recent discoveries implicating inflammatory and leukocyte-derived cytokines (West *et al.* 2012) and factors (Stossi *et al.* 2012a, Vlaicu *et al.* 2013) as extracellular agents that suppress ESR1 (discussed below).

Multiple inflammatory cytokines have been implicated in suppression of ESR1 in breast cancer (Table 1). For example, TNF was shown to reduce levels of ESR1 protein in multiple breast cancer cell lines (Bhat-Nakshatri *et al.* 2004). Furthermore, when ESR1 was overexpressed in MDA-MB-231 cells, treatment with TNF destabilised expression of ESR1 protein in a PI3K-dependent manner (Bhat-Nakshatri *et al.* 2004). However, there are also conflicting reports in the literature regarding the effect of TNF. For example, TNF has been shown to increase ESR1 occupancy of the *ABCG2* gene and to support estrogen-induced expression of *ABCG2* *in vitro* (Pradhan *et al.* 2010). Similarly, TNF may support the expression of additional ER target genes such as *CCND1* (Rubio *et al.* 2006). Both of these activities of TNF reportedly involve TNF-elicited NF κ B activation, in which NF κ B cooperates with ER at the

Table 1 Summary of inflammation-mediated ER suppression mechanisms

Inflammatory factor	Mechanism of ER suppression	Reference
Leukocyte-derived growth factors (e.g. EGF)	EGFR- and MAPK1/MAPK3 (ERK1/2) MAPK-dependent suppression of <i>ESR1</i> mRNA and ER protein	Oh <i>et al.</i> (2001), Grant <i>et al.</i> (2002) and Bayliss <i>et al.</i> (2007)
Multiple growth factors and cytokines (e.g. EGF, TNF, IL1 β) activate NF κ B signaling	NF κ B and ER signalling crosstalk results in modulation of ER protein activity	Baumgarten & Frasor (2012) and Sas <i>et al.</i> (2012)
	NF κ B subunit <i>RELB</i> -mediated activation of Blimp1 was shown to result in direct suppression of <i>ESR1</i> expression	Wang <i>et al.</i> (2009)
TNF	PI3K-dependent ER protein destabilisation	Bhat-Nakshatri <i>et al.</i> (2004) and Sas <i>et al.</i> (2012)
IL6	<i>ESR1</i> promoter methylation	D'Anello <i>et al.</i> (2010)
OSM	OSMR- and MAPK1/MAPK3 (ERK1/2) MAPK-dependent <i>ESR1</i> mRNA suppression	Grant <i>et al.</i> (2002) and West <i>et al.</i> (2012)
M1 macrophage-derived factor (amphiregulin)	<i>ESR1</i> suppression via c-SRC, MAPK and PKC-dependent ERK2 recruitment to <i>ESR1</i> locus	Stossi <i>et al.</i> (2012a,b)

level of particular ER-target gene promoters (Rubio *et al.* 2006, Pradhan *et al.* 2010).

Similarly conflicting findings have been reported for IL6, which was shown to induce methylation of the *ESR1* promoter *in vitro* resulting in reduced levels of ER and an increase in basal-like gene expression patterns (D'Anello *et al.* 2010). Epigenetic regulation of ER has also been examined (Lapidus *et al.* 1998, Stearns *et al.* 2007) and may be involved in cytokine-mediated ER suppression. Nevertheless, Speirs *et al.* (2000) showed that IL6 activates transcription of an ERE-luciferase transgene in primary breast cancer cells in a gp130-dependent manner. Oncostatin M (OSM), discussed further below, is a member of the IL6 family and has also been shown to suppress the levels of *ESR1* mRNA and protein in breast cancer cells (Grant *et al.* 2002). This occurs in a dose- and time-dependent fashion and is dependent on the expression of the OSM receptor β subunit, OSMR (West *et al.* 2012). This effect is reversible, and requires signalling by MAPK1/2 (MEK1/2) MAPKs (upstream of MAPK1/MAPK3 (ERK1/2)), with no apparent dependence on STAT3 or PI3K activity. Intriguingly, results from multiple studies of cell-extrinsic factors indicate that reversible suppression of ER by cytokines (West *et al.* 2012), hypoxia (Kronblad *et al.* 2005) and growth factor receptor signalling (Oh *et al.* 2001, Bayliss *et al.* 2007) may occur through a common mechanism involving MAPK1/MAPK3 (ERK1/2) MAPK signalling.

Beyond endocrine resistance, inflammation-mediated suppression of ER may exert significant effects on other aspects of tumour cell biology, as suppression of ER is associated with more aggressive, invasive tumours. As discussed previously, the EMT-related transcription factors Twist and Snail are associated with suppression of ER. Importantly, ER can in turn suppress another member of the Snail family, Slug; this augments expression of E-cadherin and enforces the luminal epithelial phenotype associated with ER-positive tumours (Ye *et al.* 2010). Similarly, *ESR1* signalling impairs the expression of the NF κ B subunit RELB, leading to reduced invasiveness (Wang *et al.* 2007). It is thus possible that inflammatory cytokines not only render breast cancers resistant to endocrine therapy via ER suppression, but also enhance pathways associated with EMT and cancer stemness as a consequence of ER loss. Indeed, IL6 and OSM can both suppress ER and induce EMT- and stem-like phenotypes *in vitro* (Sullivan *et al.* 2009, West *et al.* 2014). Intriguingly, while estrogen can induce expression of E-cadherin *in vitro* in ER-positive breast cancer cells, OSM blocks this via suppression of ER and thus promotes an overall mesenchymal/stem-like phenotype (West *et al.* 2014).

OSM: a key driver of inflammation-mediated suppression of ER

OSM is a member of the IL6 family of cytokines, amongst which IL6 is the prototype and has been shown to be a central factor in mediating the acute inflammatory response, the transition to chronic inflammation and the innate immune response (Naugler & Karin 2008, Taniguchi & Karin 2014). IL6 itself is produced relatively promiscuously by many types of stromal cells, immune cells and both normal and neoplastic epithelial cells (Royuela *et al.* 2004). Although IL6 is considered to promote tumour progression through several pathways (Zeisberg & Neilson 2009), results from biomarker studies (Rincon *et al.* 2006, Herschkowitz *et al.* 2007, Anglesio *et al.* 2011) have not confirmed this and clinical trials of antibodies targeting IL6 or the IL6 receptor have had modest results (Garber 2009). This may be due to the complexity of differentiating between classical and trans-signalling pathways or because of the broad nature of both positive and negative actions of IL6, and cellular sources makes inhibition in all cellular compartments difficult and/or leads to no net effect (Jones *et al.* 2011).

The closely related OSM has not been extensively studied in the context of tumours. Unlike IL6, its production appears to be largely restricted to specific inflammatory/immune cell subsets such as macrophages, T cells, neutrophils and dendritic cells (Chen & Benveniste 2004, Queen *et al.* 2005, Kastl *et al.* 2008). OSM signals through two receptor complexes defined by OSMR or leukaemia inhibitory factor receptor (LIFR) subunits in combination with a common gp130 receptor subunit (also shared with IL6R). These receptors transduce signals through the JAK/STAT3 pathway, but MAPK and PI3K signalling events also commonly occur (Heinrich *et al.* 2003). Depending on the cell type, OSM has been shown to share some effects with IL6 on breast cancer cells *in vitro*, such as enhanced cell motility and invasion, but can exert distinct effects from IL6 in some model systems, including inhibition of proliferation and promotion of cell detachment (Jorcyk *et al.* 2006, Tiffen *et al.* 2008). Results of studies of OSM using mouse mammary tumour models have indicated that OSM contributes to increased lung and bone metastasis (Bolin *et al.* 2012, Guo *et al.* 2013). Results of analyses of human tumours to date indicate that an increase in OSM and/or OSMR occurs in relationship with tumour progression in multiple tumour types including breast and cervical cancer and that this may be associated with adverse outcome (Royuela *et al.* 2004, Garcia-Tunon *et al.* 2008, West *et al.* 2012, 2014, Richards 2013).

Analyses of a small cohort of human breast tumours ($n=70$ cases) confirmed the association between OSM/OSMR signalling and reduced ER levels *in vivo*. High levels of expression of OSM and OSMR mRNA were detected in only 12% of ER-positive tumours compared with 45% of ER-negative tumours (West *et al.* 2012). Levels of OSM were significantly lower in ER-positive than in ER-negative tumours, but even within the clinically ER-positive subgroup, OSM was inversely correlated with both ESR1 and PGR levels. Further *in silico* analysis of mRNA expression based on a large previously published tumour dataset ($n=321$ cases) confirmed that high levels of expression of OSM and OSMR mRNA were associated with low levels of ESR1, low expression of a set of ESR1 regulated genes, and that high levels of expression of OSMR were associated with shorter recurrence-free and overall survival in univariate and multivariate analysis (Prat *et al.* 2010, West *et al.* 2012). Intriguingly, amongst several pro-inflammatory cytokines assessed in previous studies that were shown to regulate ESR1 *in vitro* (including IL6 and TNF), only OSM was associated with reduced expression of ESR1-regulated genes, indicating that OSM may have a unique role in the suppression of ESR1 expression (West *et al.* 2012). Moreover, unlike IL6 and TNF, which have been shown to augment the transcriptional activity of ESR1 in some studies, OSM not only reduces expression of ESR1 but also blocks estrogen-induced expression of progesterone receptor (West *et al.* 2012). This distinction between OSM and other inflammatory cytokines may in part be due to differences in their respective signal transduction mechanisms. For example, in MCF7 and T47D breast cancer cells, OSM is a more potent stimulant of MAPK signalling than IL6, correlating with its more robust effects on suppression of ER (Underhill-Day & Heath 2006, West & Watson 2010, West *et al.* 2012). This difference in MAPK-inducing capacity has also been observed in other cell types such as fibroblasts and lung alveolar epithelial cells (Blanchard *et al.* 2001, Hintzen *et al.* 2009).

Role of tumour-associated macrophages in cytokine-mediated suppression of ER

Results from multiple studies support the hypothesis that macrophage-derived cytokines may be an important factor in response to chemotherapies and radiation therapies (as reviewed by De Palma & Lewis (2013)). An additional role for tumour-associated macrophages in endocrine resistance is indicated by the inclusion of CD68 as one of the 16 genes probed in the Oncotype Dx (Genomic Health) recurrence score, consistent with a role for tumour-associated macrophages in modulating response to endocrine therapy

(Kaklamani 2006, Baumgarten & Frasor 2012). Results of clinical studies of breast cancer cohorts have indicated that tumour-associated macrophages (particularly those expressing a proliferation marker, PCNA, in addition to the general macrophage marker CD68) are associated with ER-negative status and poor prognosis in breast cancer (Campbell *et al.* 2011–2013). Campbell *et al.* (2013) probed the immune signatures of breast tumours enriched in PCNA⁺CD68⁺ macrophages and observed high levels of M1-associated genes (including TNF, IL6, and IL1 β) compared with tumours with low levels of PCNA⁺CD68⁺ macrophages, indicating that proliferation of intratumoural macrophages occurs primarily in an M1 environment. M2 macrophages have also been associated with ER-negative status. A recent, large breast cancer cohort study of CD68 and CD163 (a scavenger receptor associated with M2 macrophages) has revealed that CD163 correlated with increased tumour size, grade and hormone receptor negativity (Medrek *et al.* 2012). The key factors associated with the recruitment of tumour-associated macrophages, such as the macrophage growth factor CSF1 and its receptor CSF1R, are also associated with high grade (Beck *et al.* 2009) and poor prognosis in breast cancer (Kluger *et al.* 2004). Furthermore, recent results have indicated that specific receptors of macrophage-secreted cytokines are associated with distinct breast cancer subtypes (Levano *et al.* 2011). For example, results from gene expression analyses indicated that CD44, MET, TGFBR2, OSMR and EGFR were enriched in basal-like breast cancer cells when compared with luminal-like cell lines. While tumour-associated macrophages and their secreted factors are clearly implicated in progression of breast cancer, future studies are required to elucidate the complex role of tumour-associated macrophages in endocrine resistance.

Macrophage-derived cytokines and factors have been implicated in suppression of ER. Katzenellenbogen and colleagues observed that exposure of MCF7 cells to macrophage-conditioned media resulted in the suppression of ER levels via c-SRC-, MAPK- and PKC-dependent mechanisms (Stossi *et al.* 2012a). Briefly, THP1 macrophages were polarised to either M1 or M2 states and then the conditioned media was exposed to MCF7 cells *in vitro*. The effect on suppression of ER was strongest in M1-polarised THP1 cells, although suppression of ER was achieved with both resting THP1 and M2-THP1 cells. Tumour-associated macrophages are a source of pro-inflammatory cytokines and growth factors such as EGF, TNF, IL6 and OSM (Lewis & Pollard 2006, Biswas *et al.* 2013, Vlaicu *et al.* 2013), each of which have been implicated in suppression of ER (Table 1). Results from previous macrophage and tumour cell co-culture studies have

indicated that macrophage-derived TNF promotes invasive properties in breast tumour cell lines (Hagemann *et al.* 2004, 2005). As discussed previously, M1 type macrophage gene expression patterns have been associated with high levels of proliferating macrophages in breast tumours (Campbell *et al.* 2013). Furthermore, Katzenellenbogen and colleagues determined that the macrophage-stimulated hyperactivation of MAPK resulted in a novel mechanism of ER transcript repression via ERK2 recruitment to the *ESR1* locus. Although the specific macrophage-derived factors affecting ER regulation were not identified (Stossi *et al.* 2012a), results described in a subsequent abstract indicated that the unknown factor may be the EGF-family member amphiregulin (Stossi *et al.* 2012b). Intriguingly, Grant *et al.* (2002) observed crosstalk between OSM and EGF signalling, resulting in increased ER suppression. Results from additional studies have indicated that EGF reduces ER levels in an MAPK-dependent manner (Oh *et al.* 2001), and that OSM and the EGF family member, heparin-binding-EGF (HBEGF), are potentially often co-secreted by tumour-associated macrophages in breast cancer (Vlaicu *et al.* 2013). In breast cancer, expression of OSM correlates strongly with markers of macrophages and other myeloid leukocytes, including CD14 and CD163, but correlates very weakly with lymphocyte markers (West *et al.* 2012). Furthermore, OSM induces expression of EGF in breast cancer cell lines, indicating an autocrine mechanism of crosstalk between OSMR and EGFR-family signalling (West & Watson 2010). Further work is required to obtain better understanding of the specific tumour microenvironments in which pro-inflammatory cytokines and other inflammation-derived factors mediate suppression of ER in breast cancer.

Inflammation-induced anti-microbial peptides: potential biomarkers for cytokine action and inflammation-mediated suppression of ER

As there are many causes of resistance to endocrine therapy, it is likely that any strategy to overcome resistance will only be beneficial in certain subsets of patients where specific mechanisms are operative. Therefore, it is important to link specific mechanisms to relevant biomarkers. Amongst the various actions that different cytokines may have on epithelial cells, induction of antimicrobial peptides that mediate aspects of the innate immune response by pro-inflammatory cytokines is important, not least because of the very high levels of expression observed for these proteins. These AMPs encompass several gene families including defensins and S100 proteins. While some are

expressed very focally within tissues and induced more generally only under stress conditions, others are not expressed in normal tissues but are highly inducible by cytokines. The S100A7 protein is an inducible antimicrobial peptide, known to be involved in innate immunity and epithelial defense (Glaser *et al.* 2005, Schroder & Harder 2006, Harder *et al.* 2007, Arnett & Seveau 2011). S100A7 was originally identified in skin but was subsequently shown to be expressed in certain tumour types and stages. S100A7 is rarely expressed at high levels in normal tissues, and when present is mostly associated with hair follicles (Alowami *et al.* 2003, Webb *et al.* 2005). Induction of S100A7 is strongly associated with inflammation in skin and in tumours (Al-Haddad *et al.* 1999, Webb *et al.* 2005) and S100A7 is present at very high levels in the subsets of *in situ* and invasive tumours (Al-Haddad *et al.* 1999, Alowami *et al.* 2003). In fact, S100A7 has been identified in unbiased studies of mRNA and protein expression as amongst the most highly expressed genes in certain subsets of breast tumours (Leygue *et al.* 1996, Al-Haddad *et al.* 1999, Emberley *et al.* 2003, 2004). Some of its effects are mediated by intracellular interaction with JAB1 (Emberley *et al.* 2003, 2005), but S100A7 is also secreted and has chemotactic effects on inflammatory cells (Jinquan *et al.* 1996). Indeed, the mouse S100A7 homologue recruits tumour-associated macrophages in a murine orthotopic breast cancer model (Nasser *et al.* 2012). S100A7 may therefore regulate and be regulated by inflammatory processes associated with the innate immune response (Foell *et al.* 2007, Wolf *et al.* 2008, Ehrchen *et al.* 2009), and its high inducibility and high levels of expression are assets for any biomarker.

In common with other antimicrobial peptides, expression of S100A7 is strongly induced by pro-inflammatory cytokines in skin (Di Nuzzo *et al.* 2000, Wolk *et al.* 2006, Simanski *et al.* 2013) and can also be regulated by ESR2 (Skloris *et al.* 2007). Accordingly, S100A7 is well recognised as a marker of skin inflammation in conditions such as psoriasis. In breast cancer, OSM not only suppresses ER but is also a strong inducer of S100A7 in both ER-positive (MCF7 and T47D) and ER-negative (MDA-MB-468) breast cancer cell lines (West & Watson 2010). Although other pro-inflammatory cytokines can also induce S100A7 to some degree, several of these are most effective in synergy with OSM (West & Watson 2010). Analysis of human breast tumours has confirmed that OSM and OSMR are significantly associated with expression of S100A7. Furthermore, S100A7 only correlates with poor outcome in those tumours with high levels of expression of OSMR (West & Watson 2010). Therefore, S100A7 has the potential to be a tumour cell biomarker of OSM-mediated suppression of ER

and draws attention to the potential role of other antimicrobial peptides as biomarkers.

Potential for targeted therapy to restore expression of ESR1 and anti-estrogen sensitivity

Targeting tumour inflammation could allow the reversal of suppression of ER and restoration of sensitivity to endocrine therapy. However, a complex relationship between inflammatory cells and endocrine therapy may exist and must be studied in greater detail. For example, anti-estrogen efficacy may be modulated by the tumour microenvironment. Results from preclinical studies indicated that NK cells play a role in the anti-tumour effects of tamoxifen via a TGF β 2-dependent mechanism (Arteaga *et al.* 1999). Recent preclinical studies by Clarke and colleagues studying the ability of the autophagy inhibitor hydroxychloroquine (HQC) to target endocrine-resistant xenografts have suggested that tamoxifen and fulvestrant differentially modulate the functioning of macrophages in the breast tumour microenvironment (Cook *et al.* 2014). The combination of HQC and tamoxifen increased the anti-estrogen responsiveness and also led to an increase in peripheral infiltration of macrophages, while the combination of HQC and fulvestrant led to reduced anti-estrogen responsiveness and decreased peripheral infiltration of macrophages. The authors also observed that fulvestrant treatment alone reduced the killing ability of macrophage cells *in vitro* and reduced peripheral infiltration of macrophages *in vivo*. The results of these studies indicate that targeting inflammation may have an important role in the prevention of endocrine resistance in ER-positive breast cancer and underscore that macrophages may have multiple roles in breast cancer.

A growing body of data supports a model where suppression of ER can play a key role during inflammation-mediated tumour progression in breast cancer patients. This potentially opens a new avenue for improved therapy. Results from epidemiological studies have revealed an association of NSAID use with reduced risk and severity of breast cancer (Kwan *et al.* 2007, Holmes *et al.* 2010), and increased levels of PTGS2 (COX2) in breast cancer have been associated with increased risk of breast cancer and a poorer prognosis (Fornetti *et al.* 2014). Blockade of inflammation in breast tumours may reverse the suppression of ESR1 expression in ER-positive tumours with low levels of ESR1 or tumours that are clinically ER-negative. This in turn could enhance clinical responses to endocrine therapy (Schiff & Osborne 2005, Billam *et al.* 2009, Brinkman & El-Ashry 2009). It is well established that response to endocrine therapies is closely related levels of ER.

In ER-positive cell lines, culture conditions that promote higher levels of expression of ER result in improved response to estradiol (E₂) and effectiveness of inhibition by SERMs (Sabnis *et al.* 2011). In ESR1-negative tumours, induction of ER has not been attempted *in vivo*. But in some ESR1-negative cell lines, re-expression of ESR1 can result in inhibition of growth, restore a functional ER pathway and re-establish responsiveness to tamoxifen (Bayliss *et al.* 2007). A potential explanation for these observations lies in the complex role of the second ER, ESR2 which is not currently considered in the clinical assignment of ER status. In tumour cell line studies, both ESR1 and ESR2 bind E₂, but ESR2 is thought to mostly oppose the action of ESR1 and is typically anti-proliferative when overexpressed in ESR1-positive cells (Murphy *et al.* 2005). Expression of ESR2 in ESR1-expressing cells also confers enhanced responses to tamoxifen (Murphy & Watson 2006, Hartman *et al.* 2009). Results from recent studies have indicated that these conclusions, which are based predominantly on results from studies of transient expression, may need re-examination (Jonsson *et al.* 2014). However, consistent with these laboratory observations, an overall positive association between ESR2 expression and good clinical outcome in ESR1-positive tumours has been described (Murphy & Watson 2006, Hartman *et al.* 2009, Motomura *et al.* 2010). However, the effects of ESR2 in ESR1-negative tumours may be different. There are two subgroups of clinically ER-negative tumours; ESR1-negative/ESR2-positive (approximately two-thirds of clinically ER-negative tumours) and ESR1 negative/ESR2-negative (approximately one-third of ER-negative tumours). In the former subgroup of clinically ER-negative tumours, ESR2 expression unopposed by ESR1 correlates positively with the proliferation marker Ki67 and may confer a worse prognosis (Younes & Honma 2011, Murphy & Leygue 2012). Although largely untested in clinical settings, results from, some recent studies have indicated that these ESR1-negative/ESR2-positive tumours may also be responsive to tamoxifen (Yan *et al.* 2013). Therefore, it seems possible that restoration of expression of ESR1 in ESR1-negative/ESR2-positive tumours *in vivo* may act to either disrupt the pro-proliferative effect of ESR2 or re-engage estrogen-responsive gene pathways, and so may conceivably restore effectiveness of endocrine therapy (Yan *et al.* 2013). In the future, established assays for ESR2 (Skiris *et al.* 2006, Weitsman *et al.* 2006) and markers for the action of ESR2 (Skiris *et al.* 2007) may prove useful in discriminating the biology of ESR1-negative/ESR2-positive tumours in conjunction with progress in the generation of ESR2-specific agents.

While the patterns of intratumoural inflammation can be variable and exert profound positive and negative

Figure 2

Model depicting inflammation-mediated ER suppression. Macrophage infiltration during chronic inflammation results in macrophage-derived factors signalling to tumour cells and suppression of ER levels. The tumour ultimately becomes unresponsive to endocrine therapy and potentially

more aggressive. Identification of biomarkers of this macrophage-tumour cell interaction could identify patients that would benefit from targeted anti-inflammatory agents.

effects on behaviour of cancer in different contexts, it is important to recognise that the cells responsible for this inflammation are genetically normal. Inflammatory cells do not share the ability of the cancer cell population to evolve with new mutations to circumvent therapies, thus offering a potentially more stable target. Inflammation has been the focus of extensive and successful drug development, from aspirin to newer antibody-based therapies to revolutionise treatment of chronic inflammatory conditions (Scott 2012). The association between inflammation-derived cytokines and tumour progression has led to the development of targeted anti-inflammatory therapeutics including NF κ B signalling inhibitors, TNF/TNFR antagonists and IL6 antagonists (Goldberg & Schwertfeger 2010, Balkwill & Mantovani 2012, Coussens *et al.* 2013). Targeting tumour inflammation is thus a promising and increasingly recognised approach for providing personalised therapy to cancer patients.

Summary

Specific mechanisms are emerging to explain how the immune system and the intratumoural inflammatory

response can directly affect the level of ESR1 in breast cancer. It remains to be proven that these mechanisms are operative in patients. OSM and possibly other synergistic inflammation-derived cytokines can cause suppression of ESR1 *in vitro* and are correlated with reduced expression of ESR1 *in vivo* (West *et al.* 2012). Strategies targeting intratumoural inflammation to remove the suppression of ESR1 may therefore be effective in enhancing endocrine therapy (Fig. 2). However, these strategies are likely to be beneficial only in certain tumours where intratumoural inflammation is present and cytokine-mediated suppression of ESR1 is in evidence. Additional biomarkers are required to identify breast cancer patients who would benefit from anti-inflammatory treatment (Fig. 2). S100A7, as a functional component of the action of OSM, represents a possible biomarker for this potentially important clinical effect within both ER-positive and ER-negative breast tumours. The notion that inflammation-induced peptides may provide specific biomarkers for this aspect of cytokine activity raises the possibility that this phenomenon can be identified in clinical settings, and that specific therapies targeting cytokine pathways or cytokine-producing cells may be deployed to improve the response to endocrine therapy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Author contribution statement

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