Breast cancer anti-hormonal therapy and rheumatic diseases: linking the clinical to molecular world

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Abstract

Anti-hormonal therapies are used in the treatment of hormone dependent breast cancer. Their use may be complicated with the onset of arthralgia and autoimmune diseases. Recently a clinical relationship between oestrogen, anti-oestrogen therapy and rheumatic diseases has been reported in the literature, but, until now, experimental supporting data about the interacting biochemical pathways involved are still very limited. The understanding of this molecular link may provide important information to elucidate the relationship between autoimmunity and cancer mechanism and treatment.

This review is intended to highlight the relationship between known common molecular mechanisms which explain this association and that probably need to be investigated in future studies.

Introduction

In recent times, the association between autoimmune rheumatic diseases and breast cancer therapy has become evident,[1-3] but the molecular mechanisms at the basis of this relationship are still being debated.[4-6] Our understanding of how cancer therapy can lead to rheumatic autoimmune disease may provide a very important contribution to the elucidation of the autoimmunity "puzzle" and, on the other side, of cancer therapeutic resistance, which can occur through many different mechanism, including the host immune response in which the cancer cell resides.[7,8]

Until now, underlying common intercellular interactions and interplaying biochemical pathways have had been accompanied by minimal experimental supporting data,[9-11] but clinical experience show that this coincidence brings up an interesting observation point. Breast cancers are characterized by the expression of various protein receptors: oestrogen receptor α (ERα), progesterone receptor (PR), and ErbB2/HER2 receptor.[12-14] Approximately 70% of breast cancer are ER α positive and/or PR positive, about 20% over-express HER2, and about 10% do not express ER, PR or HER2 (triple negative). Breast cancer is also characterized by an over-expression and increased activity of the cytochrome P450 aromatase enzyme.[15,16] Aromatase is predominantly expressed in the ovaries in premenopausal woman and is regulated by the gonadotropins follicle-stimulating hormones (FSH) and the luteizing hormone (LH). Both FSH and LH are involved in a feedback regulatory mechanism in which they stimulate the synthesis of aromatase and the subsequent secretion of oestrogen in the ovaries. However, in postmenopausal women, aromatase is primarily expressed in the adipose tissue, which is stimulated by glucocoticoids, and in cancer cells. Therefore, aromatase expression in postmenopausal women is not regulated by gonadotropin signaling pathways and makes aromatase inhibitor (AIs) useful for the treatment of oestrogen-dependent breast cancers in postmenopausal patients. Therefore, endocrine therapies have different mechanism of action. Antioestrogen tamoxifen is a selective oestrogen receptor modulator (SERM) that antagonize the binding of oestrogen to the oestrogen receptor (ER) and could be an option for the treatment of premenopausal patients. On the contrary, aromatase inhibitors (AIs) directly inhibit the production of oestrogen. AIs are the standard first-line treatment in postmenopausal women with tumours positive for oestrogen–progesterone receptors and, recently, are being widely used in premenopausal woman. AIs interfere with aromatase, an endoplasmic reticulum enzyme, a key step in the biosynthesis of oestrogens in many tissues, including the gonads and adipocytes.[17,18] Aromatase is a specific component of the cytochrome P450 enzyme system that is responsible for the transformation of C19 androgen precursors into C18 oestrogenic compounds. This enzyme is encoded by the *CYP19A1* gene located at chromosome 15q21.2, which is mainly expressed in the ovary and the testis. Importantly, extraglandular aromatization of circulating androgen precursors is not only the major source of oestrogen in men (since only 15% of circulating estradiol is released by the testis), but also in women after the menopause. As a matter of fact, the CYP19A1 gene is also expressed in many extraglandular sites such as the placenta, brain, adipose tissue and bone. The regulation of the level and activity of aromatase determines the levels of oestrogens that have endocrine, paracrine, and autocrine effects on target tissues. Oestrogen levels depend also on the genetic polymorphism of CYP19A1, which may have effects on breast cancer prognosis.[19] Oestrogen suppression in premenopausal cancer patients can also be achieved by a gonadotropin (GN)-receptor hormone (RH) analogue or by an ovarian

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surgical ablation. It is well-known that sex steroid hormones may influence the onset, the development and the severity of immune-mediated pathologic conditions.[20,21] Actually in both experimental animals and in humans there is a greater prevalence of autoimmune diseases in females, compared with males and several autoimmune diseases, such as rheumatoid arthritis (RA) or Sjögren syndrome (SS), occur in postmenopausal women. Although postmenopausal oestrogen deficiency triggers the breakdown of immune tolerance and induces autoimmune diseases, the mechanism by which hormones influences autoimmunity is still unknown. Multiple direct or indirect factors that are affected by the change in the oestrogen level and unknown mechanism of action of hormones makes it still impossible to understand in depth the molecular mechanisms involved in autoimmunity. Within the menopausal period a little amount of oestrogen is synthetized from the fat tissue, while in oestrogen positive breast cancer patients, AIs, by shutting off aromatase systemically, reduce oestrogen to undetectable levels in plasma and peripheral tissues. Complete oestrogen deprivation due to AIs therapy may provide the simplest starting point for an explanation for the development of autoimmune conditions described during AIs therapy.

One of the major side effects of anti-hormonal therapy is the development of musculoskeletal symptoms, which range between 5% and 36% in different studies;[22-24] occurrence of autoimmune diseases such as SS, RA, Spondiloarthritis (SpA), Systemic lupus erythematosus (SLE), Systemic sclerosis (Scl) and other autoimmune rheumatologic conditions have been described.[2,25-30] Musculoskeletal symptoms and autoimmune diseases may have an important impact on the quality of life of breast cancer survivors and significantly reduce their adherence, thus limiting the evidence-based survival benefits of anti-oestrogen therapy. Non-adherence to a 5-year regimen of AIs, for example, is associated with increased mortality. Therefore, these symptoms can potentially impair both quality of life and drug efficacy.[31,32]

Musculoskeletal symptoms

Many theories have been proposed in order to explain the mechanism leading to arthralgia manifestations, such as the nociceptive role of oestrogens and subsequent increased sensitivity to pain stimuli following antioestrogen therapy.[33,34] The true incidence of this side effect is not entirely clear due to a lack of a consistent definition of arthralgia. In fact, unspecific joint pain had been associated with the treatment of breast cancer for years before the widespread use of AIs. Donnellan et al first described arthralgia during AIs therapy in 2001, reporting that 16% of patients treated with AIs developed joint pain.[35] Recently the expression AIs-Induced Musculoskeletal Symptoms (AIMSS) has been introduced to indicate the association of arthralgia, symmetric morning stiffness which improves with activity, a feeling of abrupt aging and soft tissue thickening.[36] Research of serum inflammatory biomarkers among women with moderate to severe arthralgia and treated with AIs compared with tamoxifen, revealed raised serum CRP, eotaxin, MCP-1, and VDBP[37]. Recently, clinical trial and case reports suggest that, in many cases, arthralgia during AIs therapy can be attributed to a misdiagnosed inflammatory rheumatologic condition, such as RA or SpA.[22,26] Interestingly, not only do genetic variations in CYP19A1 influence the prognosis of breast cancer patients, by increasing production of aromatase enzyme, but also the risk of Ais-related arthralgia. Since polymorphisms in *CYP19A1* impact oestrogen levels, the presence of functional polymorphisms in this gene is associated with severe arthralgia among postmenopausal breast cancer survivors on AIs therapy through raised IL-6 production.[37-39] These data provide understanding about the role of host oestrogen metabolism and inflammation in the etiology of Ais-associated arthralgia.

Rheumatoid arthritis

Evidence of common molecular mechanism shared by autoimmune diseases and breast cancers treatment is also evident in RA. The presence in synovial fluid of an altered sex hormone balance resulting in lower immunosuppressive androgen and higher immunoenhancing oestrogens determines favourable conditions for the development of the immuno-mediated RA synovitis and synovial hyperplasia.[40,41] This imbalance is due to increased aromatase activity in the synovium. In an experimental study on mouse models the administration of anastrozole, a third-generation AIs, significantly increased the severity of arthritis despite its function on aromatase activity.[42] A potential explanation for this contradiction is related to the effect of anastrozole that induced increased levels of proinflammatory cytokines, such as IL-6 and TNF, and decreased levels of interleukin IL-4, IL-10 secretion.[43] The ability of IL-6 to stimulate aromatase activity leading to high levels of local oestrogens in the synovial fluid is a possible explanation of the risk of RA during AIs therapy. Clinical studies have shown increased circulating levels of IL-6 in patients with breast cancer as well as an association between higher circulating levels and more advanced stages of disease including metastasis.[44,45] It should be noted that in RA anastrozole suppress the differentiation of naive T-cells to regulatory T(Treg)-cells that actively suppress the activation and expansion of autoreactive immune cells. After administration of anastrozole in rats with type II collagen-induced arthritis (CIA), there is a change of Th1/Th2 balance and an increased serum level of IgG2a anti-collagen II, which plays an important role in the pathogenesis of RA. The switching of the IgM isotype to IgG2a and IgG2b isotypes is mediated by proinflammatory cytokines secreted by Th1 cells, which are fundamental in the pathogenesis of RA. The Th1-type IgG2 subtype activates the complement cascade and plays a crucial role in the development of damage. CIA also showed that treatment with tamoxifen, compared with AIs, had no effect on postmenopausal CIA rats leading to the hypothesis that, in patients with breast cancer diagnosed after menopause and in patients treated with SERM, the occurrence of articular symptoms seems linked to the biological effect of AIs.[42]

Spondiloarthritis

Growing evidence has demonstrated that AIs can sometimes induce some subsets of SpA named Undifferentiated Spondyloarthritis (USpA).[27] For several years, studies have reported severe reduced mobility of the hand, wrist, feet and the occurrence of the *trigger finger* during AIs treatment in the absence of autoantibodies development or a correlation between pain and inflammatory markers, suggesting a localized enthesitis/tenosynovitis rather than a systemic inflammatory process.[46,47] Physical findings of the foot, ankle and hands were consistent with plantar fasciitis, Achilles tendinitis, whereas hand tenosynovitis has been also demonstrated by MRI

tendon sheath enhancement;[48] inflammation and subsequent narrowing of the A1 pulley causes pain, clicking, and loss of motion caused by a difference in diameter between the flexor tendon and its retinacular sheath of the affected finger. The aetiology of tendon disease is acknowledged to be multifactorial, however in AIs patients the involvement of local and/or systemic inflammation has been demonstrated and mechanical causes can be excluded. The pulley system is a typical example of functional enthesis in the hand and the hand involvement is considered as one of the most common presentation patterns of arthritis particularly in the SpA.[49] Studies on digital pulleys and functional enthesitis in PsA patients suggest that inflammatory changes could be related to the dactylitis process. Local inflammatory mediators are considered crucial to the onset and perpetuation of tendinopathy. Cytokines such as tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), alongside growth factors, such as transforming growth factor beta (TGF-β) and platelet-derived growth factor, are released from tendon stromal and immunoregulatory cells in response to tissue injury. It should be noted that in particular IL-17 induce the production of IL-6, TNF- α, matrix metallorpoteinase (MMPs) and inducible NO synthase by fibroblasts, macrophages, and endothelial cells.[50] The inflammation process results in the production of excessive and inappropriate matrix protein and fibrosis responsible of pulley thickening, as demonstrated in subjects affected by PsA compared with healthy controls. IL-17 plays a key role in fibroblast-driven inflammation, as it promotes an increased production of key proinflammatory cytokines and cause increased tenocyte apoptosis. IL-17 also promotes increased production of collagen III and MMP 13 indicating disrupted matrix regulation. Loss of control of Th17 cell and IL-17 signalling is a common pathogenic mechanism in chronic inflammatory diseases, such as RA and PsA, and has a documented association with entheseal involvement.[51] In AIs patients oestrogen deficiency induces the differentiation of Th17 cells and IL-17 production. The function of IL-17 in tumour immunity is a controversial subject. Recently, IL-17A has emerged as a critical factor in enhancing breast cancer-associated metastases. The effects of IL-17 on tumour development are directly influenced by the induction of the expression of chemokines and vascular endotelial growth factor (VEGF) that lead to recruitment of specific subsets of immune cells to the site of the inflammation and the induction of angiogenesis. Interestingly, systemic neutralization of IL-17A significantly reduces breast cancer associated metastasis in arthritic mice by reducing CXCL12/SDF-1 expression in the metastatic niches. Treatment with the anti-IL-17 antibody reduced the expression of SDF-1/CXCL12, which are necessary for the formation of metastasis, in bones and lungs.[52]

Sjögren syndrome and systemic lupus erythematosus

Development of SS have been described during AIs treatment.[53,54] Mice with deficiency of aromatase (ArKO) have been created by targeting the *Cyp19a1* gene. *Ar*KO mice develop marked abdominal adiposity, suggesting that aromatase/oestrogens control the adipose phenotype through the regulation of lipid metabolism.[55] Macrophages are crucial components of adipose tissues that are involved in physiological and pathological remodelling. In *Ar*KO mice, monocytes are recruited to the adipose tissues to become M1 macrophages and produce MCP-1, IL-1β, IL-6, IFN-γ, and TNF-α, promoting systemic proinflammatory signalling. Interestingly, *Ar*KO mice spontaneously develop an autoimmune disease resembling SS lesions through B-cell hyperplasia and autoantibody production.[56] Interestingly, in the salivary gland tissues of women with SS the fat tissue changes and the expression of MCP-1 is significantly up-regulated compared with those from healthy controls. Studies show that salivary gland cells with adiposity controlled by aromatase may produce MCP-1 to attract macrophages to the target organ. Accumulated M1 macrophages might secrete inflammatory cytokines to enhance SS-like lesions and function as antigen-presenting cells in the target organ to develop SS-like lesions. The expression of *Mcp-1* mRNA in the salivary gland is regulated by aromatase/oestrogens and enhanced by aromatase inhibitors (AI) treatment;[57] however, it was not enhanced in the liver and spleen. These findings suggest that the specificity of the salivary gland as a target organ in SS may be explained by the oestrogen deficiency–induced phenotypic change of salivary glands. The hallmark of SS are antibodies against the Ro52 also known as *TRIM 21, a* component of the Ro/SSA (Sjögren syndrome-associated) antigen. TRIM2 is a 52kD protein that has a RING domain with E3 ubiquitin ligase activity.[58] Pathological roles for SSA in its roles for E3 ligase activity in SS or SLE patients have been supported by the study with *Trim21* null mice which develop systemic autoimmunity, underlining that the physiological function of Trim 21 are mainly attributed to the area of the immune system pathway control and associated with signalling pathways concerning, for example, cell division by inhibiting the activation of the transcription factor NF-KB.[59] Tim 21 is expressed ubiquitously, but it is the highest in immune organs, such as lymph nodes, spleen and thymus in the mice. It is almost localized in the cytoplasm and translocates from the cytoplasm to the cell surface in apoptotic or stressed cells (by oxidative stress, UV light, oestradiol treatment, viral infectious). Trim 21 may regulate T-cell activation or proliferation, since over-expression of TRIM21 has shown to increase IL-2 production in CD28-stimulated Jurkat T-cells (immortalized line of human T lymphocyte cells that produce large amount of IL-2 after stimulation). Reduced IL-2 results in the suppression of activation-induced death and increased longevity of autoreactive T-cells in patients with SLE. TRIM 21 increased apoptotic cell death, which could be a source of TRIM 21 autoantigen and may induce the production of TRIM21 autoantibodies. The autoantibodies could cause the subsequent inflammatory condition and create a positive feedback amplification loop of inflammation. Some studies show that TRIM21 autoantigen negatively regulates the development of autoimmune diseases SLE and SS[60] and may be directly involved in reduced cellular proliferation and increased apoptotic cell death, turning off the activation of nuclear factor KB (Nf-KB). This plays an important role in pathogenesis of SLE and SS patients through its effect on the transcription of proinflammatory cytokines and antiapoptotic pathways. The same signalling pathway is an active player in human cancer initiation, development, metastasis and resistance to treatment. The observations of a lower incidence of breast cancer in SS or SLE patients and the likely inhibition of E3 ligase activity of SSA by auto-antibodies against SSA in these patients have led to speculate that there is also an oncogenic role for SSA/TRIM 21 in breast cancer.[61] Interestingly, SSA/Trim 21 dysregulation contributes to the progression of autoimmune diseases, but also of different human malignancies. In breast cancer TRIM21 serves as a potential prognostic and therapeutic biomarker[62] and functions as a tumour suppressor. Indeed, if TRIM21 is downregulated, it is associated with poor outcomes.[63] Moreover TRIM21 is capable of ubiquitination and degradation of oncoproteins involved in the maintenance of cell stemness, such as SALL4 and OCT1; it is in-

volved in the regulation of glycolysis and DNA repair and is able to affect the progression of the cell cycle, autophagy, and apoptosis by modulating the expression of p53. Also TRIM 21 is found to be capable of down regulating the expression of SAL-Like 4, a transcription factor that enhances proliferation and migration in breast cancer and inhibits also MCF-7 cell, that is an oestrogen positive breast cancer cell line.[64]

Other connective tissue diseases

Few cases are reported in the literature regardless of the occurrence of SSc and CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysmobility, sclerodactyly and telangiectasis) during anti-hormonal treatment.[28,65,66] As signal transduction pathways may be shared by breast cancer and fibrosis, and highlighted by the gene profiling revealing the oncogenic signature in SSc patients, we don't really know if SSc is a result of cancer or a side-effect of the therapy. Transforming growth factor β (TGF β) has long been implicated in fibrotic diseases, including the multisystem fibrotic diseases SSc or limited form as in CREST syndrome. During AIs therapy a trigger activates expression of cytokines and TGF β which lead to an activation of fibroblasts and an increase in collagen synthesis. TGF β induces an excessive transformation of CD-34 positive fibroblast precursor cells in myofibroblasts. This in turn leads to a thickening and sclerosis of the connective tissue. TGF β has a paradoxical role in breast cancer: in the early stage it inhibits cellular transformation and prevents cancer progression; in late stage TGF β plays a key role in promoting tumour progression: facilitating epithelial to mesenchymal transition, stimulating angiogenesis and inducing immunosuppression. The effect of tamoxifen on TGF β expression have also demonstrated that tamoxifen leads to the release of active TGF β from the latent precursor via a non-transcriptional pathway and that this is a potent antimitogenic and pro-apoptotic mediator in many cancer cells.[67] Indeed, TGF β has been involved in tamoxifen-induced cellular signalling in breast cancer and in dose and time dependent effects, increase of TGF-β transcription and production in ER-dependent tumour following oestrogen ablation and appears to be directly linked to G1/G0 arrest, cytostasis and pro-apoptotic effect of therapy.

Conclusions

This review showed possible common pathogenetic mechanisms that link anti-oestrogen therapy and the development of autoimmune diseases in breast cancer patients. Indeed, this connection needs to be investigated in future studies to better understand the intricate interconnection of autoimmunity and cancer. Therefore, gaining knowledge of the effects of anti-oestrogenic drugs on immune function may bring us closer to elucidating some drug resistance pathways and possibly developing drugs. It must be pointed out that breast cancer itself may induce the appearance of both clinical manifestations and serum autoantibodies and only appropriate longitudinal study may really confirm or not an autoimmune paraneoplastic syndrome or a response of the body to cancer, which can explains, for example, a reduction in the risk of breast cancer among elderly women with RA and SLE[60] and lower autoimmune disease incidence rates in female breast cancer patients.[1] Moreover the suspicion of drug-induced autoimmune disease must be taken into consideration with the onset of symptoms with the use of a new drug, such as AIs.[68]

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