REVIEW

The Spectrum of Triple-Negative Breast Disease

High- and Low-Grade Lesions

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Triple-negative breast cancer is viewed clinically as an aggressive subgroup of breast cancer. In fact, most triple-negative breast cancers are poor-prognosis tumors with a complex genomic landscape. However, triple-negative disease is vastly heterogeneous, encompassing multiple entities with marked genetic, transcriptional, histologic, and clinical differences, with neoplasms in this group ranging from low to high grade. Among the less common low-grade triple-negative lesions, two large subgroups, both with a rather indolent behavior, can be distinguished: a low-grade triple-negative breast neoplasia family, which includes nonobligate precursors of triple-negative breast cancer, and, despite being low-grade, harbors the complex genomic landscape of usual triple-negative breast cancer, and the salivary gland-like tumors of the breast, lacking all the cardinal molecular features of conventional triple-negative breast cancer and underpinned by specific fusion genes or hotspot mutations, which may be of diagnostic and possibly therapeutic utility. Progression to high-grade triple-negative breast cancer likely occurs in both subgroups but at different rates. In this review, we describe the heterogeneity of triple-negative disease, focusing on the histologic and molecular features of the low-grade lesions. Recognition that triple-negative breast cancer is an operational term and that triple-negative disease is heterogeneous and includes low-grade forms driven by distinct sets of genetic alterations is germane to the successful implementation of precision medicine. (*Am J Pathol* 2017, 187: 2139–2151; <http://dx.doi.org/10.1016/j.ajpath.2017.03.016>)

Triple-negative (TN) breast cancers (TNBCs), defined by the lack of expression of estrogen receptor (ER) and progesterone receptor (PR) and absence of human epidermal growth factor receptor 2 (HER2) protein overexpression and *HER2* gene amplification, account for 12% to 17% of breast cancers.¹ As a group, TNBCs are viewed clinically as an aggressive subtype, with an earlier age of presentation and requiring adjuvant chemotherapy to improve survival. Indeed, conventional TNBCs are high-grade carcinomas, with complex genomes, high levels of genetic instability, and a high degree of intertumor and intratumor heterogeneity. The sole gene mutated at high frequency is *TP53*; however, many more genes are affected by mutations at low frequency.^{2,3} Clinically, patients with TNBCs have a high risk of early metastasis and death from breast cancer within 5 years after diagnosis¹ but high rates of complete

pathological response (pCR) after neoadjuvant chemotherapy.⁴ Whereas patients who achieve pCR have a favorable long-term outcome, patients with residual disease after neoadjuvant chemotherapy have a shorter overall survival than those with non-TNBCs.¹

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TNBCs are, however, vastly heterogeneous, encompassing a wide spectrum of entities with genetic, transcriptomic, histologic, and clinical differences.^{1,5} A subset of TNBCs comprises histologically low-grade lesions whose natural history, molecular features, and optimal therapy vastly differ from those of high-grade TNBCs. Recent studies have provided evidence of the existence of a low-grade TN breast neoplasia family, including nonobligate precursors of TNBCs that share genetic abnormalities with high-grade TNBCs.⁶ For example, microglandular adenosis (MGA), initially thought to be a mere hyperplastic lesion, is now best considered a neoplastic lesion with potential to progress to high-grade TNBCs.^{6–10} In contrast, some low-grade TNBCs lack all the cardinal molecular features of high-grade TN disease and may be underpinned by pathognomonic genetic alterations.

We review the heterogeneity of TNBCs, focusing on the low-grade forms of TN disease, and discuss the notion that TN neoplasms may undergo progression. The realization that TNBC is merely an umbrella term and that low-grade TN disease exists and may harbor specific genomic profiles is essential to the accurate classification of these lesions into clinically meaningful subsets that reflect the biology of the disease.

Molecular Features of Conventional TNBCs

When compared with ER-positive breast cancers, common forms of TNBC have distinctive genetic and transcriptomic features.² TNBCs are significantly associated with *BRCA1* germline mutations¹ and collectively characterized by high levels of genetic instability and complex patterns of copy number alterations (CNAs) and structural rearrangements.¹¹ Akin to ER-positive breast cancers, *TP53* (82%) and *PIK3CA* (10%) are the two genes most frequently mutated.² In TNBCs, however, *TP53* somatic mutations are more frequent and enriched for nonsense single-nucleotide variants and indels.^{2,3} Although *PIK3CA* mutations are more frequent in ER-positive breast cancers, the levels of phosphatidylinositol 3-kinase (PI3K)–AKT–mechanistic target of rapamycin pathway activation are higher in TNBCs.² Somatic genetic alterations that affect additional known cancer genes are found in small subsets of TNBCs, in particular those inactivating tumor suppressor genes, such as *PTEN*, *RBI*, and *INPP4B*.²

A clinically relevant finding in common forms of TNBC is a high rate of homologous recombination DNA repair defects similar to those found in tumors that arise in *BRCA1* and *BRCA2* mutation carriers, a concept known as BRCAness.¹ Therefore, patients with TNBC may benefit from platinum-based chemotherapy or inhibitors of poly (ADP-ribose) polymerase, which exploit homologous recombination deficiency (HRD). Recent clinical trials have found that the addition of platinum-based agents to current chemotherapy regimens increases the rates of pCR in TNBC.⁴ Given that HRD induces specific mutational signature and

pattern of CNAs (large-scale state transitions), these two genomic features may predict benefit from these agents. A recent retrospective analysis of clinical trial samples from patients treated with neoadjuvant platinum-based chemotherapy found that a commercially available predictor of HRD, including LST assessment, predicts higher rates of pCR.¹² Nonetheless, these genomic predictors actually indicate scars caused by HRD present in the early stages of tumor development rather than current HRD and may not be optimal approaches. Secondary genetic alterations may restore homologous recombination capacity in tumor cells and elicit resistance to those agents.¹³

Although the TN phenotype was initially considered a surrogate for basal-like breast cancer, several lines of evidence have indicated this is an unjustified oversimplification. Gene expression analyses after the development of the intrinsic gene classification of breast cancer provided evidence of the existence of additional molecular subtypes enriched for TNBCs, such as the claudin-low subtype, characterized by an epithelial-mesenchymal transition phenotype,¹⁴ and the molecular apocrine subtype, which displays activation of the androgen receptor (AR) pathway.¹⁵ Subsequent studies by Lehmann et al¹⁶ led to a transcriptomic classification of TNBCs into six subtypes: basal-like 1, basal-like 2, luminal AR, immunomodulatory, mesenchymal, and mesenchymal stem-like. These subtypes have differences in clinicopathologic features and response to therapy. An independent group described a similar TNBC classification into 4 subtypes: basal-like/immune-suppressed, basal-like/immune activated, luminal AR, and mesenchymal.¹⁷ These two classifications partially overlap, in particular for the luminal AR and mesenchymal subtypes.⁵ The most parsimonious number of TNBC transcriptomic subtypes is likely to be four, given that the immunomodulatory and mesenchymal stem-like subtypes¹⁶ are actually contributed by infiltrating lymphocytes and stromal cells, respectively.¹⁸ The luminal AR subtype, which is perhaps the most stable and distinctive subtype, is significantly associated with older age at presentation, lower grade, higher incidence of lymph node and bone metastases, and late recurrences when compared with other subtypes.^{18,19} These results indicate clinical similarities between luminal and TN luminal AR breast cancers, which may be related to the hormonally driven biology.

The classification of TNBCs into subtypes based on patterns of gene expression may predict benefit from specific therapeutic agents. The rates of pCR after standard neoadjuvant chemotherapy were lower in luminal AR (10% to 29%) and basal-like 2 (0% to 18%) than in basal-like 1 (41% to 50%).^{18,19} Preclinical models found that the basal-like 1 and 2 subtypes might be sensitive to platinum salts, the mesenchymal subtype to PI3K pathway inhibition,¹⁶ and the luminal AR subtype to antiandrogen therapy,¹⁶ PI3K inhibitors,²⁰ and CDK4/6 inhibitors.²¹ Although TNBC subtyping has the potential to improve treatment decision

Table 1 Reported Prevalence of ER and/or PR Positivity, HER2 Positivity, and TN Phenotype in Breast Neoplasms Consistently of or Enriched for the TN Phenotype

Neoplasm	ER and/or PR positivity, %	HER2 positivity, %	TN phenotype, %	Reference(s)
MGA and AMGA	0	0	100	7,9,10
Carcinoma with apocrine differentiation	0–24	10–55	38–90	23,24
Carcinoma with medullary features	0–14	0–27	64–100	25,26
Metaplastic breast carcinoma	3–9	3–10	85–94	27,28
Acinic cell carcinoma	0–20	0	80–100	29,30
Adenoid cystic carcinoma	0–15*	0	85–100	31,32
Secretory carcinoma	0–45*	0	65–100	33,34
Mucoepidermoid carcinoma	0	0	100	35
Low-grade fibromatosis-like metaplastic carcinoma	0	0	100	36,37
Low-grade adenosquamous carcinoma	0	0	100	38
Solid papillary carcinoma with reverse polarity	50*	0	50	39

*The cases of solid papillary carcinoma with reverse polarity, secretory carcinoma, and adenoid cystic carcinoma reported as ER-positive most often had low levels of ER expression in 1% to 10% of tumor cells.^{32,39}

AMGA, atypical microglandular adenosis; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MGA, microglandular adenosis; PR, progesterone receptor; TN, triple negative.

making and an algorithm based on minimal gene sets has been developed,²² it is unclear whether this classification will have a role in routine clinical practice.

High-Grade Special Histologic Types of TNBC

Most TNBCs are high-grade invasive ductal carcinomas (IDCs; also known as invasive carcinomas of no special type), which have pushing borders, marked nuclear pleomorphism, and numerous mitoses and often have geographic zones of necrosis and brisk lymphocytic infiltrates.¹ Nevertheless, a multitude of rare histologic special-type breast cancers are consistently of or significantly enriched for TN phenotype (Table 1 and Figure 1). High-grade special types of TNBC include carcinomas with apocrine differentiation, carcinomas with medullary features, and metaplastic breast carcinomas (MBCs). These histologic types share with conventional TNBCs a rather similar genomic landscape, albeit still having some clinically relevant singularities.

Carcinoma with Apocrine Differentiation

Carcinomas with apocrine differentiation are typically ER/PR negative, but their rate of *HER2* amplification may be higher than in unselected breast cancers.²³ Differences in diagnostic criteria among studies make it difficult to draw firm conclusions about the prognostic significance of this subtype⁴⁰; however, when compared with nonapocrine TNBCs, TN apocrine carcinomas occur in older patients, are less likely to be of grade 3, and seem to have a favorable prognosis.²⁴ These differences are also found between luminal AR and non-luminal AR TNBCs.¹⁸ In fact, there is a large overlap among apocrine, AR-positive, and luminal AR TNBCs.¹⁵ TNBCs defined as AR positive or with

apocrine differentiation harbor a higher frequency of mutations in *PIK3CA* and other PI3K pathway genes^{20,41} but a lower rate of *TP53* mutations and *MYC* gains compared with other TNBCs.⁴¹ Therefore, the findings suggesting that luminal AR TNBCs may be sensitive to the AR pathway, PI3K pathway, and CDK4/6 inhibitors^{16,20} may perhaps be extrapolated to patients with TN carcinomas with apocrine differentiation. The identification of TNBCs with apocrine differentiation may trigger AR or molecular testing and help guide patient selection for clinical trials. Proof of principle for the efficacy of minimally toxic androgen blockade in ER-negative/AR-positive breast cancers has been documented in a phase 2 clinical trial.⁴² Clinical trials testing the efficacy of PI3K and CDK4/6 inhibition in AR-positive and/or luminal AR TNBCs are warranted.

Carcinoma with Medullary Features

Carcinoma with medullary features is a histologic pattern characterized by well-circumscribed borders, a syncytial growth pattern, and brisk lymphocytic infiltrate.⁴⁰ Most typical medullary carcinomas are TN,²⁵ and a rate of *TP53* mutations comparable to that observed in IDCs has been reported.²⁶ Despite worrisome cytologic features and high mitotic activity, this controversial entity has been historically perceived to have a favorable outcome; however, typical medullary carcinomas may not have a better prognosis than atypical ones (those not fulfilling all diagnostic criteria),⁴³ and accurate identification of this histologic subtype is limited by poor interobserver agreement.⁴⁰ Thus, a diagnosis of carcinoma with medullary features does not carry therapeutic implications, and patients with these cancers should be treated according to the same protocols for common forms of TNBC. In fact, the good prognosis historically reported for medullary carcinomas may be related

Figure 1 Low-grade and high-grade histologic types of triple-negative breast carcinomas (TNBCs). Representative micrographs of low-grade and high-grade variants of TNBC. Several histologic types of low-grade TNBC, including salivary gland–like tumors of the breast and solid papillary carcinoma with reverse polarity, are underpinned by specific/pathognomonic genetic alterations. In contrast, acinic cell carcinoma and high-grade variants of TNBC have somatic genomic landscape similar to those of conventional TNBC. Their genetic alterations are compared with those reported for common forms of TNBC. Low-grade variants of metaplastic breast carcinomas (MBCs) are unlikely to be underpinned by specific genetic alterations; however, the genetic analyses performed to date included only a few or single cases. Progression to high-grade TNBC has been described in most low-grade forms of TNBC; however, it occurs at a different rate. Whereas fairly common in acinic cell carcinoma, it is a rare event in the salivary gland–like tumors of the breast and solid papillary carcinoma with reverse polarity. *It should be noted that evidence for the presence of *PRKD1* E710D mutations or *PRKD1/2/3* rearrangements in polymorphous carcinoma of the breast remains to be documented. Original magnification, $\times 200$. PI3K, phosphatidylinositol 3-kinase.

to the brisk lymphocytic infiltrate these tumors have, which has been validated by level I evidence as a prognostic and predictive marker for patients with TNBC treated with chemotherapy.^{44–46}

MBCs

MBCs encompass a spectrum of tumors with squamous and/or mesenchymal differentiation.⁴⁷ These tumors are most often high grade, with conspicuous nuclear pleomorphism and mitotic activity. Unlike conventional TNBCs, MBCs are resistant to chemotherapy and have a worse outcome.²⁷ Significant intertumor and intratumor heterogeneity are observed at the transcriptomic and genetic levels and correlate with the morphologic heterogeneity.^{48,49} Histologically distinct components within individual MBCs may have distinct patterns of CNAs, despite being clonally

related.⁴⁹ Likewise, the histologic subtype of MBCs (ie, spindle cell, squamous, and matrix producing, including those with chondroid or osseous differentiation) has an effect on their gene expression profiles: spindle cell MBCs are of claudin-low intrinsic subtype, whereas squamous and chondroid MBCs are more frequently of basal-like subtype.⁴⁸ When applying the classification of Lehmann et al,¹⁶ chondroid and spindle cell MBCs are preferentially of mesenchymal subtypes, whereas squamous MBCs are of multiple subtypes.⁴⁸

MBCs have similar genomic complexity and rate of *TP53* mutations as usual TNBCs²⁸ but have enrichment for mutations that affect members of the PI3K^{28,50,51} and Wnt^{28,50,52,53} pathways, which are associated with increased activation of the respective pathways. The PI3K pathway is predominantly affected by mutations in *PIK3CA* (29%), *PIK3R1* (11%), and *PTEN* (11%).²⁸ Wnt pathway genes

Figure 2 Low-grade triple negative breast neoplasia family. Representative micrographs of microglandular adenosis (MGA) and associated lesions (**A**, **B**, and **C**) and an acinic cell carcinoma (ACC) (**D**, **E**, and **F**), lesions comprising the low-grade triple-negative breast neoplasia family, grouped together based on their histologic, immunophenotypic, and genetic overlap.⁶ It comprises MGA and atypical MGA, which are non-obligate precursors of high-grade triple-negative breast carcinoma (TNBC), and ACC, which is characterized by diffuse expression of serous differentiation markers, such as lysozyme, and frequently progresses to high-grade TNBC. **A:** MGA is shown. **B:** MGA is shown in the **bottom left** corner, whereas MGA-associated invasive TNBC is shown in the **top right** corner. **C:** Atypical MGA is shown. **D:** Low-grade ACC is shown. **E:** ACC is shown on the **right**, whereas an associated high-grade TNBC is shown on the **left**. The **inset** shows lysozyme expression in the TNBC component. **F:** Lysozyme expression is shown in a low-grade ACC. The lesions comprising the low-grade triple-negative neoplasia family have a somatic genomic landscape indistinguishable from common forms of TNBC, despite the low-grade morphologic features and indolent behavior. Original magnification: $\times 200$ (**A**, **C**, **D**, **E**, **inset**, and **F**); $\times 40$ (**B**); $\times 20$ (**E**).

mutated in MBCs include *FAT1* (11%) and *AXIN1* (6%).²⁸ Although a subset of MBCs expresses nuclear β -catenin consistent with Wnt pathway activation,⁵³ *CTNNB1* mutations are likely absent or vanishingly rare.^{28,50,52,53} Taken together, these data provide a genetic basis for the mesenchymal differentiation in a subset of MBCs because activation of the PI3K and Wnt pathways has been associated with and may interact in epithelial-mesenchymal transition⁵⁴ and suggest that inhibiting these pathways may be beneficial in patients with this chemotherapy-resistant form of TNBC. In fact, a clinical trial testing the mechanistic target of rapamycin inhibitor temsirolimus combined with anthracycline-based chemotherapy in patients affected by metastatic MBC found efficacy in 6 of 19 patients.⁵¹

Low-Grade TNBC

Despite being rare, low-grade TN disease includes a variety of lesions, ranging from neoplasms with no or uncertain metastatic potential⁵⁵ to well-characterized special types of invasive carcinoma (Figure 1). Current evidence suggests that at least two subsets of low-grade TN neoplasms can be distinguished: a subset of lesions that comprise a low-grade TN breast neoplasia family,⁶ which includes MGA, atypical MGA (AMGA), and acinic cell carcinoma (ACC) and that,

despite their low-grade morphologic features and good outcome, recapitulate the complex genomic landscape of usual TNBCs, and the salivary gland–like tumors of the breast, which are defined by salivary gland–like morphologic features and are often underpinned by specific/pathognomonic genetic alterations. Low-grade variants of MBCs and solid papillary carcinoma with reverse polarity (SPCRP) are additional rare histologic special types of low-grade TNBC.

Low-Grade TN Breast Neoplasia Family

As opposed to ER-positive breast lesions, which include several low-grade and precursor lesions, only high-grade ductal carcinoma *in situ* and pleomorphic lobular carcinoma *in situ* of TN phenotype have been historically viewed as precursor lesions of high-grade ductal and lobular invasive TNBCs. In the last decade, however, a distinctive subgroup of low-grade lesions has been identified as precursors of high-grade invasive TNBCs based on their histologic, immunophenotypic, and genetic similarities. This subgroup includes MGA, AMGA, and ACC, which feature microglandular, S100-positive, and TN proliferations (Figure 2). Although diffuse morphologic and/or immunohistochemical serous differentiation defines ACCs,⁴⁰ it has also been described in MGA and AMGA.^{6,7} By contrast to the

salivary gland–like tumors, specific/pathognomonic somatic genetic alterations have yet to be found in these lesions.^{10,30} Actually, a direct comparison revealed no significant differences in mutation burden and repertoire between them individually and as a group and TNBCs from the TCGA study.⁶ These findings led us to propose the existence of a low-grade TN breast neoplasia family, the lesions of which may ultimately give rise to conventional high-grade TNBC.⁶

In addition to a common somatic genomic landscape, MGA, AMGA, and ACC share an association with *BRCA1* germline mutations. Biallelic inactivation of *BRCA1* by a combination of germline mutation, somatic mutation, and/or somatic loss of heterozygosity has been described in three ACCs.^{30,56} We also observed MGA-associated carcinomas in *BRCA1* germline mutation carriers (F.C.G. and J.S.R.-F., unpublished data) and one case where both MGA and concurrent carcinoma harbored somatic mutations coupled with loss of heterozygosity in *BRCA1* and *TP53*.¹⁰ These findings, together with data indicating that somatic abrogation of *BRCA1* and *TP53* in mice may give rise to well-differentiated tumors,⁵⁷ support the contention that the concurrent loss of function of *BRCA1* and *TP53* can result in the development not only of high-grade but also low-grade TNBCs.

ACC

ACC is characterized by a low-grade epithelial proliferation with diffuse serous differentiation depicted by the presence of cytoplasmic zymogen–type granules.⁴⁰ Most ACCs have a microglandular growth pattern, but solid architecture and clear cell features can be present.³⁰ If pure, ACCs have an excellent outcome. A coexistent high-grade component is not rare, however,^{29,30,40} and is associated with local and distant recurrences.⁴⁰ Unlike the salivary gland–like tumor subgroup, ACCs arising in the breast and salivary glands constitute different disease.⁵⁸ Whereas salivary gland ACCs are usually circumscribed lesions, with basophilic zymogen–type granules, breast ACCs are infiltrative and have eosinophilic zymogen–type granules. At the molecular level, breast ACCs have a high mutational burden, with *TP53* and *PIK3CA* mutations in 80% and 10% of cases, respectively. This is in stark contrast to salivary gland ACCs that lack mutations affecting these genes.^{30,58} In addition, breast ACCs harbor a complex pattern of CNAs, with recurrent 8q gains and 5q losses, and somatic mutations in other genes altered in common forms of TNBC, such as *ERBB3*, *INPP4B*, and *FGFR2*.³⁰

MGA

MGA is defined as a haphazard proliferation of small, rounded, bland-looking glands that infiltrate adipose tissue and collagenous stroma and lack a myoepithelial cell layer akin to invasive carcinomas but not eliciting a desmoplastic reaction.⁴⁰ MGA was initially regarded as a benign hyperplastic lesion. However, the highly infiltrative nature of this

lesion and the presence of a histologic spectrum with increasing cytologic atypia and architectural complexity ranging from MGA to AMGA to MGA-associated carcinomas together with the lack of peripheral myoepithelial cells and the diffuse lack of ER expression favor categorization of MGA as a neoplastic lesion.^{6–10} Immunohistochemical and molecular analyses have demonstrated similar phenotype, pattern of CNAs, and mutational repertoire in samples of concurrent MGA, AMGA, and/or invasive carcinoma, providing further evidence that at least a subset of MGA and AMGA are clonal neoplastic lesions and nonobligate precursors of TNBCs.^{6–10}

As a group, carcinoma-associated MGA and AMGA have complex CNA profiles with recurrent 5q losses and 8q gains,^{9,10} highly recurrent (>80%) *TP53* mutations, and a vast repertoire of mutated genes at low frequency, including *BRCA1*, PI3K pathway genes (*PTEN*, *PIK3CA*, and *INPP4B*), and genes that encode for receptor tyrosine kinases (ie, *ERBB3*, *FGFR2*).¹⁰ In line with the lack of histologic atypia, uncomplicated MGAs appear to harbor lower levels of genetic instability^{8–10} and to lack *TP53* mutations and CNAs commonly present in TNBCs.¹⁰ Inactivation of p53 may therefore be required for genetic instability, acquisition of additional genetic alterations, and subsequent progression from MGA to AMGA and invasive carcinomas, including ACC and high-grade TNBCs.⁶ Additional studies are required to define whether pure MGA and carcinoma-associated MGA and AMGA share the same early founder genetic event or represent a convergent phenotype.

Salivary Gland–Like Tumors of the Breast

This group of TNBCs recapitulates primary neoplasms of the salivary glands histologically and genetically. In contrast to conventional TNBCs, these tumors lack recurrent *TP53* aberrations, have few CNAs, and harbor specific/pathognomonic genetic alterations. Furthermore, identical genetic drivers underpin at least some of these tumors regardless of the anatomical site of origin, indicating a high degree of genotypic-phenotypic correlation. The prototypical components of this group are the well-characterized adenoid cystic carcinoma (AdCC) and secretory carcinoma, which are underpinned by the *MYB-NFIB* and *ETV6-NTRK3* fusion genes, respectively.⁵⁹ Polymorphous carcinoma, mucoepidermoid carcinoma (MEC), and adenomyoepithelioma (AME) are additional salivary gland–like tumors, which, although less extensively studied than their salivary gland counterparts, are potentially underpinned by similar oncogenic drivers when arising in the breast.

AdCC

AdCC is composed of a dual population of luminal and myoepithelial or basal cells, growing in cribriform, tubular, and/or solid patterns. Although originally described in the salivary glands, histologically identical AdCCs can arise in

other anatomical sites (eg, lungs, breast, prostate, cervix). In the breast, AdCCs account for <0.1% of primary carcinomas. Most breast AdCCs are TN³² and, in contrast to the poor long-term outcomes in head and neck AdCCs, typically have a highly favorable outcome.^{32,60}

The histologic similarities among AdCCs from all sites are mirrored by remarkably similar molecular profiles. Regardless of the anatomical location, activation of *MYB* or *MYBL1*, two members of the same gene family and encoding transcription factors that share similar target genes, drive most AdCCs. Several genetic mechanisms can result in the overexpression of either gene, the most common being the *MYB-NFIB* fusion gene, resulting from the t(6;9)(q22-23;p23-24) translocation⁵⁹ and present in 23% to 100% of breast AdCCs.³² Alternative mechanisms that lead to activation of the same downstream pathways include the *MYBL1-NFIB* fusion gene, as well as rearrangements of *MYB* and *MYBL1* with other partners.^{61,62} Although not yet documented in the breast, *MYBL1* rearrangements theoretically occur in AdCCs of all sites.

As neoplasms driven by fusion genes, AdCCs have quiet genomes. CNAs frequently present in usual TNBCs are not encountered.³¹ Breast AdCCs rather have recurrent CNAs present in salivary gland AdCCs, such as 12q12-q14.1 losses.^{31,63} Likewise, breast AdCCs have a mutation burden and repertoire comparable to that observed in head and neck AdCCs.^{31,63} They lack *TP53* and *PIK3CA* somatic mutations and preferentially harbor mutations that affect genes associated with chromatin remodeling, cell adhesion, and signaling cascades and in the cancer genes *SF3B1*, *FBXW7*, and *FGFR2*.^{31,63} Because of the striking molecular similarities between breast and salivary gland AdCCs, the significant differences in outcome come as a surprise.³² Although breast AdCCs are more easily completely removed surgically and tissue-specific posttranscriptional differences⁶⁴ may play a role, the underpinning of the divergent clinical courses remains to be uncovered.

High-grade forms of breast AdCCs⁶⁵ or high-grade TNBCs arising in low-grade AdCCs⁶⁶ may also harbor recurrent *MYB/MYBL1* rearrangements. It is unknown, however, how dependent on *MYB/MYBL1* activation these high-grade lesions are because acquisition of additional genetic events has been described. In the salivary glands, p53⁶⁷ or PTEN⁶⁸ inactivation may play a role in high-grade transformation, whereas PTEN inactivation has been implicated in metastatic progression to the kidney in a single breast AdCC.⁶⁹ Our group has recently reported on two breast AdCCs progressing to high-grade TNBC.⁶⁶ The first case had two distinct mutations in both *EP300* and *NOTCH1* genes in the AdCC component, of which only one mutation in each gene was present and clonal in the high-grade component, strongly suggesting clonal selection. In the second case, an increasing number of mutations were detected from the cribriform to solid to high-grade TNBC components, including a *MYB* mutation. However, these two cases, including the high-grade components, still had

lower levels of genetic instability compared with conventional TNBCs, indicating that high-grade TNBCs arising in AdCCs are more similar to low-grade AdCCs than the usual TNBCs at the genetic level.

Secretory Carcinoma

Although secretory carcinoma was first described in the breast and analogous lesions subsequently recognized in the salivary gland⁷⁰ and skin,⁷¹ secretory carcinoma is included in the salivary gland–like subgroup because, akin to AdCCs, this histologic type has similar morphologic features and an identical genetic driver regardless of the site of origin. Secretory carcinoma accounts for <0.15% of breast cancers.⁴⁰ Initially named juvenile carcinoma because it was first described in children, a descriptive term was later adopted when the carcinoma was found to occur at a median age of 53 years.⁷² The presence of intracellular and extracellular dense eosinophilic secretions and mildly atypical epithelial cells characterizes secretory carcinomas. The clinical outcome is favorable when compared with usual TNBCs.⁷² Although most secretory carcinomas are low-grade TNBCs, high-grade or weakly ER-positive cases have been reported.^{33,34}

Secretory carcinomas of the breast and mammary-analog secretory carcinomas of the salivary gland⁷⁰ or skin⁷¹ are underpinned by a t(12;15)(p13;q25) translocation, which creates the *ETV6-NTRK3* fusion gene.⁷³ This fusion gene also drives a variety of nonepithelial neoplasms of other sites; however, in the context of breast tumors, it is pathognomonic of secretory carcinoma.⁷⁴ *ETV6* rearrangements with an unknown partner (*ETV6-X*) have been reported in salivary gland lesions⁷⁵ and theoretically also occur in the breast lesions. Importantly, the *ETV6-NTRK3* fusion gene is of use not only for diagnostic purpose but also as a therapeutic target because small molecule inhibitors can target the chimeric protein.⁷⁶

Secretory carcinomas have relatively quiet genomes.^{34,77,78} Rare high-grade secretory carcinomas have been documented, one of which harbored an increased number of CNAs compared with typical secretory carcinomas, but still lower than that expected in conventional TNBCs.³⁴ A metastatic high-grade secretory carcinoma of the salivary gland was reported to harbor mutations in *RB1* and *MYC*, in addition to a *NTRK3*^{G623R} mutation, which was likely driving acquired resistance to TrkC inhibition.⁷⁶ Further studies of secretory carcinomas with high-grade features are warranted to define their prognosis and molecular underpinning. We hypothesize that akin to high-grade AdCCs, high-grade secretory carcinomas may be more similar to typical secretory carcinomas than to common forms of TNBC.

AME

AME of the breast is a heterogeneous tumor type, ranging from adenosis-like lesions to infiltrative neoplasms histologically identical to epithelial-myoepithelial carcinomas (EMCs) of the salivary glands.⁴⁰ AME is defined by a proliferation of outer myoepithelial cells and inner columnar or cuboidal epithelial

cells, arranged in tubular or papillary architecture.⁴⁰ Expression of hormone receptors is not uncommonly observed in the epithelial component, but a TN phenotype can be observed in a subset of cases⁷⁹ and is likely more frequent in the EMC-like lesions. Most AMEs have a benign clinical course, but progression to carcinomas of different grades, often revealing metaplastic and myoepithelial differentiation, and metastatic disease in AMEs without recognizable histologically defined carcinoma can occur.^{40,79}

Recent data suggest that the phenotypic similarities between a subset of breast AMEs and salivary gland EMCs may be underpinned by a similar constellation of mutations, including *HRAS* and/or *PIK3CA* hotspot mutations and no *TP53* mutations.^{80,81} *HRAS* mutations found in breast AMEs and salivary gland EMCs all affected codon 61 and are exceedingly rare in unselected cohorts of breast cancer, being found in only 3 (2 codon 61 and 1 codon 12) of 2433 cases from METABRIC targeted sequencing study.⁸² Because of the morphologic and genetic similarities, one can hypothesize that AMEs that harbor *HRAS*^{Q61} mutations may represent EMCs of the breast, an entity currently not recognized in pathology practice. Molecular testing for the *HRAS*^{Q61} mutation should be investigated as a diagnostic marker of breast EMC. Moreover, dependency on ERK and/or PI3K pathways activation may indicate therapeutic options for the rare patients with malignant AMEs.

Polymorphous Carcinoma

Polymorphous carcinoma of the breast is defined as a tumor with histologic features similar to those of polymorphous low-grade adenocarcinoma (PLGA) of the salivary glands.⁴⁰ Despite architectural and cytologic similarities, the clinical behavior of breast lesions seems to be more aggressive than that of the salivary gland counterpart.⁴⁰ Therefore, the term *low grade* was considered inappropriate.⁴⁰ Nonetheless, few cases have been reported in the literature, and the outcome of polymorphous carcinoma of the breast might be best considered uncertain. The results of staining for ER, PR, and HER2 have been consistently negative.⁴⁰

Most PLGAs (73%) of the salivary glands are underpinned by *PRKD1*^{E710D}-activating mutations. *PRKD1* mutations at this residue are not found in other salivary gland lesions, indicating *PRKD1*^{E710D} as a specific marker of PLGA. Interestingly, rearrangements in the *PRKD* gene family, including *PRKD1*, *PRKD2*, and *PRKD3*, are found in cribriform adenocarcinoma, a low-grade carcinoma of the salivary gland that shares histologic and clinical features with PLGA.⁸³ The presence of *PRKD1*^{E710D} mutations or *PRKD* rearrangements in polymorphous carcinoma of the breast remains to be investigated; if confirmed, their presence would support the existence of polymorphous carcinoma as a discrete subtype of breast cancer.

MEC

Breast MECs are very rare tumors, defined by an admixture of squamoid, intermediate, and mucinous cells.⁴⁰ Occasionally, clear and goblet-type cells and oncocytic change can be seen. A TN phenotype has been documented.^{35,40} The clinical

behavior is significantly associated with grade; of 27 patients with reported outcome, 5 of 10 patients with high-grade MECs died of disease, whereas all patients with low- or intermediate-grade tumors died of other cause or were alive at last follow-up.³⁵ Importantly, MECs must be distinguished from MBCs with squamous differentiation. The presence of overt squamous differentiation favors the diagnosis of squamous MBC.⁴⁰ Moreover, *MAML2* rearrangements are found in MECs regardless of the anatomical site of origin and can be used as a diagnostic tool.^{35,84} *MAML2* is usually fused with *CRCT1* [t(11;19)(q21;p13)], creating a fusion protein with oncogenic activity through Notch signaling.⁸⁴ This translocation is more prevalent in low- and intermediate-grade MECs of the salivary glands and has been associated with favorable outcome and lower rates of anaplasia and mitotic activity even within high-grade lesions.⁸⁵ By contrast, mutations in *TP53*, the most frequently mutated gene in MECs of the salivary gland (28%), are more frequent in high-grade MECs.⁸⁶ Taken together, these results suggest the existence of two subsets of high-grade MECs (with and without fusion) and that perhaps fusion-negative high-grade MECs are distinct lesions.⁸⁵ When extrapolated to breast tumors, these data may indicate that high-grade TNBCs bearing resemblance to MECs but lacking *MAML2* rearrangements might be best considered squamous MBCs or IDCs with squamous features.

Low-Grade Variants of MBCs

Two low-grade and less aggressive variants of MBC have been well characterized: low-grade fibromatosis-like metaplastic carcinoma (LG-FLMC) and low-grade adenosquamous carcinoma (LG-ASC). Both invariably have a TN phenotype.^{36–38} Both lesions have rather infiltrative borders and a high risk of local recurrence after conservative surgical treatment,^{87,88} even though their metastatic potential is low.^{36,55}

LG-FLMC is defined by a proliferation of bland spindle cells arranged in wavy fascicles with limited clustered epithelioid cells, which frequently have squamous differentiation and aid in the distinction from desmoid-type fibromatosis.^{36,40} These epithelioid cells and a subset of the spindle cells express cytokeratin and p63. Akin to high-grade spindle cell MBCs, LG-FLMCs have a claudin-low phenotype.⁸⁹ Genetic analyses revealed low levels of genetic instability, recurrent losses of *CDKN2A* (2/3), one of which was a homozygous deletion, and no hotspot mutations that affect *EGFR*, *TP53*, and *KRAS*.^{37,89}

LG-ASC is characterized by bland glandular and tubular elements, admixed with solid nests of squamous cells, in a spindle cell background.⁴⁰ A differential diagnosis is syringomatous adenoma of the nipple⁴⁰; however, these two lesions may have a similar origin because a detailed lineage-tracing analysis concluded that the lesions are identical or nearly identical.⁹⁰ A single case has been described in a *BRCA1* germline mutation carrier, but documentation of

somatic loss of the wild-type allele of *BRCA1* for complete *BRCA1* loss of function was not provided.⁹¹ Somatic genetic alterations found in single cases include a *PIK3CA* hotspot mutation⁹² and *EGFR* amplification.³⁸ Notably, progression from LG-ASC to high-grade TNBCs, usually of metaplastic morphologic subtype, has been documented.^{38,93}

A commonality between LG-ASC and LG-FLMC is that some of these lesions arise in direct association with sclerosing papillary or adenomyoepitheliomatous lesions.^{92–94} Our group provided molecular evidence to support that a sclerosing lesion was the substrate for the development of a synchronous low-grade MBC.⁹² Two identical mutations that affect *PIK3CA* and *SF3B1* were found in both components of a case composed of LG-ASC and infiltrating epitheliosis, which likely represents a high-proliferation end of the spectrum of complex sclerosing lesions of the breast.⁹² In addition, a microarray-based comparative genomic hybridization analysis coupled with fluorescence *in situ* hybridization found that the spindle cells surrounding the epithelial structures of LG-ASCs have the same CNAs as those found in the epithelial cells, suggesting that a subset of the spindle cells are actually neoplastic and clonally related to the epithelial cells.³⁸ Taken together, these findings may suggest that LG-ASC and LG-FLMC constitute a spectrum of lesions, sharing not only a similar clinical course but also a common origin and similar neoplastic histologic components (glandular, squamous, and spindle), intimately admixed, but present in varying proportions in each subtype.

SPCRPs

SPCRP, also known as breast tumors resembling the tall cell variant of papillary thyroid carcinoma and tall cell variant of papillary breast carcinoma,⁹⁵ is not recognized as a histologic special type by the current World Health Organization classification of breast tumors,⁴⁰ but recent data suggest it is a distinct entity, underpinned by a pathognomonic genetic alteration.³⁹ SPCR is defined as an invasive carcinoma composed of solid and circumscribed nodules of epithelial cells with fibrovascular cores.³⁹ Tumor cells lack significant nuclear atypia and have abnormal apical nuclear localization, resulting in a reverse polarity appearance that mimics the tall cell variant of papillary thyroid carcinoma. As opposed to conventional solid and encapsulated papillary carcinomas of the breast, which typically express high levels of ER,⁴⁰ at least 50% of SPCRPs are TN,^{39,96} whereas the remaining cases express low levels of ER (1% to 10%) and lack HER2 expression.³⁹ On the basis of a small number of cases, SPCRPs appear to have a favorable prognosis, but local recurrence and metastatic disease have been reported.⁹⁶

A recent sequencing analysis of 13 SPCRPs described a low mutation burden and hotspot mutations that affect the R172 residue of *IDH2* in 77% of cases, which often co-occurred with mutations in the PI3K pathway genes (*PIK3CA* and *PIK3R1*).³⁹ *IDH2* mutations are vanishingly

rare in breast cancer and were found in only 1 (other codon than 172) of 971 breast cancers in a reanalysis of cases from the TCGA. *IDH2* hotspot mutations are gain-of-function alterations that result in hypermethylation and subsequent lack of differentiation. Functional studies found that forced expression of mutant *IDH2* in breast epithelial cells harboring a *PIK3CA* mutation could recapitulate the SPCR phenotype.³⁹ Taken together, their unique histologic appearance and genomic landscape strongly favor that SPCR constitutes a discrete entity of breast cancer.

Evolutionary Pathways in TN Disease of the Breast

Breast cancer evolution is a complex process that follows multiple pathways. A hypothetical grade-centric model (low versus high grade) was initially put forward, replacing the historical linear hyperplasia–atypical hyperplasia–*in situ* carcinoma–invasive carcinoma sequence.⁹⁷ In this grade-centric model, progression from low to high grade was considered a rare event.⁹⁷ Given that ER expression levels define two groups of fundamentally distinct breast cancers and that progression from low- to high-grade lesions is not a rare event in luminal cancers,⁹⁸ we have subsequently suggested a revised model stratified according to ER pathway activation.⁹⁷ In fact, most low-grade breast lesions are ER positive, including a spectrum of preinvasive (columnar cell lesions, flat epithelial atypia, atypical ductal hyperplasia, lobular neoplasia, and low-grade ductal carcinoma *in situ*) and invasive lesions (tubular, cribriform, lobular, and low-grade ductal carcinomas). Because of their frequent coexistence and similar pattern of genetic alterations (eg, *PIK3CA* mutations and deletions of 16q and gains of 1q^{97,99}), low-grade ER-positive nonobligate precursors and invasive carcinomas have been grouped together under the term *low-grade breast neoplasia family*.^{97,100} Progression from low-grade ER-positive to high-grade ER-positive lesions is supported by the high frequency of the aforementioned genetic signature in ER-positive high-grade carcinomas.^{97,99}

Nonetheless, such progression is not limited to ER-positive lesions, and the ER-negative branch may be histologically and genetically more diverse than the ER-positive one. Most TN lesions evolve rapidly and are not uncommonly diagnosed as interval cancers. Some, however, are detected at early or low-grade and low-stage forms. Importantly, the genetic features of the resulting high-grade TNBC appear to parallel those of the low-grade lesion from which they originate. Pathologists are thus encouraged to discriminate between these lesions because the presence of a low-grade component may indicate a distinct genetic profile and potential sensitivity to specific therapeutic agents.

Akin to the low-grade ER-positive breast neoplasia family, a low-grade TN breast neoplasia family, consisting of MGA, AMGA, and ACC can be distinguished.^{5,6} These lesions not uncommonly give rise to high-grade TNBCs,

usually in the form of IDCs or MBCs.^{7–10,30} It is unknown whether MGA, AMGA, and ACC—associated high-grade TNBCs behave differently than high-grade TNBCs not arising from these lesions, even though they are nearly indistinguishable at the genomic level.⁶ When not associated with high-grade TNBCs, MGA, AMGA, and ACC are unlikely to behave aggressively, despite the worrisome genetic alterations, and they, therefore, should be managed accordingly. We recommend, however, complete excision for MGA and AMGA lesions because their rate of progression is uncertain and possibly high. Combining 4 MGA and 1 ACC cohorts, 24 (47%) and 7 (14%) of 51 cases had concurrent invasive or *in situ* carcinoma, respectively.^{7–10,30} Given that functional p53 may be a limiting step in the progression from MGA to an atypical or malignant phenotype, p53 expression or *TP53* mutation analyses may perhaps help define the best surgical therapy for patients with extensive pure MGA.

Progression and/or high-grade variants have also been documented in salivary gland—like tumors of the breast.^{34,66} High-grade TNBCs that originate from these tumors usually harbor additional genetic alterations, which vary across cases, and include genetic alterations that affect bona-fide cancer genes, such as *TP53*, *CDKN2A*, and *PTEN*. It is plausible that signaling from these additional alterations becomes the driving force for tumor growth, making the oncogenic signaling from the early genetic driver (eg, *MYB-NFIB* and *ETV6-NTRK3*) superfluous and/or the high-grade lesion resistant to therapies that target the early oncogenic driver.⁷⁶ However, high-grade variants of salivary gland—like tumors seem to differ from common forms of TNBCs and likely respond differently to chemotherapy and/or targeted therapies potentially active in conventional TNBCs, such as poly (ADP-ribose) polymerase inhibitors.

Conclusions

TNBC is an operational term that encompasses a wide spectrum of entities with different biology, histologic features, and clinical behavior. Most TNBCs are high-grade, poor-prognosis tumors, but rare and clinically relevant subsets of low-grade TN disease have a favorable outcome. The low-grade TN breast neoplasia family recapitulates the complex genomic landscape of conventional TNBCs, despite an indolent behavior. By contrast, the salivary gland—like tumors of the breast lack the genomic features of common forms of TNBCs and are each underpinned by specific fusion-genes or hotspot mutations, which may be of diagnostic and therapeutic utility. Progression from low- to high-grade lesions has been documented in both subgroups but likely occurs at a higher rate within the second group. Importantly, the molecular features of high-grade TNBCs arising in either subgroup appear to parallel those of the low-grade lesions from which they originate, which can help define personalized treatment. Additional methods to stratify TNBCs into

clinically meaningful subtypes might be implemented in the clinic^{16,22}; however, histologic subtyping of TN disease should not be neglected, given that the therapeutic approaches for the rare low-grade subtypes of TNBC are fundamentally different from those of high-grade TNBC.

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