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Review

The "portrait" of hereditary breast cancer

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Summary

Five to ten per cent of all breast carcinomas are of hereditary origin. Many of them have been associated to mutations in the *BRCA1* and *BRCA2* susceptibility genes. No "*BRCA3*" gene has been found to account for the non-BRCA1/BRCA2 breast cancer (BRCAx) families, and BRCAx tumors are increasingly believed to originate from multiple distinct genetic events. Phenotype studies have questioned the existence of specific "portraits" among hereditary breast carcinomas (HBC). They have shown that most BRCA1 tumors have a "basal (epithelial)-like" aspect, while BRCA2 and BRCAx HBC are more heterogeneous. HBC have also been submitted to genetic analyses, notably with the objective of resolving the heterogeneity of BRCAx lesions. The present review aims to summarize recent data on BRCA1, BRCA2, and BRCAx HBC, including hypotheses on the origin of BRCA1 tumors and their paradoxical relations to estrogen-sensitivity.

Introduction

A family history of breast cancer is one of the most significant risk factors for the development of the disease. It is estimated that 5–10% of all breast carcinomas is inherited, the other 90–95% of cases being considered as "sporadic". The *BRCA1* and *BRCA2* genes account for autosomal dominant transmission of susceptibility in a majority of families with hereditary breast-ovarian (*BRCA1*/*BRCA2*) or male breast cancers (*BRCA2*). On the other hand, searches for a "*BRCA3*" gene as basis of non-BRCA1/BRCA2 (BRCAx) breast cancer families have been unsuccessful.

Both *BRCA1* and *BRCA2* are long genes that may be targeted by hundreds of different mutations, of which many have been observed only once. To data, their sequencing is costly, so that it cannot be generalized to all patients suspected to have developed a hereditary breast carcinoma (HBC). It has been previously hypothesized that tumors resulting from mutations in *BRCA1* or *BRCA2* might be identified through their expression of a specific "portrait". According to this, phenotype and genotype analyses of HBC (including BRCAx) have been performed. Meanwhile, the introduction of tools supporting the massive analysis of proteins or genes in tumor samples (tissue and DNA microarrays) has evidenced the existence of only a few classes among non-selected populations of breast tumors. One of

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these, the "basal (epithelial)-like" class appears to be over-represented in BRCA1 tumors, which raises interesting questions on the genesis of these tumors. BRCA2 and BRCAx tumors constitute more heterogeneous groups.

BRCA1 and BRCA2

Detailed descriptions of the *BRCA1* and *BRCA2* genes, including the numerous distinct mutations that can alter the function of their corresponding protein, have been the subject of many reviews (see for instance [1–7] and will not be further discussed here. Data on *BRCA1* and *BRCA2* mutations may be found in the Breast Information Core (http://research.nhgri.nih.gov/bic/) and Human Gene Mutation (http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html) databases.

The development of BRCA1 or BRCA2 tumors has been attributed mainly to the loss of the DNA repair function ensured by these proteins. Indeed, both BRCA1 and BRCA2 are involved in DNA double-strand breaks (DSB) repair. In eukaryotes, two major pathways exist to repair DSB: non-homologous end joining (NHEJ) and homology-directed recombination (HR). NHEJ repairs adjacent broken DNA ends with little or no requirement for extensive sequence homology, whereas the more accurate HR requires an intact template of a homologous sequence either in a homologous chromosome or in a sister chromatid. HR may occur either by "gene conversion" (GC) or by an error-prone "single-strand annealing" (SSA) mechanism. BRCA2 is involved mainly, if not solely, in HR by GC, through its interaction with the essential DSB repair protein RAD51. BRCA1 mutations seem to impair both classes of HR [8], but BRCA1 is also possibly involved in NHEJ by a way implying its colocalization with the RAD50-MRE11-NBS1 complex (see notably [9]). In addition to its importance in DSB repair, BRCA1 could also play some role in nucleotide-excision repair (NER) (reviewed in [10]). Thus, the implication in DNA repair appears to be greater for BRCA1 than for BRCA2.

BRCA1 and BRCA2 must not be seen as single components of linear chains of molecules linking DNA alterations to DNA repair. It is increasingly recognized that they are members of complex and versatile protein network(s) involved in multiple functions. They have been associated to transcription regulation and chromatin remodeling, cell cycle and centrosome regulation, apoptosis induction, ubiquitination and protein degradation ... In breast cancer cells (BCC), their expression level is coupled to cell proliferation, being highest at the G_1-S-phase [11–13] and in proliferating cells, as compared to confluent ones [14]. BRCA1 and BRCA2 mRNA levels are coordinately elevated by estrogens in BCC [15]. The BRCA1 level is also induced in MCF-7 and T-47D BCC lines by prolactin (PRL), which may exhibit a proliferative activity on these cells [16].

While induced by mitogenic (estrogens, PRL) and/or differentiating agents (PRL), BRCA1 appears in turn able to counteract proliferation and differentiation by repressing estrogen receptor (ER) [17], c-Myc [18] and Stat5a (activated by PRL in BCC) [19] transcription activity. Regarding ER, BRCA1 is able to specifically block the AF-2 transcription activation domain of the receptor, leading to reduced transcription of at least two ER-regulated genes, *TFF1* (encoding pS2) and *CTSD* (cathepsin D) [17]. This activity of BRCA1 has been correlated with its down-regulation of the cellular levels of the transcription co-activator p300 in breast cancer cells [20]. Of interest, p300 is also a co-activator for Stat5a [21]. These results raise the possibility that wild-type BRCA1 suppresses estrogen-dependent transcription pathways related to mammary epithelial cell proliferation and that loss of this property by mutant BRCA1 contributes to tumorigenesis. The potential effect of BRCA1 loss on cell differentiation is largely unknown as yet [22].

Genetic bases of BRCAx tumors

To account for the development of non-BRCA1/BRCA2 HBC, no "*BRCA3*" gene has been identified to date. Part of these BRCAx tumors may be associated to rare syndromes, of which breast cancer is only one component. Such syndromes result notably from mutations in *TP53* (Li-Fraumeni), *ATM* (Ataxia Telangiectasia), *STK11*/*LKB1* (Peutz-Jeghers Syndrome), *PTEN* (Cowden Syndrome) [3, 23].

Other BRCAx tumors (and even some sporadic carcinomas) are believed to result from the expression of weakly penetrant but highly prevalent mutations in various genes. For instance, polymorphism has been identified in genes

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associated to the metabolism of estrogens and/or carcinogens (*CYP1A1*, *CYP1B1*, *CYP17*, *CYP19*, *COMT*, *NAT2*, *GSTM1*, *GSTP1*, *GSTT*, ...), to estrogen, androgen and vitamin D action (*ESR1*, *AR*, *VDR*), to co-activation of gene transcription (*AIB1*), to DNA damage response pathways (*CHEK2*, *HRAS1*, *XRCC1*, *XRCC3*, *XRCC5*) (reviewed in [24, 25]). Sequence variants of these genes that are relatively common in the population may be associated with a small to moderate increased relative risk for breast cancer. Combinations of such variants could lead to multiplicative effects. Sporadic cancers likely result from the complex interplay between the expression of low penetrance gene(s) (''risk variants'') and environmental factors. It must be noted, however, that the suspected impact of most of these variants on breast cancer risk should, in most cases, be confirmed in large populations studies. Indeed, low penetrance genes cannot be easily tracked through families, as is true for dominant high-risk genes.

The phenotype of BRCA1, BRCA2 and BRCAx HBC

Numerous studies have allowed to collect pathobiological data on BRCA1, BRCA2 and BRCAx tumors and to define the phenotype of these HBC [26–38].

According to these studies, the phenotype spectrum of BRCA1 tumors appears clearly different from that of sporadic or non-selected tumors. BRCA1 tumors are less frequently ER-, progesterone receptor (PR)-, androgen receptor (AR)-, BCL2-, $P27^{KIP1}$-, ERBB2- and lymph node-positive; in contrast, they are more frequently P-cadherin-, cytokeratins (CK) 5/6- and P53-positive. Most of them are of high grade and they have a higher level of proliferation markers and of necrosis than controls. BRCA1 HBC have a higher level of glomeruloid microvascular proliferations (GMPs), which are focal proliferative buddings of vascular endothelial cells resembling a renal glomerulus. Finally, medullary carcinomas are over-represented among BRCA1 tumors and these latter HBC are less likely to have an *in situ* component than controls. Of note, two cell lines/xenograft have been established to date from carriers of a BRCA1 germline mutation. One cell line, HCC1937, is ER- and PR-negative, with a very low ERBB2 level and an acquired mutation of *TP53* with wild-allele loss [39]. A xenograft and a derived cell line have been obtained from another tumor: their characterization revealed an ER-, PR- and ERBB2-negativity, an absence of CK 8 and an over-expression of P53. Again, an acquired mutation (nucleotide substitution) of *TP53* was found [40].

Contrasting with BRCA1 HBC, BRCA2 and BRCAx tumors are more heterogeneous and express an extended phenotype spectrum that is closer to that exhibited by sporadic or non-selected tumors. However, as compared to these latter, BRCA2 tumors are more frequently of high grade, but this has been attributed mainly to a decreased tubule formation, while no difference is generally seen for mitotic count and nuclear polymorphism. For their part, BRCAx tumors are less frequently P53 and ERBB2-positive than sporadic tumors; moreover, they have a lower level of proliferation markers and are of lower grade, with a lesser amount of nuclear pleomorphism.

Data from pathology, biology and genetics now support the existence of only a few major subclasses among breast cancers. According to this, most ER-positive, low-grade tumors may be grouped into a ''luminal (epithelial)-like'' subclass, notably characterized by a high expression level of luminal CKs (CK 8/18/19), ER, PR, BCL2, $P27^{KIP1}$,..., a low expression level of P53 and ERBB2, and a low grade. This subclass groups about 65–75% of breast cancers. Another class, known as the ''basal (epithelial)-like'', includes lesions (about 15–20% of all breast cancers) that are ER- and PR-negative, have a low level of luminal CKs, BCL2, P27, ERBB2 and a high expression level of P53 and of the basal CKs 5/6 and 17. Most of these tumors have a high grade. An ''ERBB2'' group of tumors is also frequently found, which, as its name implies, is exclusively composed of ERBB2-overexpressing tumors; these are generally characterized by a low, if any, expression level of ER, PR, and P53. These three main classes (''luminal-like'', ''basal-like'', ''ERBB2'') have been identified at both the mRNA and protein levels [41–46].

Based on their characteristics, most BRCA1 tumors are to be classified in the ''basal-like'' subtype. Indeed, in a microarray-based analysis of 115 tumors including 18 samples from carriers of *BRCA1* mutations, these latter were strongly associated with the ''basal-like'' subclass. In contrast, two BRCA2 tumors were classified among

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the "luminal-like" group [42–44]. Analysis of a higher number of BRCA2 tumors should help to precise the subtype distribution pattern of these HBC.

As mentioned above, the phenotype spectra of BRCA2 and sporadic cancers are very similar. Intriguingly, a link between BRCA2 and sporadic breast cancers has been recently suggested by the discovery of EMSY. EMSY is a protein which binds BRCA2 precisely within exon 3 (a highly conserved trans-activating region in the N-terminus that has endogenous transcription repressor activity when recruited to a high basal promoter) and is capable of silencing the activation potential of this exon, associates with chromatin regulators HP1beta and BS69, and localizes to sites of repair following DNA damage. EMSY gene maps to chromosome 11q13.5, a region known to be involved in breast and ovarian cancer. EMSY gene is amplified almost exclusively in sporadic breast cancer (13%) and higher-grade ovarian cancer (17%). However, it has not yet been possible to show how (or if) BRCA2 is really involved in sporadic breast cancer [47].

Genetic analysis of BRCA1, BRCA2, BRCAx

As yet, only a few studies have aimed to identify gene signatures that could be specific to BRCA1, BRCA2, or BRCAx HBC. The data obtained need to be confirmed by additional investigations, as the number of samples analysed was generally low.

In a microarray analysis of primary tumors, lesions from seven carriers of a BRCA1 mutation, eight carriers of a BRCA2 mutation, and seven patients with sporadic cases of breast cancer were considered. Statistical analyses were used to identify a set of genes that could distinguish the BRCA1 genotype from the BRCA2 genotype. Permutation analysis of multivariate classification functions established that the gene expression profiles of tumors with *BRCA1* mutations, tumors with *BRCA2* mutations, and sporadic tumors differed significantly from each other. An analysis of variance between the levels of gene expression and the genotype of the samples identified 51 genes that best differentiated among the three types of tumors [48]. This suggests that either a heritable mutation influences the gene expression profile of the cancer, or specific mutations are viable only in a specific gene environment. Of note, and maybe as a consequence of the low number of tumors, the gene signature specifically associated to BRCA1 HBC did not appear to constitute a part of the "basal-like" signature. However, as expected, the expression of the luminal CK 8 gene was low in these tumors, in accordance with previous data. On the other hand, among genes more highly expressed in BRCA1 HBC, as compared to BRCA2, were some that are known to be induced by P53 in response to DNA damage: *MSH2*, *MSH6*, *GADD34*,... As P53 is mutated in a majority of BRCA1 tumors, this raises the possibility of a p53-independent activation of DNA damage response pathways in these HBC. This observation is also in agreement with the fact that the role of BRCA1 in DNA repair is more extended than is the case for BRCA2.

As the BRCAx HBC comprise a histopathologically heterogeneous group, it has been suggested that they may originate from multiple distinct genetic events. Thus, while intensive efforts have not allowed the identification of BRCAx (breast cancer) predisposition genes, attempts have been made to identify distinct and specific genetic signatures. In a small series ($n = 16$) of BRCAx tumors, gene expression profiling identified at least two classes, and differentiated them from BRCA1 and BRCA2 HBC. Moreover, microarray-based comparative genomic hybridization (CGH) to cDNA arrays revealed specific somatic genetic alterations within the BRCAx subgroups [49].

BRCA1 and p53

One of the proteins interacting with BRCA1 is P53. This transcription factor regulates the cellular responses to stress, including DNA damage, by activating the expression of genes involved in cell-cycle arrest or apoptosis. The molecular mechanisms by which P53 senses whether to initiate one process or the other remain, however, largely unknown. Many factors, including cell type as well as expression levels of P53 and other survival factors, are believed to be important for this decision.

Loss of BRCA1 function in cells appears to activate a P53-dependent response, as illustrated by the partial phenotypic rescue observed when homozygous $Brca1^{null}$ mice are crossed to a P53-deficient background ($Tp53^{-/-}$). Homozygous $Brca1^{null}$ embryos die around 6.5 days post-coitus (dpc) due to a cell-cycle block and up-regulation of the P53-activated cell-cycle regulator p21. Cross-

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ing *Brca1*^{null} mice with *Tp53*$^{-/-}$ mice to generate *Brca1*$^{null/null}$/Tp53$^{-/-}$ embryos reveals that in the complete absence of P53, the lethality due to BRCA1 deficiency is postponed to 9.5–10.5 dpc [50]. This indicates that, at least in some cases, cell survival after *BRCA1* mutation could require an alteration of P53. Along the same line, conditional knockout of *Brca1* in mouse mammary epithelium generates breast tumors in 25% of mice. The additional loss of P53 results in the development of breast tumors in 50% of these mice [51]. Again, these data strongly suggest that loss of P53 is important for the development of BRCA1 breast cancers. Numerous studies have shown that overexpression of an abnormal P53 resulting from *TP53* mutation is much more frequent in BRCA1 tumors than in non-HBC and in non-BRCA1 HBC. For instance, 54%, 0% and 5% of P53 alterations were found in BRCA1, BRCA2 and BRCAx tumors, respectively, by [37]. If, as is the case in mouse embryos, BRCA1 deficiency in human breast tissue activates a P53-dependent checkpoint, a strong selective pressure to somatically inactivate P53 in the tumor will result.

As BRCA1 is involved in DNA repair, it is possible that its inactivation by mutation could explain, at least partly, the high frequency of P53 mutations observed in BRCA1 tumors. However, a high level of P53 expression is indeed characteristic of the "basal-like" subtype of breast tumors, no matter whether they have or not a mutation in *BRCA1*, and reflects indeed a higher genetic instability in this subtype of lesions [46]. On the other hand, a role of BRCA1 in generating *TP53* mutations is suggested by the fact that the mutation spectrum of *TP53* is different in BRCA1 tumors, as compared to sporadic, both in mutation distribution and base changes. In BRCA1 HBC, changes are common at *TP53* codons that are not mutation hotspots. Most of the resulting "non-hotspots amino-acids" are physically clustered and are distributed in a region of the protein on the opposite side of the DNA-binding surface [52]. This suggests that the development of BRCA1 lesions might need the modification of the interaction(s) between P53 and one or several regulatory protein(s).

It has been proposed that BRCA1 could serve as a molecular scaffold, assembling proteins involved in the fine-tuning of the P53 response, such as ATM, CHK2 and p300. Depending on the (maybe p300-mediated) acetylation of its C-terminus [50], P53 binding to DNA sequences could induce cell-cycle arrest or apoptosis. A truncated BRCA1 could render a normal P53 unable to arrest cell cycle, while still allowing it to trigger apoptosis. Mutation of P53 could in turn prevent apoptosis, blocking thus any action of P53. A P53-interacting region of BRCA1 is situated in the C-terminal region of the protein, which is frequently truncated after mutation.

While P53 mutations could contribute to the development of BRCA1 tumors, they are clearly not required to generate BRCA2 or BRCAx HBC.

BRCA1 and ER-negativity/"basal-like portrait"

Why are BRCA1 HBC so frequently ER-negative? It has been suggested that this be due to the fact that these lesions occur frequently in young women. Indeed, sporadic tumors occurring at an early age are more likely to be ER-negative than tumors observed in post-menopausal patients. However, in a study of 1131 women with invasive breast cancer, *BRCA1*-mutation carriers were more likely to be ER-negative breast cancers than were women in other groups, after adjustment for age, grade, and histological subtypes ($P < 0.001$) [51].

The reasons behind the preferential "basal-like", ER-negative phenotype of BRCA1 HBC are still a matter of speculation.

One hypothesis is that loss of BRCA1 activity could lead to down-regulation of the ER at a specific time in the development of BRCA1 cancers. This would, indeed, imply extended changes in gene expression patterns, as microarray data have indicated that most ER-positive tumors are "luminal-like", while most BRCA1 HBC are "basal-like". Highly different gene signatures characterize these two tumor subtypes. It increasingly appears that a phenotype conversion from a "luminal-like" to a "basal-like" portrait is rare during tumor progression [46]. It could, however, occur very early in the development of BRCA1 HBC and cannot be excluded as yet.

Along the same line, it has been suggested that BRCA1 activity could be needed to promote an orderly transition of breast cells from a "primitive" "basal-like" phenotype, reminiscent of a breast stem cell portrait, to a "luminal-like" (glandular) phenotype, which is expected in most terminally differentiated cells. BRCA1 loss could prevent this transition [54].

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Another hypothesis is that, in contrast to "basal-like" cells, "luminal-like" ER-positive BCC could be unable to survive their loss of BRCA1 activity. As mentioned above, BRCA1 level is increased by estrogens in breast cancer cells and the protein is a repressor of ER transcription activity [55]. In absence of BRCA1 activity, ER-positive cells could enter an uncontrolled proliferation process favoring the multiplication of non-corrected genetic alterations. It has been repeatedly suggested that metabolic products of estrogens might cause genetic instability, perhaps by inducing free radical-mediated DNA damage and mutations [56–59]. A deficiency in BRCA1 activity in ER-positive cells could prevent the correct repair of DNA damages [60], leading *in fine* to cell death. The considerable extent of BRCA1 involvement in DNA repair (see above) could constitute therein a crucial factor. In contrast to BRCA1, "luminal-like" ER-positive cells could succeed in managing their loss of BRCA2 activity.

An intriguing feature of BRCA1 is its implication in X chromosome silencing. Indeed, mutation, or loss of function of BRCA1 results in an altered phenotype of X chromosome inactivation, a process by which a major heterochromatin domain is established over one X chromosome. XIST is an RNA molecule that coats the inactive X chromosome in female cells and is central to the process by which the entire chromosome is repressed [61]. When BRCA1 is not present in a cell, XIST RNA fails to localize to the X chromosome. The presence or absence of functional BRCA1 does not affect the level of the XIST transcript, just its localization and effectiveness in silencing [62]. Whether the XIST RNA localization phenotype might promote breast cancer or explain the basal phenotype (see above) of BRCA1 cancers remains, however, unknown. We can hypothesize that de-repressed X chromosome could express some oncogene at higher levels than in cells that have one inactivated X chromosome. It is also possible that a gene product expressed only in BRCA1 tumors could prevent the development of the luminal epithelial phenotype or even contribute to reverse it.

Paradoxical relations between BRCA1 and estrogens

As summarized above, the expression spectrum of most biological markers is very similar in BRCA2 HBC and in sporadic tumors. In contrast, the phenotype of BRCA1 HBC is "basal-like" (and thus ER-negative) in the vast majority of cases. This suggests that the development of BRCA1 tumors is largely incompatible with hormone-sensitivity.

On the other hand, there are data suggesting a specific positive association between the occurrence of BRCA1 tumors and a high estrogen level. First, in a combined analysis of 22 studies, the relative risk of breast cancer was shown to decline significantly with age (after 49 years) in *BRCA1*-mutation carriers; this was not observed in *BRCA2*-mutation carriers [63]. This suggests that the high estrogen levels characterizing pre-menopause could favor the development of BRCA1 HBC. Second, contrasting with *BRCA2*, no increased incidence of breast cancer is observed in men heterozygous for *BRCA1* mutations [64]. Circulating estrogen levels are low in men and most of the male breast tumors are ER-positive, as also observed in post-menopausal women [65]. Third, *BRCA1*-mutation carriers are also predisposed to cancer of the ovary, another organ subjected to regulation by estrogens. Fourth, *BRCA1*-mutation carriers are particularly susceptible to develop a breast cancer as a result of pregnancy [66]. Pregnancy increases circulating estrogen levels by approximately 10-fold. Fifth, prophylactic oophorectomy in *BRCA1*-mutation carriers, resulting in estrogen deprivation, led to highly significant 47% reduction in the risk of breast cancer [67].

In general, hormone-based treatments, such as tamoxifen, are not effective in preventing or treating ER-negative breast cancers [68, 69] and doubts have thus been cast about the efficacy of hormonal chemoprevention for BRCA1 HBC [31]. Surprisingly, in a large retrospective case-control study of patients with or without contralateral breast cancer, tamoxifen was highly effective in preventing second primary cancer in *BRCA1*-mutation carriers [70]. According to another study, tamoxifen appeared to be effective in reducing both local recurrence and contra-lateral breast cancer among women with *BRCA1* mutations [71].

In this paper, the term "ER" stands for "ER-alpha". This isoform of the receptor has been evaluated in tumors (including HBC) for more than 30 years and its essential role in breast cancer biology is well-established. ER-alpha expression is

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strongly associated to the "luminal-like" and the receptor represents indeed the main discriminator in breast tumor classification (for a review, see [41, 46]). ER-alpha was long believed to be unique, until an isoform named ER-beta was identified [72]. According to various reports, ER-alpha seems to be the most abundant and functionally the most important in breast tumors (see for instance [73]). However, the exact role of ER-beta is still under investigation. ER-beta has notably been described to act as a dominant negative regulator of ER-alpha-mediated transcription, thus attenuating massive estrogenic stimulation [74]. The role of ER-beta in favoring the antagonistic effect of anti-estrogens is supported by the association between protein expression and favorable outcome after tamoxifen treatment [75].

It has been proposed that the presence of ER-beta could explain, at least in part, the responsiveness of BRCA1 HBC to estrogens/anti-estrogens [76]. In an immunohistochemical analysis ER-beta positivity was observed in 84% (37/44) of HBC compared with 69% of non-familial cases matched for age and year of initial diagnosis. Despite its presence, it seems unlikely that ER-beta could exert any effect by regulating negatively the action of ER-alpha, since this latter is very rare in BRCA1 tumors. ER-beta might play a role that does not need the presence of ER-alpha. It has recently been suggested that ER-beta is localized in the mitochondrion, and could thus play a role in regulating the oxidative metabolism [77]. Mitochondria are central in the regulation of cytoplasmic redox state. Estradiol can protect against ATP depletion, mitochondrial membrane potential decline, and the generation of reactive oxygen species induced by 3-nitroproprionic acid [78]. This effect is possibly ER-beta-mediated. At least in some cases of BRCA1 HBC, ER-beta could permit to reduce the generation of free radicals [77].

To explain the responsiveness of BRCA1 HBC to estrogens/anti-estrogens, another possibility must be taken into consideration, although it remains purely speculative to date. The first BRCA1-mutated "basal-like" (and thus ER-negative) tumor cells appearing in the mammary gland could be protected from (P53-mediated?) apoptosis by factors secreted by their neighboring "luminal-like", ER-positive normal cells in response to estrogens. Anti-estrogens could prevent this effect. However, how to explain that these tumor cells could continue to proliferate in the growing lesion when the relative abundance of the surrounding "luminal-like" ER-positive normal cells decreases? We propose that the tumor cells could progressively escape their need for exogenous factors, possibly as a consequence of *TP53* mutation.

Conclusions

It increasingly appears that a few "portraits" may be found among breast tumors. The subclasses that they defined are characterized by specific gene and marker expression profiles.

As observed with sporadic carcinomas, most BRCA2 and BRCAx HBC express the features of the "luminal-like" phenotype. Further genetic studies should precise the distribution of these tumors among subtypes, as well as to further resolve the heterogeneity of BRCAx HBC.

BRCA1 tumors are mainly, if not exclusively, "basal-like" at both the genotype and phenotype levels. The mechanisms underlying this restricted distribution are far from being understood, but they are likely related to the complex involvement of BRCA1 in proliferation, differentiation, and apoptosis processes. This implication is notably illustrated by the control exerted by BRCA1 on ER, Stat5a, and P53 activity in "luminal-like" epithelial cells. In line with this, one factor deserving further investigations is p300. This histone acetyltransferase may interact with BRCA1, P53, ER, Stat5 and is considered to play a central role in co-ordinating and integrating multiple signal-dependent events with the transcription apparatus [79]. The loss of control of p300 by BRCA1 could trigger mechanisms ultimately leading to apoptosis in "luminal-like" but not in "basal-like" cells.

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