REVIEW

Recent Progress in Triple Negative Breast Cancer Research

Fatima Zahra Mouh[1,2], Mohammed El Mzibri[2], Meriem Slaoui[1,2], Mariam Amrani[1]*

Abstract

Triple-negative breast cancer (TNBC) is defined as a type of breast carcinoma that is negative for expression of oestrogene and progesterone hormone receptors (ER, PR) and HER2. This form of breast cancer is marked by its aggressiveness, low survival rate and lack of specific therapies. Recently, important molecular characteristics of TNBC have been highlighted and led to the identification of some biomarkers that could be used in diagnosis, as therapeutic targets or to assess the prognosis. In this review, we summarize recent progress in TNBC research focusing on the genetic and epigenetic alterations of TNBC and the potential use of these biomarkers in the targeted therapy for better management of TNBC.

Keywords: Triple-negative breast cancer (TNBC) - biomarkers - targeted therapy

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Introduction

It is known worldwide that breast cancer is the most common malignancy among women representing 23% of all diagnosed cancer cases (Sheikh et al., 2015). Triple Negative Breast Cancer (TNBC) accounts for approximately 15 - 20 % among breast cancer cases. TNBC is the subgroup of tumors that do not clinically express significant levels of estrogen receptor (ER), progesterone receptor (PR) and lack of human epidermal growth factor receptor 2 (HER-2) overexpression.

TNBC has recently been recognized as an important subgroup of breast cancer, with an aggressive clinical behavior and a distinct outcome. It is a poor prognostic factor for disease-free and overall survival. It is responsible for a disproportionate number of breast cancer deaths and no effective specific targeted therapy is readily available for it, as patients with TNBC cannot be treated with endocrine therapy or therapies targeted HER2 protein.

TNBC is a distinct pathological subtype of breast cancer with specific clinical and pathological characteristics. It does not allow physicians and patients to determine eligibility for determining eligibility for clinical trials and guide individual patient treatment. This eventually has pushed laboratories and research department to deepen their investigation on the issue. A better understanding of the molecular and histo-pathological features of TNBC is of great importance to unravel the heterogeneous nature of this tumor subgroup and to identify the molecular biomarkers, to be used for diagnosis and/or as therapeutic targets.

The aim of this review is to highlight clinico-pathological features of TNBC, review the important studies conducted and the most relevant findings that should be more investigated to improve the prognosis and treatment of patients.

Epidemiological and Clinicopathological Features

It's widely accepted that TNBC is a very heterogeneous group. This heterogeneity is further highlighted by the high prevalence of rare histopathological subtypes, such as metaplastic (90%), medullary (95%), adenoid cystic (90-100%) and apocrine (40-60%) carcinomas (Lehmann and Pietenpol, 2014). TNBC is sometimes used as a surrogate term for basal-like breast cancer; even if they are not biologically synonymous (Alluri and Newman, 2014). Indeed, clinical data, microarray and immune-histo-chemical analyses show that triple negative and basal phenotypes breast cancers subtypes are not synonymous. The basal subtype is frequently defined by a distinct gene-expression such as cytokeratins 5, 6 and 17; EGFR staining and encompasses a diverse group of tumors. However, no clear criteria or cutoff values have been standardized yet. Both basal-like and triple negative breast cancers are associated with aggressive pathologic features, poor clinical outcomes and show higher prevalence in African women.

Studies all over the world have reported different risk factors associated with TNBC development, including young age at breast cancer diagnosis (<50 years) (Bauer

*[1]Equipe deRecherche ONCOGYMA, University of Mohamed V,, Faculty of Medicine and Pharmacy of Rabat, [2]Unité de Recherche Médicale et Biologique. Centre National de l'Energie, des Sciences et des Techniques Nucléaires, Rabat, Morocco *For correspondence: m.amrani@um5s.net.ma*

et al., 2007), young age at menarche (Early menarche <13 years), high parity, Young age at time of first birth (First Early Pregnancy: <26 years), lack of breastfeeding (lower duration of breastfeeding) (Millikan et al., 2008), high body mass index (> 25kg/m^2, more frequent in women with abdominal obesity) (Stead et al., 2009) and African American ethnicity (Carey et al., 2006; Morris et al., 2007; Dawood, 2010). TNBC were more likely to have grade III (66%) and larger size tumors (mean tumor size of 3.0) when compared with patients diagnosed with non-TNBC (Dent et al., 2007).

TNBC has been reported to be an aggressive form of breast cancer. It usually associated with very aggressive clinical behaviors and is more prevalent in cases with distinctive metastatic patterns (Gazinska et al., 2013).

An interesting study on a large series of Triple-Negative Breast Cancers derived from a single institution with long-term follow-up conducted by Dent et al. have clearly showed that patients with TNBC have a shorter median time to death (4.2years) compared to other cancers (6 years), and all deaths due to breast cancer in patients with TNBC occur within 10 years of diagnosis (Dent et al., 2007). Patients with TNBC have more likely experienced distant recurrence compared with patients with other breast cancers (33.9% versus 20.4%) and have shorter mean time to local (2.8 versus 4.2 years) and distant recurrences (2.6 versus 5.0 years) compared with those with other breast cancers. This suggests that the biology of Triple-Negative Breast Cancer is likely distinct from other breast cancers (Dent et al., 2007). Different studies confirm that TNBC are more likely to be occult on mammography and ultrasonography imaging and Patients with TNBC have a much lower proportion of breast cancers first detected by these approaches than patients with other breast cancers (Dent et al., 2007; Alluri and Newman, 2014). Furthermore, TNBC did not show a clear association between tumor size and positive lymph node status and is significantly more aggressive than tumors of other molecular subtypes (Dent et al., 2007). TNBC is also characterized by a frequent ductal histology, high grade, and high proliferation and mitotic rates. Furthermore, TNBC is associated with a higher risk of locoregional recurrence (LRR) and with lower disease-free survival (DFS) and cancer-specific survival (CSS). For instance, Lara-Medina et al. clearly showed that patients with TNBC had a higher risk of LRR, lower DFS (hazard ratio, 1.62; 95% confidence interval, 1.13-2.32; P=009), and a lower CSS rate (hazard ratio, 1.66; 95% confidence interval, 1.20-2.30; P= 002) than patients with non-TNBC (Lara-Medina et al., 2011).

Genetic Aspects of TNBC

Recent advances in molecular genetics have highlighted the role of genetic predisposition and specific point mutations in mammary carcinogenesis. BRCA1 and BRCA2, implicated in the DNA repair pathway, are the most important cancer susceptibility genes found in breast cancer (Wong et al., 2015). Germline mutations of the BRCA1 and BRCA2 are responsible for 30-40% of familial breast cancer cases (Lux et al., 2006; Ben et al., 2012). However, somatic mutations of BRCA1 and BRCA2 are rare in sporadic breast carcinomas (Ben Gacem et al., 2012).

Many studies have shown that 20% of women with TNBC carry a BRCA mutation and 75% of breast cancer cases with BRCA1 mutations are TNBC (Wong-Brown et al., 2015). BRCA1 is a tumor suppressor gene located on chromosome 17q and encodes a protein 1,863 amino acids protein with a zinc finger C3HC4 standard domain (Murphy and Moynahan, 2010). BRCA1 plays several roles in the cells related to the transcriptional regulation and repair of DNA double strand breaks. Repair default double strands of DNA breaks are the source of their association with increased cancer susceptibility (Roy et al., 2012). The alteration of BRCA1 expression is an important key in the development of sporadic basal-like breast cancer (Han et al., 2013). BRCA2 is located on chromosome 13q and encodes a protein of 3,418 amino acids (Murphy and Moynahan, 2010) and has an important role in protecting the genome.

It is important to note that TNBC cases carrying BRCA1 mutations are significantly younger if compared to non-carriers. The vast majority of BRCA1 mutations in the TNBC group was diagnosed in women under 50 years, which highlights the importance of the implementation of BRCA1 mutation testing for all patients with TNBC (Maksimenko et al., 2012). Potential candidates for BRCA1 testing are typically identified according to a qualitative and/ or quantitative analysis of personal and family history of cancer and to the proportion of mutation carriers, as well as the distribution of BRCA1mutations significantly differed by patient-reported race/ethnicity and age at diagnosis (Peshkin et al., 2010). Research and clinical studies worldwide have highlighted that the main BRCA1 mutations in breast cancer cases are present in TNBC. Table 1 summarizes the main mutations in BRCA 1 and 2 genes as reported in TNBC cases around the world.

Recently, genome-wide association study have identified 25 breast cancer susceptibility loci were identified as risk factors for TNBC : LGR6, MDM4, CASP8, 2q35, 2p24.1, TERT-rs10069690, ESR1, TOX3, 19p13.1, RALY, PEX14, 2q24.1, 2q31.1, ADAM29, EBF1, TCF7L2, 11q13.1, 11q24.3, 12p13.1, PTHLH, NTN4, 12q24, BRCA2, RAD51L1-rs2588809, MKL1 (Jiao et al., 2014).

Moreover, it is widely accepted that cancer development might be achieved by other genetic mechanisms such as epigenetic silencing or regulatory changes. Indeed, epigenetic alterations that activate or inactivate the expression of some genes are important keys in the development of various cancers. Thus, in many human cancers, epigenetic hypermethylation in the promoter regions of a number of genes has been recognized as an important change in the carcinogenesis (Jones et al., 2004). In this field, hypermethylation of the CpG islands of gene promoters is an important epigenetic mechanism for gene silencing, and one of the earliest and frequent alterations that lead to cancer (Feinberg, 2004). Despite the important role of DNA hypermethylation in mammary carcinogenesis (Tan et al., 2012), little information is available on the status of DNA methylation in TNBC

Table 1. BRCA 1/2 Mutations Reported in TNBC Cases

Author	Population	Country	Gene	Mutation	% of BRCA1
Young et al., 2009	Caucasian	United States	BRCA1	1294del40 exon 11	11%
	Irish/Scottish			2800delA exon 11	
	Caucasian			4731C>T exon 15	
	Caucasian			5382insC exon 20	
	African American		BRCA2	4936delAG exon11	
Gonzalez-Angulo et al., 2011	Texasian	United States	BRCA1	187delAG (n=3)	15.6% One Somatic
				2795delAAAG	
				M1775R (5443T>G)	
				3829delT	
				C61G (300T>G)	
				E29X (204G>T)	
				S451X (1471C>G)	
				E1134X (3519G>T)	
				Del Exon 17	
				BRCA1 S451X (1471C>G)	
			BRCA2	5804del4	3.9%
				5578delAA	
				E3111X (9559G>T)	
Comen et al., 2011	Ashkenazi Jewish	Central and Eastern Europe	BRCA1	185delAG	6.0%
				5382insC	
			BRCA2	6174delT	4.7%
Muendlein et al., 2015	Caucasian	Germany and Austria	BRCA1	c.181T>A or G Exon 5	21%
				c.213-12A>G Intron 5	
				c.843_846delCTCA Exon 11	
				c.952_1015del64 Exon 11	
				c.1504_1507_delTTAAA Exon 11	
				c.3016_3019delCATT Exon 11	
				c.3915delC Exon 11	
				c.4065-4068delTCAA Exon 11	
				c.4986+3G>C Intron 16	
				c.5161C>T Exon 19	
				c.5230_5237delAGAAACCA Exon 20	
				c.5265_5266insC Exon 20	
			BRCA2	c.2437_2444_delATTCCCAT Exon 11	
				c.2743_2774_delACTTG Exon 11	
				c.7795G>A Exon 17	
				c.9104A>C Exon 23	
Villarreal-Garza et al., 2015	Mexican	Mexico	BRCA1	185delAG Exon 2 (n=3)	97.7% BRCA1
				2415delAG Exon 11	
				2925del4 Exon 11 (n=4)	
				330A>G (R71G) Exon 5 (n=4)	
				3717C>T (Q1200X) Exon 5	
				3878delTA Exon 11 (n=2)	
				4446C>T (R1443X) Exon 13 (n=4)	
				5242C>A (A1708E) Exon 18	
				943ins10 Exon 11 (n=5)	
				del exon9-12 (n=18)	
			BRCA2	2452C>T (Q742X) exon 11	
Wong-Brown et al., 2015 2	Australian	Australia	BRCA1	c.4523G>A	63%
				c.5272A>T	
			BRCA2	c.1860del	
				c.4354C>T	
	Polish	Poland	BRCA1	c.80+2T>C	54.5%
			BRCA2	c.2886dup	

(Hafez et al., 2015).

DNA hypermethylation studies in breast carcinoma have focused on the methylation status of some tumor-related genes in invasive breast cancer as compared to normal breast tissue (Gheibi et al., 2012; Sturgeon et al., 2012; Yamamoto et al., 2012). Several studies have highlighted the epigenetic regulation of some genes including DAPK (gene associated with DNA apoptosis),

TWIST, PAX5 and ID4 (transcription factors), GSTP1 (gene involved in detoxification pathway of xenobiotic), p16 (tumor suppressor gene), CDH13 (involved in cell adhesion) and RARβ (retinoic acid receptor). Cyclin D2 (cell cycle regulators)

DAPK: Death-associated protein kinase gene is a positive mediator of gamma-interferon induced programmed cell death (Suijkerbuijk et al., 2010). It is an important tumor suppressor gene.

DAPK1 is involved in the development of many diseases, including pediatric lymphoma, central nervous system lymphoma, glioma and some cancers (Holleman et al., 2006; Gao et al., 2015).

The loss of DAPK1 expression, mainly by hypermethylation of its promoter region, has been observed in multiple tumor types, and has been associated with aggressive and metastatic phenotype (Suijkerbuijk et al., 2010). In cervical cancer, the frequencies of DAPK1 promoter hypermethylation ranges from 30.0% to 78.6% (median, 59.3%) and is more pronounced in more advanced stages (Narayan et al., 2003). It can then be regarded as a valuable biomarker for cervical cancer development (Xiong et al., 2014).

In breast cancer, DAPK gene is more hypermethylated in TNBC cases when compared to non-TNBC cases (Hafez et al., 2015) In addition, a higher association between DAPK hypermethylation and tumor grade and size has been found in both TNBC and non-TNBC, suggesting a potential implication of DAPK in breast carcinogenesis. Moreover, DAPK1 is essential for the growth of p53-mutant cancers, which accounts for over 80% of TNBCs. Zhao and coll. have showed that depletion or inhibition of DAPK1 suppresses growth of p53-mutant but not p53-wild type breast cancer cells (Zhao et al., 2015).

ID4 gene: The Inhibitor of DNA binding 4 gene encodes a member of the inhibitor of DNA binding (ID) protein family. These proteins are basic helix-loop-helix transcription factors which can act as tumor suppressors but lack DNA binding activity. Consequently, the activity of the encoded protein depends on the protein binding partner. Diseases associated with ID4 include oligoastrocytoma and acute leukemia. ID4 gene has regulative functions for cell differentiation and growth of the developing brain. The role of ID1, ID2 and ID3 are expected to be oncogenic due to their overexpression in pancreatic cancer and colorectal adenocarcinomas, respectively. (Kleeff et al., 1998; Wilson et al., 2001).

Several studies have reported a potential correlation between ID4 promoter methylation and tumour initiation/progression, e.g. in colorectal carcinoma (Umetani et al., 2004), human leukaemia (Yu et al., 2005) and prostate cancer (Asirvatham et al., 2006). In human breast tissue ID4 mRNA has been found to be constitutively expressed in normal mammary epithelial cells, but suppressed in oestrogen receptor (ER)-positive breast carcinomas and pre-neoplastic lesions (de Candia et al., 2006). ID4 is considered as a novel tumor suppressor gene in normal human breast tissue and is epigenetically silenced during cancer development, indicating increased risk for tumor relapse. Frequent ID4 promoter methylation has been observed in primary breast cancer samples. Hafez and coll. have shown a differential increase of ID4 hypermethylation in TNBC than non-TNBC cases, and the incidence of ID4 hypermethylation has been increased with a mounting tumor size and the number of lymphnode positive in both TNBC and non-TNBC cases, which suggests that hypermethylation of ID4 gene promoter is a potential tumor suppressive gene and could serve as a prognostic biomarker in human breast cancer and for prediction of early metastasis and that could explain the aggressiveness of TNBC compared to non-TNBC (Hafez et al., 2015).

GSTP1: Glutathione S-transferase P1 gene is located on chromosome 11q13 and encodes a phase II metabolic enzyme that detoxifies reactive electrophilic intermediates. GSTP1 is a polymorphic gene that encodes different active and functionally GSTP1 variant proteins that are thought to function in xenobiotic metabolism. Several classes of GST, including alpha, mu, pi, and theta, have previously been found in human tissue with specific expression level. Altered GSTP1 expression and activity have been reported in many tumors and are largely due to GSTP1 DNA hypermethylation at the CpG island in the promoter-5' (Zhang et al.,2015). Indeed, an association between hypermethylation of the GSTP1 promoter and gene silencing in prostate cancer and kidney cancer has been well documented (Lee et al., 1994; Brooks et al., 1998; Cairns et al., 2001; Jerónimo et al., 2002; Dulaimi et al., 2004).

In breast cancer, as for other cancers, colon, stomach, pancreas, bladder, lung, head and neck, ovary, and cervix, the expression of GST pi is highly increased as compared to benign tissues (Niitsu et al., 1989; Randall et al., 1990; Kantor et al., 1991; Satta et al., 1992; Toffoli et al., 1992; Green et al., 1993; Inoue et al., 1995; Bentz et al., 2000; Tratche et al., 2002; Simic et al., 2005; Arai et al., 2006). Of particular interest, Hafez et al. have showed that GSTP1 gene has been highly hypermethylated in TNBC cases as compared to non-TNBC cases. Moreover, the hypermethylation of GSTP1 with high frequency in different tumor grade was pathologically correlated with early stage of cancer (Hafez et al., 2015).

TWIST gene: TWIST genes belong to the basic helix-loop-helix family of antiapoptotic and prometastatic transcription factors (Sung et al., 2011). This potential oncogene acts as a transcriptional regulator that inhibits apoptosis, and may be important to the biology of tumor distant metastases (Je et al., 2013). The two Twist isoforms, Twist1 and Twist2, are highly conserved and are frequently reactivated in a wide range of human cancers. Their expression was found to be active in multiple carcinomas (breast, bladder, lung, kidney, colon, gastric, liver, pancreas, ovarian, prostate, head and neck, and esophageal squamous cell carcinomas) and are also frequently expressed in melanomas and sarcomas (Puisieux et al., 2006; Ansieau et al., 2008). In all cancer types, their expression is associated with poor prognosis, high grade, invasive and metastatic lesions (Puisieux et al., 2006).

In breast cancer, Twist overexpression has been correlated with cancer development and poor overall survival in patients and promotes cancer cell migration

by decreasing Ecadherin expression (Je et al., 2013). No specific difference of twist expression has been observed between TNBC and non-TNBC cases according to age, tumor grade, lymphnode status and tumor size (Bae et al., 2005; Hafez et al., 2015). In the last decade, the role of TWIST proteins in cancer was deeply investigated offering a general overview on the role of these genes on tumor progression. Moreover, Je et al. show that some chemotherapy agents can modulate Twist expression in several cell lines giving evidence that twist proteins could be interesting candidates to be used as target proteins for cancer treatment (Je et al., 2013).

p16: Also known as cyclin-dependent kinase inhibitor 2A and as multiple tumor suppressor 1, is a tumor suppressor protein, encoded by the cdkn2a gene located on chromosome 9. p16 has a central function in the regulation of cell cycle activation. The p16 protein is regarded as a negative regulatory protein that regulates the progression of eukaryotic cells through G1 phase of the cell cycle (Serrano et al., 1997). p16 is a well-documented tumor suppressor gene in many cancers, notably melanoma, oropharyngeal squamous cell carcinoma, cervical cancer and esophageal cancer. In these tumours, the functions of p16 may be lost due to mutations or suppression of its transcription by promoter methylation (Demokan et al., 2012; Jha et al., 2012; Peurala et al., 2013; Khor et al., 2013; Wani et al., 2013).

In BC, p16 was suggested to play a significant role in early stage of cancer development and in cancer progression (Hafez et al., 2015). In TNBC cases, hypermethylation of p16 was significantly associated tumor grade (Hafez et al., 2015) and stage of cancer (Radpour et al., 2011).

CDH13: Cadherin 13, also called T-cadherin, is a member of the cadherin superfamily of cell-cell adhesion molecules that modulate epithelial phenotype and morphogenesis in a variety of tissues. CDH is regarded as a tumor suppressor gene, is expressed on the surface of normal cells, plays a pivotal role in maintenance of normal cell adhesion. This expression is decreased in invasive carcinomas and results in decreasing cell-cell adhesion enhancing tumor progression and invasion (Ellmann et al., 2012). In many types of cancer, down regulation of CDH13 is caused by hypermethylation of the promoter region and is associated with poorer prognosis. Jung et al. have clearly demonstrated that CDH13 gene is highly hypermethylated in BC cell lines as compared to non malignant and control tissues (Jung et al., 2013). CDH13 was reported to be frequently hypermethylated in breast cancer samples, suggesting that CDH13 methylation might have a role in the phenotype of breast tumor subtypes (Wang et al., 2012). Of particular interest, CDH13 hypermethylation gene is significantly increased in TNBC compared to non-TNBC, and is increased in LN positive TNBC cases because of the association between this gene and the hormone receptor (Feng et al., 2007; Hafez et al., 2015). CDH13 re-expression in most cancer cell lines inhibits cell proliferation and invasiveness, increases susceptibility to apoptosis and reduces tumor growth in vivo models (Andreev and Kutuzov, 2010). CDH 13 is therefore a key biomarker for breast cancer and especially TNBC management. It can be used as a marker for breast cancer development and invasion, and may represent a possible target for breast cancer therapy.

RARβ1: Retinoic Acid Receptor β, is involved in the regulation of the inhibition of cell growth and apoptosis. The RARβ gene, mapped at 3p24, is a member of the thyroid-steroid hormone receptor superfamily of nuclear transcriptional regulators that binds retinoic acid (the biologically active form of vitamin A), and also mediates cellular signaling during embryonic morphogenesis, cell growth and differentiation (Soprano et al., 2004). Retinoic acids exhibit tumor suppressor activity due to their anti-proliferative and apoptosis-inducing effects and loss of its expression is found in variety of tumors (Brtko, 2007); Liu et al., 2011). RARβ1 gene mediates the growth inhibitory effects of retinoic acids in breast cancer cells and also several studies established RARβ1 gene promoter hypermethylation in breast carcinoma (Raffo et al., 2000; Feng et al., 2007; Hafez et al., 2015). Hypermethylation of RARβ1 is a frequent event in both TNBC and non-TNBC (Hafez et al., 2015) and is correlated with HER2-positive tumors and with poor prognosis (Mehrotra et al., 2004).

TNBC and Viruses

The role of viral infection in cancer was established towards the beginning of 20th century. Overall, 15 to 20% of all cancer cases worldwide are associated with infectious agents and the list of definite and possible carcinogenic agents is growing each year. Viral oncogenic mechanisms generally include: generation of genomic instability, increase in the rate of cell proliferation, resistance to apoptosis, alterations in DNA repair mechanisms and cell polarity changes, which often coexist with evasion mechanisms of the antiviral immune response (Morales-Sanchez and Fuentes-Panana, 2014). It is widely accepted that human tumor viruses induce malignancies after a prolonged latency and in conjunction with other environmental factors. Viral agents also indirectly contribute to the development of cancer mainly through immunosuppression or chronic inflammation, and also through chronic antigenic stimulation (Morales and Fuentes, 2014).

To date, seven viruses, EBV, KSHV, high-risk HPV, MCPV, HBV, HCV and HTLV1 have been consistently linked to the development of different types of human cancer. Unfortunately, few studies have explored the association between viral infection and breast cancer development, particularly TNBC. However, there is evidence that assessment of the viral etiology of breast cancer, including TNBC, and evaluation of possible risk factors is of a great interest to understand the pathogenesis of cancer and to develop new therapeutic strategies.

Recent publications have showed the presence of Epstein-Barr virus (EBV), human papillomavirus (HPV), Mouse Mammary Tumor Virus like (MMTV-like) and polyomaviruses JC (JCV) in BC cases, including TNBC cases, and data converge to a possible role of these viruses in the etiology of cancer or their role as cofactors in the oncogenic process, increasing the aggressiveness of the disease. There is evidence that all reported data relating

viral agents and breast cancer are premolar and need to be further explored and studied to consolidate the possible role of these virus in BC development.

EBV, also known as HHV-4 "Human Herpesvirus Type 4", is a member of the herpesvirus family with 184-kbp long, double-stranded DNA genome that encodes more than 85 genes (Kieff et al., 2001). EBV was the first human virus to be directly implicated in carcinogenesis, infecting more than 90% of the world's adult population (Ahuja et al., 2014) and was classified by the International Agency for Research on Cancer (IARC) as a class I carcinogen (Alibek et al., 2013). EBV has been implicated in the etiology of several different lymphoid and epithelial malignancies including the pathogenesis of Burkitt's lymphoma (BL), Hodgkin's disease, non-Hodgkin's lymphoma, nasopharyngeal and gastric carcinoma, and lymphomas, as well as leiomyosarcomas arising in immunocompromised individuals.(Thompson and kurzrock, 2004). Most of these cancers are more common in Africa and parts of Southeast Asia. Recently, EBV has been reported in human breast cancer cases and associated with more aggressive cancer phenotype (Aboulkassim et al., 2015). Interestingly, Corbex et al. have showed that EBV is significantly more frequent in TNBC as compared to non-TNBC cases (24% / 2%, p<0.003) (Corbex et al., 2014). Overall, EBV was associated with BC phenotypes, tumor size and nodal status but not with DFS or OS, suggesting that the possible role of EBV in the aggressiveness of BC phenotype does not affect the patient's survival (Mazouni et al., 2015). Better understanding of the association between EBV's infection and breast cancer initiation and progression will be of a great interest in view of elucidating the role of EBV in BC, especially triple negative one, carcinogenesis, which may provide a basis for specific therapy

HPV is one of the most common causes of sexually transmitted disease in both men and women around the world. HPV is a relatively small circular, non-enveloped virus which can induce squamous epithelial tumors in many different anatomical localizations. HPV are the etiological agents of many anogenital malignancies; including cervix, penis, vulva, vagina, anus, oropharynx; and also in oral cavity, larynx, and hypopharynx (Bosch et al., 2013). Lately, many studies have reported the presence of high-risk HPV (HR-HPV) infections in BC specimen from diverse populations across the world (Li et al., 2011; Piana et al., 2014). More recently, Fernandes et al., have detected HPV genome in 41.67% of all breast cancer samples, and high-risk oncogenic HPV have been the main detected genotypes (Fernandes et al., 2015). HPV prevalence in TNBC specimen has also been confirmed and 15% of TNBC cases are HPV positive (Piana et al., 2014).

MMTV-like is an infectious retrovirus that belongs to the Betaretrovirus genus. The MMTV is 9 kb long and like all retroviruses, is flanked by 5' and 3' long terminal repeats (LTRs), which in the case of MMTV is regarded as exceptionally long (approximately 1.3 kb). Several groups have established that MMTV-like sequences are present in human breast cancer samples, but absent in normal tissues (Alibek et al., 2013). However, despite the large number of molecular epidemiological studies, the association of MMTV-Like infection with the risk of human breast cancer remains inconclusive mainly due to the heterogeneity in populations involved. MMTV-like env sequences have been detected in 30- 40% of breast cancer cases in several Western countries, including the United States, Italy, Brazil and Argentina (Wang et al., 2004). In Morocco, MMTV-like env sequences have been detected in 57.14% of BC cases with no specific association with BC hormonal status as MMTV have been detected in both TNBC and non TNBC cases (Slaoui et al., 2014).

JCV are oncogenic viruses in animal models and readily transform animal and human cells in vitro (Hachana et al., 2012). These viruses are widespread in the human population and establish subclinical infections in immunocompetent hosts, but can produce pathologic effects in immunocompromised individuals by destroying infected cells Imperiale (2000). Genomic sequences of these viruses have been reported in different human tumor types. JCV has been found in a large percentage of brain tumors, such as astrocytomas, oligoastrocytomas, glioblastomas, and ependymomas (Kunitake et al., 1995; Rencic et al., 1996; Bofill-Mas and Girones, 2001; Del Valle et al., 2002), in colorectal cancers (Bofill-Mas and Girones, 2001; Del Valle et al., 2002) and in gastric cancers (Shin et al., 2006; Murai et al., 2007). Hachana et al. have found that JCV DNA in 23% of BC cases In Tunisian population, and have highlighted the inverse correlation between JCV infection and the expression of estrogen (P = 0.022) and progesterone (P = 0.008) receptors. Moreover, JCV DNA presence correlates also with "triple negative" phenotype (P = 0.021). More importantly, significant correlation has been found between multiple viral infection (JCV, and/or SV40, and/or MMTV-like in the same tumor) and triple negative phenotype (P = 0.001) and also with p53 accumulation (P = 0.028), suggesting that triple negative" breast carcinomas are viral-related tumors (Hachana et al., 2012).

Triple Negative Breast Cancer Treatment

The absence of high-frequency molecular alterations and a limited number of known biomarkers in TNBC have limited the development of specific and adequate therapeutic strategies. Therefore, the basic principles of diagnosis and management of breast cancer are applied to TNBC, even epidemiological, histological, molecular aspects and chemo-sensitivity profiles, are very different. Overall, survival rate of treated patients with TNBC tends to be lower as compared to other forms of breast cancer, and relapse is more likely frequent especially in the first years after treatment (Dent et al., 2007).

Currently, chemotherapy remains the only systemic treatment option used as target therapy for TNBC; hence there's an urgent need to develop new targeted therapies for an effective management of TNBC.

Worldwide, several studies highlighted that TNBC cases treated with neoadjuvant chemotherapy exhibited high pathological complete response (pCR) rates as compared to hormone receptors positive breast cancer

Table 2. Main Potential Treatments Used in TNBC Management

Target	Agent
DNA Repair Mechanisms	✓ PARP Inhibitors: Olaparib, Iniparib, Veliparib
	✓ Platinum Salts: Carboplatin, Cisplatin
Non-Taxane Microtubule Stabilising Agents	✓ Ixabepilone
	✓ Eribulin
Angiogenic Inhibition	✓ Anti-VEGF Monoclonal Antibody: Bevacizumab (Avastin®Genetech/Roche)
	✓ Angiogenesis: Endo TAG-1, metronomic chemotherapy
EGFR/P13K/AKT/mTOR Signalling Pathways	✓ Anti-EGFR Monoclonal Antibody: Cetuximab
	✓ EGF/Src tyrosine kinase inhibitors: Dasatinib, Neratinib, Sunitinib
	✓ mTOR Inhibitor: Temsirolimus, Everolimus, Deforolimus, RAD001
Checkpoint Kinase 1	✓ UCN-01
Androgen receptor inhibition	✓ Bicalutamide
TRAIL	✓ Lexatumumab
TGF-beta	✓ GC1008, AP 12009, LY2157299
PDGFR, c-KIT	✓ PDGFR, c-KIT
Histone Deacetylase Inhibition (HDAC)i	✓ Vorinostat
Other Novel Signalling Pathways	✓ Hedgehog: monoclonal antibodies, small molecular inhibitors
	✓ NOTCH: monoclonal antibodies
	✓ WNT/β-catenin signaling: monoclonal antibodies, ligand receptor inhibitors

cases (von Minckwitz and Martin, 2012). TNBC seems to be particularly chemo-sensitive to anthracyclines and taxanes which are part of the standard therapy used for high risk patients (O'Reilly et al., 2015).

Currently, neo-adjuvant and adjuvant chemotherapies for TNBC are the same treatments used for the non-TNBC (O'Reilly et al., 2015). These therapies include:

Anthracyclines: Doxorubicin or Epirubicin

AC: Doxorubicin and Cyclophosphamide

CMF: cyclophosphamide, methotrexate and 5-Fluorouracil

Paclitaxel and Docetaxel. These drugs are frequently used in combination with Cyclophosphosphamide or 5-Fluorouracil.

Antimetabolites: Gemcitabine or Capecitabine, and other microtubule inhibitors or stabilizers like Vinorelbine.

Non-taxane anti-tubulin agents: Eribulin and Ixabepilone, that are associated with limited clinical efficacy in TNBC as compared to non-TNBC presentations.

Recently, other treatments are under trails and are of particular interest giving promising results to treat more specifically TNBC. The main potential therapies are reported in Table 2 (Hudis and Gianni, 2011; O'Reilly et al., 2015).

Biomarkers for TNBC Treatment

Usually, there are some prognostic and predictive factors that are used to guide the treatment of patients. The main factors include the tumor diameter, the histological grade, the presence of lymphovascular invasion, lymph node status, ER / PR and HER2 expression. Interestingly, there are also some biomarkers that can be used to guide patients' treatment (chemotherapy, hormonal therapy and targeted therapy) (van de Vijver, 2014). In TNBC, as in other diseases, biomarkers are classified as prognostic biomarkers, used to predict the evolutionary and clinical outcomes after treatment, and predictive biomarkers to predict the treatment's efficacy and/or the tumor response to a drug targeting a molecule involved in the biology of this tumor. However, identifying biomarkers to detect cellular abnormalities in a functionally critical step of the progression of the cancer can be challenging, especially if the molecular pathway contains many regulatory genes (True, 2014).

Prognostic Biomarkers

EGFR and ALDH1 are the main prognostic biomarkers used worldwide in TNBC treatment, but interest is growing on the use of other biomarkers as lysyloxydase-Like 2 proteins (LOXL2), Synuclein gamma (SNCG) and LDHB (lactate deshydrogenase B).

LOXL2: Initially, LOXL2 was an independent prognostic factor for BC patients. Higher expression of LOXL2 was associated with poor outcome after a median follow-up time of 9.3 years. Moreover, preclinical and clinical data have clearly confirmed that the positive rate is higher in LOXL2 TNBC than non-TNBC tumors (Ahn et al., 2013).

SNCG: SNCG was an independent predictive marker for recurrence and metastasis in BC. Moderate to strong positive SNCG expression has been observed in 34.3% of TNBC and this expression is significantly associated with tumor size. Moreover, shorter DFS and a higher probability of death has been observed in patients with high expression of SNCG, when compared with those whose tumors did not express SNCG (Wu et al., 2013).

LDHB: Lactate Dehydrogenase B, is an essential gene for triple-negative BC by an integrated genomic screen (McCleand et al., 2012). Denison et al. have suggested that LDHB is closely linked to basal-like subtype and TNBC and is able to predict the prognosis of TNBC with a high degree of power (Dennison et al., 2013). Moreover, breast

cancer cases with high LDHB expression have most been responsive to neoadjuvant chemotherapy independently of established prognostic factors (grade, tumor size) and molecular markers (HR status and PAM50 subtyping) (Dennison et al., 2013).

PI3K/Akt. The phosphatidylinositol 3-kinase (PI3K) pathway regulates many cellular functions including cell proliferation, survival and migration (Willems et al., 2012), and are frequent in breast cancer. Activation of the PI3K pathway was significantly associated with the state of ER-negative and PR-negative, high tumor grade, basal-like phenotype and had been associated with loss of PTEN (Wang et al., 2012; Willems et al., 2012).

Forkhead box C1: Also known as FOXC1, is a protein encoded in humans by the FOXC1 gene. The specific function of this gene has not yet been determined; however, it has been shown that FOXC1 plays a role in the regulation of embryonic and ocular development (Silla et al., 2014; Haldipur et al., 2014). Previous studies have found that FOXC1 is a biomarker that is specific for TNBC (Ray et al., 2010) and the high expression of FOXC1 predicts poor overall survival of TNBC which makes it a potential therapeutic target in this molecular subtype of breast cancer (Ray et al., 2010; Han et al., 2013).

P-cadherin is a cell-cell adhesion molecule. Liu et al., have shown that P-cadherin is a reliable biomarker for TNBC (Liu et al., 2012). In addition, P-cadherin is associated with subtypes of high-grade tumors and poor prognosis marker (Turashvili et al., 2011). The expression of P-cadherin is negatively correlated with ER and PR in invasive ductal tumors and positively with recurrence and distant metastases (Liu et al., 2012).

Lysine specific demethylase 1, LSD1, is encoded in humans by the KDM1A gene. Aberrant expression of LSD1 has been shown in many types of cancers (Li et al., 2016). In breast cancer, LSD1 has also been overexpressed in some cases and may function as a biomarker of the disease aggressiveness . Nagasawa et al., have shown that LSD1 is amplified in the basal-like breast cancer, and its protein product is considered a poor prognostic biomarker in TNBC. Moreover, overexpression of LSD1 is correlated with the regulation of BRCA1 in TNBC, suggesting the interest of the use of PARP inhibition as a therapeutic strategy (Nagasawa et al., 2015).

Predictive Biomarkers

The term predictive biomarker is defined as a marker which can be used to identify subpopulations of patients who are most likely to respond to a given therapy. With predictive biomarkers it should be possible to select the therapy with the highest likelihood of efficacy to the individual patient. Thus, predictive biomarkers are the basis for individualized or tailor-made treatment. Some good examples of predictive biomarkers being used in the daily clinical oncology practice are estrogen and progesterone receptors to predict sensitivity to endocrine therapy in breast cancer, HER2 to predict sensitivity to Herceptin treatment and KRAS mutations to predict resistance to EGFR antibody therapy. New predictive biomarkers such as assays for Topoisomerase 2α DNA aberrations may turn some types of conventional chemotherapy into targeted drugs.

Biomarkers for Targeted Therapy

ATargeted therapies for patients suffering from TNBC remain under study and much further research may be mentioned:

MicroRNAs, miRNAs or miRs, are small non-coding regulatory molecules that contain about 21 to 25 nucleotides, and play an essential role in cell signaling pathways Bartel (2009). Recently, Medimegh et al. have explored the expression level of seven micro-RNAs: miR-10b, miR-17, miR-21, miR-34a, miR-146a, miR-148a and miR-182 in both TNBC and non TNBC cases, and have showed that (Medimegh et al., 2014):

miR-21, miR-146a and miR-182 are significantly expressed in TNBC. miR-10b, miR-21 and miR-182 are significantly associated with lymph node metastasis occurrence in TNBC. miR-10b is associated with grade III in non TNBC.

In the non-TNBC groups studied, micro-RNAs have highly been correlated to the use of contraceptive pills, and excepted miR-34 and miR-146a, the addition of hormonal factors have showed an association with the miRs in the case of TNBC (Medimegh et al., 2014).

Currently, there is evidence that micro-RNA profiles play a key role in cancer initiation, progression and metastasis and might also be used to develop valuable predictive biomarkers, making them a promising therapeutic tools for the management of cancer.

TTK/hMPS1: The human protein kinase monopolar spindle 1 (hMPS1), also known as TTK and involved in mitotic checkpoint, is specifically overexpressed in TNBC samples, compared to the other BC subgroups and healthy tissues (Maire et al., 2013). Maire et al. have showed that TTK/hMPS1 is an attractive therapeutic target for TNBC. High levels of TTK mRNA have been found in BC, particularly in TNBC where it has shown to protect cancer cells from aneuploidy (Jiao et al., 2014). The depletion of TTK in TNBC cells leads to a strong reduction in cell viability as a result of an induction of apoptosis. These results indicate TTK as a protein kinase over-expressed in TNBC. This may represent an attractive therapeutic target and a promising approach for patients with TNBC (Maire et al., 2013).

RB1 (Retinoblastoma 1): The RB1 gene provides instructions for making a protein called pRB. This protein acts as a tumor suppressor, which means that it regulates cell growth and keeps cells from dividing too fast or in an uncontrolled way. Under certain conditions, pRB stops other proteins from triggering DNA replication, the process by which DNA makes a copy of itself. The tumor suppressor RB1 is often lost by mutation, deletion or transcriptional silencing as well as by hyper-phosphorylation of its gene product, pRb, in many human malignancies (Sherr, 1996; Sharma et al., 2007).

The retinoblastoma (RB1) tumor suppressor is deleted or rearranged in ~20-25% of BC cell lines (Wang et al., 1993; Herschkowitz et al., 2008) and is frequently lost in human TNBC (Robinson et al., 2013); It is therefore

important to determine the effect of RB1 status in TNBC lines on response to therapy.

Robinson, et al. have also demonstrated that RB-negative TNBC cell lines are highly sensitive to gamma-irradiation and moderately more sensitive to doxorubicin and methotrexate compared to RB-positive TNBC cell lines (Robinson et al., 2013). In contrast, RB1 status do not affect sensitivity of TNBC cells to multiple other drugs including cisplatin (CDDP), 5-fluorouracil, idarubicin, epirubicin, PRIMA-1met, fludarabine and PD-0332991, some of which are used to treat TNBC patients (Jiao et al., 2014)

Aldehyde dehydrogenase 1 (ALDH1): The stem cell marker ALDH1 has been of particular interest to scientists since it has been successfully used as a reliable marker to isolate cancer stem cells from breast cancers. Several investigators have demonstrated its clinical significance as a prognostic indicator of breast cancer, and may become a promising target for cancer therapy. ALDH1 expression in carcinoma cells is an independent prognostic factor in TNBC patients (Ohi et al., 2011). In addition, Li et al. study support the concept that the expression of ALDH1 is higher in TNBC than in non-TNBC, which may be clinically meaningful for a better understanding of the poor prognosis of TNBC patients (Liu et al., 2013).

Cyclooxygense 2 (Cox-2): is an inducible, proinflammatory enzyme that catalyzes key steps in the conversion of arachidonic acid to prostaglandins and thromboxanes. The expression of COX-2 is lower in normal tissues, but increases in neoplastic tissues and inflammatory conditions (Alikanoglu et al., 2014). It is overexpressed in a variety of solid tumors and is involved in tumor processes including tumor cell proliferation, tumor invasion, and metastasis of TNBC (Jiao et al., 2014). The role of COX-2 expression is shown in different malignancies (Masferrer et al., 2000; O'Byrne and Dalgleish, 2001). COX-2 protein regulates the production of prostaglandins and is regulated by transcriptional and translational processes that are mediated by cytokines, growth factors and oncogenes (Singh-Ranger et al., 2008). In breast cancer, the overexpression of COX-2 is associated with indicators of poor prognosis, such as lymph node metastasis, poor differentiation and large tumor size (Mosalpuria et al., 2014). The COX-2 protein is overexpressed in the primary tumors of TNBC patients and both TNBC status and COX-2 overexpression are known poor prognostic markers in primary breast cancer (Mosalpuria et al., 2014).Therefore, Cox-2 may be an ideal target for developing agents for TNBC treatment (Zhou et al., 2013).

Mucin1 (MUC1): MUC1 is a tumor antigen expressed on adenocarcinomas and on differentiated tumor cells, including BC. It represents an ideal target for MUC1-based vaccination (Siroy et al., 2013). MUC1, a glycoprotein associated with chemoresistance, is aberrantly overexpressed in TNBC and facilitates growth and metastasis of TNBC cells. Miedler et al. suggest that the vast majority of cases of early stage TNBC expresses MUC1 (Miedler et al., 2009). Interestingly, Siroy et al. have demonstrated that MUC1 has been was expressed in 94% of early-stage high-grade TNBC, and according to 52 cases patients and the expression of MUC1 in most TNBC provide a rationale to treat patients who have completed standard therapy for early-stage TNBC with a vaccine that generates immunity against MUC1 (Siroy et al., 2013).

Androgen receptor (AR): Androgen receptor is one of the newly emerging biomarkers in TNBC and has been proved to play an important role in the genesis and in the development of breast cancer (Kneubil et al., 2015). AR expression has been observed in about 50% of patients with TNBC (McNamara et al., 2013). Available studies have provided divergent opinions on the role of androgens in TNBC and correlation of AR expression with prognosis, clinical outcome and chemosensitivity in various settings (Koo et al., 2009; Gucalp et al., 2010; Carey, 2011). Moreover, the expression of AR among TNBC has also been shown to be associated with a better survival and its assessment would have prognostic value as well. AR-positive TNBC is more common in older patients and has a higher propensity for LN metastases (Safarpour and Tavassoli, 2014). AR-positive TNBC may represent a breast cancer subtype with unique features that may be amenable to treatment with alternative targeted therapies (McGhan et al., 2014).

Triple Negative Breast Cancer and Vitamin D Levels

Vitamin D is the name given to a group of fat-soluble vitamin with a great specter of activities. In addition to its role in calcium homeostasis and bone health, vitamin D has also been reported to have anticancer activities against many cancer types, including breast cancer. There are two major forms of vitamin D in the body; 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D (1,25(OH)2D) (Rainville et al., 2009). Importantly, higher serum vitamin D levels are associated with better cancer outcomes, including survival (Goodwin et al., 2009; Peiris et al., 2013). The protective effects of vitamin D result from its role as a nuclear transcription factor that regulates cell growth (Holt et al., 2002), differentiation (Murillo et al., 2007) and a wide range of cellular mechanisms crucial to the development and progression of cancer. Vitamin D acts as an immunomodulator through multiple pathways and enhances immune tolerance (Krishnan and Feldman, 2011).

1,25(OH)2D, also known as calcitriol, is the biologically active form of vitamin D and exerts its action by binding to an intracellular receptor, the vitamin D receptor (VDR). VDR, first identified in a breast cancer cell line in 1979, belongs to the superfamily of nuclear receptors for steroid hormones and regulates gene expression by acting as a ligand-activated transcription factor. In addition to its main function of maintaining extracellular calcium levels, the activation of VDR influences up to 200 genes that mediate cellular growth, differentiation, and apoptosis (Shao et al., 2012).

Rainville et al. (2009) have clearly illustrated that triple-negative breast cancer patients have lower vitamin D levels than the other breast cancer phenotypes. Moreover, the highest percentages of patients that are vitamin D deficient have the TNBC form, suggesting that vitamin D's

deficiency is a characteristic of TN phenotype (Rainville et al., 2009).

TNBC and Diet

Diet and physical exercise play an important role in maintaining a healthy lifestyle. Diet can also be a risk factor for many chronic diseases, and some food intake and dietary habits are considered as a high risk for cancer development (Castelló´ et al., 2014). However, to our knowledge, there is no research study that supports the association between a specific diet and TNBC development.

For instance, alcohol consumption is still the individual dietary factor thought to have a detrimental effect on BC risk (WCRF/AICR, 2007; WCRF/AICR, 2010; IARC, 2012). The evidence on the effect of other individual dietary factors on BC risk is inconclusive (Romieu, 2011). It is widely accepted that too much alcohol is linked to liver disease, inflammation of the stomach, pancreas, high blood pressure, and increased risk for cancers of the mouth pharynx, larynx, and esophagus. Moreover, alcohol is associated with hormonally related breast cancer and not especially TNBC cases.

Some studies have confirmed the harmful effect of a Western diet on BC risk. Treatments or foods that reduce the production of estrogen or block its effects on the body are not useful for this type of breast cancer. Also, women with metabolic syndrome are more likely to have TNBC upon diagnosis than women without it. Moreover, a high cholesterol diet has been shown to induce angiogenesis and accelerate mammary tumor growth in a mouse model of triple negative breast cancer (Castellō et al., 2014). Interestingly enough, Castellò et al. have highlighted the benefits of a diet rich in fruits, vegetables, legumes, oily fish and vegetable oils to prevente all BC subtypes, and particularly triple-negative tumors (Castello et al., 2014).

In recent years, more attentionhas been directed to the association between dietary fat and breast cancer development, but results are very controversial (Prentice et al., 2006; Martin et al., 2011; Trichopoulou et al., 2010; Buckland et al., 2013). A slightly lower incidence of recurrence has been observed in women with estrogen negative breast cancer, suggesting that less dietary fat consumption is a wise change.

Food containing omega-3 fatty acids have also attracted much attention over the years. Omega-3 fatty acids may have a favorable effect on the immune system and reduce the risk of heart disease but there is no conclusive data on its benefit for breast cancer prevention (Ford et al., 2015) For instance, food containing omega-3 fatty acids are much recommended for general good health and must be consumed three times or more weekly. Fructose has also been shown to induce changes in triple negative breast cancer cells that may increase their aggressiveness (Dong et al., 2015).

The studies related to diet or a specific food-linked to triple negative cancer focus on hormone receptor status; HER2/neu status tends to be studied separately. However, the information concerning ER-/PR- breast cancer and diet is likely to be relevant to triple negative breast cancer since HER2- is the "normal" state. There is specific food that is found to be associated with lower risk of this type of breast cancer and some food is associated with higher risk (Saleh et al., 2013).

Conclusions

TNBC is a subtype of breast cancer characterized by its aggressiveness and its biological heterogeneity, poor prognosis, specific model of distant metastases and a high rate of recurrence with standard chemotherapy. The lack of specific molecular targets and the low sensitivity and specificity of available immune-histo-chemical markers are the main limitation to set up a target therapy to better manage this aggressive form of breast cancer. Thus, adequate prevention, early detection and more effective treatment strategies rest on a good understanding of TNBC biology and etiology and remain the main keys to be explored for better management of TNBC.

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