Review

Update on inflammatory breast cancer

Florence Lerebours, Ivan Bieche and Rosette Lidereau

INSERM E0017/Oncogénétique, Centre René Huguenin, St-Cloud, France

Corresponding author: Florence Lerebours, f.lerebours@stcloud-huguenin.org

Published: 20 January 2005

Breast Cancer Res 2005, **7**:52-58 (DOI 10.1186/bcr997)

Abstract

Inflammatory breast cancer (IBC) is both the least frequent and the most severe form of epithelial breast cancer. The diagnosis is based on clinical inflammatory signs and is reinforced by pathological findings. Significant progress has been made in the management of IBC in the past 20 years. Yet survival among IBC patients is still only one-half that among patients with non-IBC. Identification of the molecular determinants of IBC would probably lead to more specific treatments and to improved survival. In the present article we review recent advances in the molecular pathogenesis of IBC. A more comprehensive view will probably be obtained by pan-genomic analysis of human IBC samples, and by functional *in vitro* and *in vivo* assays. These approaches may offer better patient outcome in the near future.

Introduction

Inflammatory breast cancer (IBC) is diagnosed on the basis of signs of rapid progression, such as localized or generalized breast induration, redness and edema [1]. IBC accounts for less than 5% of all diagnosed breast cancers [2].

IBC is the most lethal form of primary breast cancer [2]. Surgery and/or radiation therapy offers a 5-year survival rate of less than 15% [1]. The current consensus treatment is first-line chemotherapy with an anthracycline-based regimen, possibly combined with a taxane, followed by mastectomy and axillary lymph node dissection for responders, locoregional radiotherapy and, when appropriate, hormone therapy [3,4]. The benefits of dose-intensive therapy and bone marrow transplantation are not clearly established in this setting [5,6]. Maintenance adjuvant chemotherapy and new therapeutic approaches are under study. Despite multimodality treatments, the prognosis remains poor, with a 3-year survival rate of only about 40%, compared with 85% among patients with non-IBC [2,3]. These survival data have hardly improved in the past 5 years [3,7].

The main issue in IBC is to identify the specific pattern of genetic changes accounting for this particular phenotype and aggressiveness, so that we can develop more effective targeted treatments. Little is known of these biological and molecular mechanisms, for several reasons. First, IBC is rare. Second, the small size of diagnostic samples may have hindered past molecular studies. Third, because of their similar treatment, IBC is rarely studied separately from other forms of locally advanced breast cancer (LABC), despite differences in age-specific incidence rates, clinical presentation, histology, hormone receptor status and, finally, prognosis [8–11]. The molecular mechanisms underlying these distinct clinicopathological entities are likely to differ, and should thus be studied comparatively.

It is highly probable that the identification of significant molecular changes in IBC would help with diagnosis, with treatment response prediction, and with the development of new therapeutic targets. As about one-third of patients are disease-free 10 years after treatment, it would be useful to be able to identify the two-thirds of patients requiring intensified, prolonged, or new treatments. Most of the prognostic parameters used in non-IBC are unfortunately not relevant to IBC. The two main prognostic factors in early breast cancer (stages I and II) are the number of involved axillary nodes and the tumor size, but precise tumor measurement is often impossible at IBC diagnosis and most patients have axillary lymph node involvement.

The present review will focus on clinicopathological and biological knowledge of IBC.

Clinicopathological data

Briefly, women with IBC present at a younger age than women with non-IBC [2,8,12], with a rapidly (within 6 months) progressing inflammatory tumor associating redness, warmth, pain, induration, and edema (also known as 'peau d'orange' [i.e. 'orange skin']). A tumor mass may

bFGF = basic fibroblast growth factor; ER = estrogen receptor; IBC = inflammatory breast cancer; IL = interleukin; LABC = locally advanced breast cancer; RT-PCR = reverse transcriptase-polymerase chain reaction; VEGF = vascular endothelial growth factor.

or may not be present. Most patients have palpable invaded axillary lymph nodes, and up to 30% have distant metastases at diagnosis [1].

There is disagreement over whether breast cancer with secondary inflammatory signs qualifies as IBC. Several authors consider that survival rates among patients with these neglected LABCs are similar to those of women with 'primary inflammatory breast cancers' [13,14]. Biological differences have been found between primary IBC and other forms of LABC, however, and there is a growing consensus that it is preferable to distinguish between these two forms [8,10,15–17]. The rapid onset of IBC in a previously healthy breast, one of the most important characteristics of the disease, is likely to be subtended by particular molecular alterations. For these reasons, we feel that the term 'secondary inflammatory breast cancer' is inappropriate.

Dermal lymph emboli on skin biopsy are a pathological signature of IBC, and are generally associated with clinical inflammatory signs. However, dermal lymphatic invasion is identified in fewer than 75% of IBC patients, mainly because of sampling heterogeneity [18]. IBC can be reliably diagnosed in the absence of this pathological feature. It should also be noted that dermal lymphatic invasion can be associated with all breast carcinoma subtypes [19].

The percentage of infiltrating ductal carcinoma and other histological subtypes is similar to that of non-IBC [1]. About two-thirds of IBCs are of high grade, a rate far higher than in non-IBC [1,20]. Angiolymphatic invasion by tumor cells is frequent in IBC, while invasion of the dermis outside the lymphatic vessels is uncommon; this feature distinguishes IBC from neglected secondarily inflammatory breast tumors [9].

Finally, the diagnosis of IBC is based on clinical signs and is reinforced by several pathological findings.

Biological data

Hormone receptors and proliferation rates

Given its high histological grade, IBC is more frequently estrogen-receptor (ER)-negative than non-IBC [1,10,20]. Up to 60% of IBCs lack hormone receptor expression, whereas other forms of LABC are more likely to be ER-positive [8,10].

Higher proliferation rates than in non-IBC, including other forms of LABC, have been observed with several methods (labeling index, Ki67 and S-phase fraction) [10,12,21].

Classical genes involved in non-IBC

As alterations to *ERBB2*, *EGFR* and *TP53* can be associated with greater breast tumor aggressiveness, their roles in IBC have also been investigated.

In a series of 80 IBC samples, *ERBB2* assessed using Southern blotting was amplified in 41% of cases, compared with 19% of 141 non-IBC samples [22]. Using the same method, Prost and colleagues found that 39% of 96 IBC tumors were amplified for *ERBB2*, compared with only 18% of 224 non-IBC tumors [23]. *ERBB2* mRNA expression, studied with northern blotting, is also high in IBC (overexpressed in 61%, compared with 39% in non-IBC) [22]. In the same study, *EGFR* transcripts were observed more frequently in IBC than in non-IBC [22]. Based on real-time quantitative RT-PCR, *ERBB2* mRNA overexpression is also more frequent in IBC (36%) than in non-IBC (26%) [17].

TP53 is mutated in approximately 30% of breast tumors. *TP53* mutations can be detected at the nucleic acid level or at the protein level using immunohistochemistry, although this technique is not always reliable [24]. The *TP53* gene is more frequently mutated in advanced-stage breast cancer and/or aggressive breast cancer. Likewise, *TP53* is mutated in 30–60% of IBCs, with most mutations located in exons 5–8, the mutational hot-spot of *TP53* [17,25–27]. Based on a functional *TP53* expression assay in yeast 57% of 63 IBC samples were mutated, compared with 37% of 27 non-inflammatory LABC samples [17].

Despite a few discrepancies [21,28], the protein expression of the *ERBB2*, *EGFR* and *TP53* genes studied by means of immunohistochemistry is higher in IBCs than in non-IBCs [16,21,29]. Two recently published tissue microarray-based studies of 80 and 34 IBCs, compared with 552 and 41 non-IBCs, respectively, confirmed these results [12,30].

IBC is thus more likely than non-IBC to be hormone receptor-negative, rapidly proliferative, and ERBB2-positive, EGFR-positive, and TP53-positive.

Inflammatory genes

The rapid onset of inflammatory signs and the very high rate of distant metastasis suggest that cytokines, growth factors, and angiogenic factors are involved in IBC. It appears, however, that IBC tumors produce negligible levels of most inflammatory cytokines, including interferon gamma, IL-1, and IL-12 [9].

We used real-time quantitative RT-PCR to quantify the mRNA expression levels of 538 selected cancer genes in human IBC relative to non-inflammatory LABC. None of the best-known inflammatory cytokines (*IFNγ*, *TNF*, *IL-1A*, *IL-1B*, *IL-8*, and *IL-10*) was overexpressed in IBC compared with the other samples, tending to confirm that the inflammatory phenotype of IBC is due to dermal lymphatic blockage by tumor cells rather than due to infiltration by inflammatory cells [31].

Angiogenesis

In addition to being lymphotactic, IBC tends to be highly angiogenic. Using the Weidner method of quantification to study 45 IBC and 22 non-stage-matched non-IBC samples, McCarthy and colleagues observed a significant increase in intratumoral microvessel density in IBC [28]. Colpaert and colleagues obtained histological evidence of intense angiogenesis in samples of 35 IBC samples compared with 104 non-IBC samples, especially in terms of the endothelial cell percentage [32]. This intense angiogenesis could be due to hypoxia, as a correlation has been observed between the hypoxia marker carbonic anhydrase IX and endothelial cell proliferation [32]. Among nine angiogenic factors quantified by means of RT-PCR (vascular endothelial growth factor [*VEGF*], *VEGFR1*, *VEGFR2*, *Ang-1*, *Ang-2*, *TIE-1*, *TIE-2*, *COX-2*, and basic fibroblast growth factor [*bFGF*]), the same authors found that Ang-1, TIE-1, TIE-2, and bFGF were strongly expressed in IBC when compared with non-IBC [33]. High levels of VEGF, bFGF, IL-6 and IL-8 have been found in IBC samples by another group [9].

We identified several angiogenesis-related genes (namely *VEGF*, *TBXA2R*, *PTGS2/COX2*, *THBD/thrombomodulin*, and *ANGPT2/angiopoietin 2*) that were upregulated in IBC. However, other major angiogenic genes (*VEGF2*, *VEGF3*, *VEGF4*, *VEGFR1*, *VEGFR2*, and *VEGFR3*) had similar expression levels in IBC and non-IBC [31].

***In vitro* and *in vivo* models**

SUM-149 and SUM-190 are two cell lines established from primary IBC tumors [34]. Both are able to form tumors in nude mice after mammary fat pad injection. They have been characterized with respect to their ER, *TP53*, and other classical gene expression status. These cell lines have been studied by comparative genomic hybridization and by differential display technology, and the results are outlined in the next section [34,35].

Some insights into the pathogenesis of IBC have also been obtained by studying two human IBC xenografts designated MARY-X and WIBC-9 [36,37]. Nude mice transplanted with MARY-X inflammatory breast carcinoma xenografts develop tumors within lymphatics and blood vessels, and erythema of the overlying skin, as in human IBC [36]. Like most human IBC samples, MARY-X is ER-negative, progesterone receptor-negative, p53-positive, and epidermal growth factor receptor-positive, but is Her-2/neu-negative. MARY-X has been screened for many molecules: integrin and immunoglobulin families, angiogenic factors of the VEGF, fibroblast growth factor, and transforming growth factor families, and candidate proteases and their receptors.

Only two molecules were overexpressed relative to non-inflammatory xenografts, namely E-cadherin and MUC1 [36]. Expression of E-cadherin is thought to be 'lost' during malignant progression. Surprisingly, E-cadherin overexpression and overfunction is present in MARY-X relative to normal non-IBC cell lines and xenografts [36,38]. This overexpression was observed using a primary anti-E-cadherin antibody to examine the pulmonary lymphovascular emboli spontaneously produced in MARY-X-grafted animals [38]. Interestingly, the anti-E-cadherin antibody caused the emboli to disappear. According to that finding, dominant-negative E-cadherin mutants transfected with MARY-X are weakly tumorigenic and do not form lymphovascular emboli. Two studies have reported E-cadherin immunoreactivity within lymphovascular emboli in 90–100% of human IBC samples [16,38]. At the functional level, E-cadherin may cooperate with sialyl-Lewis X/A-deficient MUC1 to favor passive dissemination of tumor emboli, resulting in more frequent and larger pulmonary metastases in MARY-X [39].

The other inflammatory breast cancer xenograft WIBC-9, originating from a patient with IBC, frequently metastasized and induced erythema of the overlying skin, like MARY-X and human IBC [37]. WIBC-9 exhibits aneuploidy and *ERBB2* gene amplification, and lacks hormone receptors. Among the four epidermal growth factors, 18 angiogenic genes and six cytokines, only seven genes (namely IL-8, VEGF, bFGF, angiopoietin 1, flt-1, Tie-2 and Tie-1) are overexpressed in WIBC-9 when compared with non-inflammatory models [37]. The therapeutic potential of VEGF and angiopoietin pathway blockade was explored by injecting vectors encoding soluble Flt-1 and Tie-2 into WIBC-9. Both treatments inhibited the growth of WIBC-9 and suppressed WIBC-9 lung metastasis [40].

Despite some discordant results, these *in vitro* and *in vivo* models have facilitated the characterization of IBC.

Other genes involved in IBC

None of the genetic alterations cited is specific to the inflammatory phenotype of IBC. Other genes are likely to be specifically involved in IBC.

The two inflammatory breast cancer cell lines SUM-149 and SUM-190 have been characterized by means of comparative genomic hybridization: frequent deletions were observed at 3p, 8p, 11p, 11q and 13q, with gains at 1q, 7q, 8q and 17q, suggesting the presence of candidate genes in these regions [34].

In a series of 66 human IBC samples, we found a 52% overall rate of loss of heterozygosity using 71 microsatellite markers located at 21 chromosomal regions on 12 chromosomal arms associated with primary breast cancer (1p, 3p, 6p, 6q, 7q, 8p, 9p, 11p, 11q, 16q, 17p, and 17q), pointing to high genomic instability in

inflammatory breast tumor cells [41]. Furthermore, 3p21-p14, 6p, 8p22, 11q, 13q14, and 17q21 were more frequently altered in IBC than in non-IBC. These findings should facilitate the identification of candidate suppressor genes in IBC.

Candidate genes may also be identified by global analytical approaches to gene expression. By comparing the expression of transcripts from SUM-149, actively growing normal mammary epithelial cells, and the patients' matched lymphocytes, van Golen and colleagues identified 17 differentially expressed genes. Only two genes, *RhoC* GTPase and the lost in inflammatory breast cancer gene *LIBC* (also known as *WISP3*), were respectively overexpressed and underexpressed in inflammatory versus stage III non-inflammatory breast tumor samples by *in situ* hybridization [35]. *LIBC* was underexpressed in 80% of IBC samples versus 21% in non-inflammatory LABC samples, and *RhoC* was overexpressed in 90% and 36%, respectively [35].

LIBC/WISP3 appears to be a good candidate gene in IBC: it is located at 6q22-q23, a frequently deleted region in breast tumors, and *LIBC/WISP3* seems to be a member of the *IGFBP* family, already known for a role in cancer progression [35]. Finally, functional data indicate that *LIBC/WISP3* acts as a tumor suppressor gene in the breast, and that loss of its expression contributes to the proliferative and invasive phenotype of IBC [42].

Using stable human mammary epithelial-RhoC transfectants, van Golen and colleagues demonstrated that *RhoC* GTPase is a transforming oncogene in human mammary cells, leading to a highly invasive phenotype akin to that seen in IBC [43]. *RhoC* GTPase expression seems to be modulated by *WISP3*, and these two genes might thus act in concert to give rise to IBC [44]. Using quantitative RT-PCR, however, we found *RhoC* overexpression only in three of 32 inflammatory breast tumor samples [17].

Among the 538 selected genes that we studied by real-time quantitative RT-PCR in IBC samples, 27 (5.0%) were significantly upregulated compared with non-inflammatory LABC [31]. None of the genes was downregulated. The 27 upregulated genes encoded seven transcription factors (*JUN*, *EGR1*, *JUNB*, *FOS*, *FOSB*, *MYCN*, and *SNAIL1*), four of which are components of the AP-1 transcription factor family (*JUN*, *JUNB*, *FOS*, and *FOSB*). AP-1 has been implicated in a variety of tumoral processes [45]. The other 20 upregulated genes encoded growth factors (*VEGF*, *DTR/HB-EGF*, *IGFBP7*, *IL-6*, *ANGPT2*, *EREG*, *CCL3/MIP1A*, and *CCL5/RANTES*) or growth factor receptors (*TBXA2R*, *TNFRSF10A/TRAILR1*, and *ROBO2*), mainly involved in angiogenesis. Finally, IBC and non-IBC showed similar expression levels of the genes *WISP3/LIBC*, *RhoC* and *E-cadherin*, a finding that conflicts with several other reports [31].

One should be cautious in interpreting biological studies on IBC since many of them have been performed at the RNA level, which may not reflect the functional protein level.

Prognostic factors

By definition, patients diagnosed with IBC have at least stage IIIB disease. Up to 30% of these patients become long-term disease-free survivors, however, and it would be of interest to be able to identify those patients requiring intensified, prolonged, or novel therapies. Unfortunately, specific prognostic factors are lacking in IBC.

Pathological factors

Although a large initial tumor size has been linked to a poorer prognosis [46,47], this criterion would not be very useful as a measurable tumor mass is rare in patients with IBC. Lymph node involvement at diagnosis has also been linked to poorer outcome [48,49]. However, physical examination can overestimate lymph node status in up to 50% of cases and cytologic evaluation is rarely done.

In an attempt to refine prognostication in IBC, Gustave-Roussy investigators developed a staging system named 'Poussee Evolutive' (PEV) based on signs of inflammation and tumor aggressiveness [50]. At diagnosis, about one-third of IBC patients have PEV3 tumors, with inflammation involving the entire breast, whereas the remaining patients (PEV2) have only localized breast inflammation (less than 50% of the breast). We sought correlations between several molecular features, clinicopathological features, and clinical outcome in a series of 64 IBC patients [51]. Respectively one-third and two-thirds of the 64 patients had PEV3 tumors and PEV2 tumors. With the exception of stage IV disease, extensive breast inflammation (PEV3) at the first clinical examination was the main factor associated with poor outcome, in keeping with previous studies [48,49,51,52].

The presence of dermal lymphatic invasion, while not necessary for diagnosis, could also be associated with poor prognosis [18,53], but this is controversial [1,12,46,54].

The response to chemotherapy may be the best prognostic indicator in IBC, as in other forms of LABC and operable breast tumors first treated with first-line chemotherapy. The prognostic value of the response to chemotherapy has mainly been studied in terms of clinical characteristics. There is increasing evidence, however, that the pathologic response, and particularly a complete response, could predict outcome more reliably [55,56]. In IBC, the clinical response has been correlated with survival [48,52,57,58]. The few papers reporting

pathological responses tend to confirm the prognostic value of this criterion [4,59–61].

It is now recognized that IBC patients who respond to chemotherapy are candidates for a mastectomy and axillary lymph node dissection [4,62,63]. As in 'not otherwise specified' breast tumors, lymph node involvement at this stage has prognostic value [7,11,57].

Biological factors

Classical markers of poor outcome in breast cancer have been thought to contribute to poor outcome in IBC too. For example, ER negativity has been linked to poor prognosis in inflammatory breast tumors by some authors [1,20,52,62], but not by others [10,51].

As in non-IBC, the prognostic value of *ERBB2* and *TP53* is controversial [12,22,23,26]. *ERBB2* amplification was not associated with poorer outcome in a series of 67 IBC patients, contrary to a series of 178 non-IBC patients [23]. Applying multivariate analysis to data on 24 patients with IBC, Riou and colleagues found a positive correlation between p53 nuclear overexpression and poor clinical outcome [26]. In another series of 32 IBC patients, *TP53* mutations were associated with large tumors and metastases at diagnosis [25].

In a recent immunophenotypic study of 80 IBC patients compared with 552 non-IBC controls, tissue arrays were used to determine the protein expression of ER, progesterone receptor, EGFR and ERBB2, MIB1, P53, MUC1 and E-cadherin [12]. Five variables were significantly associated with IBC in multivariate analysis: MIB1, *ERBB2* and E-cadherin overexpression, ER negativity, and MUC1 cytoplasmic staining. This five-gene molecular signature of IBC was further explored for its possible prognostic significance. The 5-year survival rates of patients with IBC were not significantly different from those of non-IBC controls fulfilling four or five of these criteria. Furthermore, this non-IBC group had a significantly worse outcome than their counterparts with between none and three of these criteria [12].

Among 538 selected genes, we identified a three-gene expression profile – based on *MYCN*, *EREG*, and *SHH* – which discriminated subgroups of IBC patients with good outcome, intermediate outcome, and poor outcome [31]. *EREG* (epiregulin) belongs to the EGF growth factor family that binds both ERBB1 and ERBB4. *SHH* codes for the most important molecule of the Hedgehog-Gli signaling pathway. Inappropriate activation of the *SHH* pathway occurs in several malignancies [64]. Although unexpected in the context of breast tumorigenesis, *MYCN* was recently identified as a major direct target of *SHH* pathways [65]. This three-gene expression signature of poor-prognosis IBC warrants validation in larger series.

Conclusions

Substantial progress has been made in our knowledge and management of IBC in the past 20 years. In our opinion, the most important factors are the development of *in vivo* models that can be used to determine the role of candidate genes in IBC, and the demonstration that IBC is a disease entity distinct from other forms of LABC. There is now a need for more comprehensive molecular analyses of IBC, using cDNA microarrays or comparative genomic hybridization arrays, as in non-IBC. These global approaches will probably be more fruitful than studies focusing on one or just a few genes. If successful, these studies should pave the way for novel treatments that will improve the currently dismal survival rates of patients with IBC.

Competing interests

The author(s) declare that they have no competing interests.

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