Crosstalk in Tri-positive Cancer: Predictor and Diagnostic Mirnas in Focus

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Abstract Cancer is a complex multifaceted disease caused by alterations at the genetic or epigenetic level in cells. Cancers in females majorly consist of ovarian, breast and cervical cancers, all of which, occurring concurrently, are referred to as 'Tri-positive cancer (TPC)'. Genetic and epigenetic mechanisms in TPC involve microRNAs; which are a class of endogenous, small, non-coding RNAs of 22 to 24 nucleotides that control gene expression. In TPC, upregulated oncogenic miRNAs includes: miR-21, miR-146a, miR-155, miR-182 and miR-200c while the downregulated tumour suppressor miRNAs includes: let-7b, miR-125b, miR-143 and miR-145. Cross-talk in TPC, which is the interaction between miRNAs and pathways, is an upshot of a complex network engaging the interplay of target genes such as PTEN, Muc-1, ERB2/3, ZEB1/2, RAS, Bcl-2 and c-Myc among others, and occurring mostly through the P13k/Akt signaling pathway. Furthermore, an inverse relationship between miR-146a and miR-182, and BRCA gene with a direct relationship between miR-125b and BRCA gene was observed in the emergence of TPC. This review also showed that there are variations in the expression of let-7, miR-21, miR-125b and miR-200c between Tumour Initiating Cells (T-ICs) and TPC. Thus, since some of these miRNAs are dysregulated in chronic inflammations which play a critical role in tumourigenesis, proper investigation of these miRNAs and target genes in high risk individuals may aid prediction and early diagnosis of cancer and effective therapy with high reduction in mortality.

Keywords Ovarian Cancer, Breast Cancer, Cervical Cancer, Mirna Expression, Crosstalk, BRCA Gene

suppressor and oncogenes either at the genetic or epigenetic level [1]. Epigenetic alterations include DNA methylation, histone modifications, and small noncoding RNA molecules, including miRNAs [2]. MicroRNAs are a class of endogenous, small, non-coding RNAs (22-24 nucleotides in length) that control gene expression by interacting with target mRNAs [3]. Tumor formation may arise from downregulation of a tumor suppressor miRNA or upregulation of an oncogenic miRNA [4]. Upregulation of tumorigenic miRNAs in human cancers can result from amplification, deregulation of a transcription factor, or demethylation of CpG islands in the promoter regions of the corresponding genes. Tumor suppressor miRNAs can be downregulated in cancer through several pathways or mechanisms which include deletions, epigenetic silencing, or loss of transcription factor expression [5] among others.

The interaction between miRNAs, genes and pathways is referred to as cross-talk [2]. An alteration of this cross-talk in cells may result in cancer. Dysregulation of 5 oncogenic miRNAs (miR-21, miR-146a, miR-155, miR-182 and miR-200c) and 4 tumour suppressor miRNAs (Let-7b, miR-125b, miR-143 and miR-145) have been implicated in TPC. However, reports of miR-214 expression in TPC appear to be controversial. Reports have shown that a BRCA1 or BRCA2 mutation in women increases the risk of Tri-positive cancer by 3 fold [6-9]. Despite the fact that several studies have suggested that BRCA and miRNAs play crucial roles in cell activities, the pathways through which BRCA mutation and miRNA dysregulation result in TPC is yet to be fully elucidated. This review paper aimed to evaluate the connection between BRCA mutation and miRNA cross-talk in the manifestation of Tri-positive cancers.

1. Introduction

Tri-positive cancer (TPC) refers to the simultaneous occurrence of ovarian, breast and cervical cancers in the female reproductive tract of an individual. Cancer is a complex multifaceted disease caused by alterations in tumor

2. Tumour Suppressor miRNAs

Underexpression of tumour suppressor miRNAs such as let-7b, miR-125b, miR-143 and miR-145 has been reported in TPC (Table 1). Despite the fact that the expression of

miR-214 in TPC is controversial in literature, its regulation in different cancers is discussion worthy.

2.1. Repression of Let-7b in Neoplastic Diseases

Let-7b, a tumour suppressor, is one of the twelve variants of the let-7 family reported in literature. It is overexpressed during embryonic cell differentiation [10] and underexpressed in various cancers. It regulates apoptosis and cancer stem cell differentiation when compared with normal tissues [11-14]. However, overexpression of let-7b has been reported in some cancers which suggest that let-7b does not play a tumor suppressor role in all cases. Such phenomenon is observed in a case of malignant mesothelioma, where let-7b was overexpressed [15]. The underexpression of let-7b offers cancer stem cells unlimited self-renewal and metastatic capabilities [16,17]. During tumorigenesis, the let-7b targets embryonic genes (regulons) which are unexpressed in adult tissues promote de-differentiation and cancer progression [18]. An example of such regulons is HMGA2. The target, HMGA2, is a direct target of let-7b [19] and also a chromatin associated nonhistone protein which controls chromatin architecture.

Let-7b alterations in tumours are adduced to chromosomal aberrations on 12q13-15. It is untraceable in most differentiated tissues, but overexpressed in many cancers such as neuroblastoma, pancreatic, lung and thyroid cancers, and hematopoietic and fetal neuronal stem cells [20-26]. Overexpression of HMGA2 and underexpression of let-7b have strong correlation with larger tumor size in cases of uterine leiomyomas [27]. According to Watanabe et al. [28], oncogenic RAS signaling modulates HMGA2 expression which determines the manifestation of epithelial phenotype of pancreatic cancer cells. Under stimulated differentiation (normal circumstance), overexpression of let-7b reduces ras and HMGA2 expression, resulting in inhibited cell proliferation and apoptosis induction. However, underexpression of let-7b and overexpression of c-Myc [29], transcriptionally induces Lin28B to suppress the maturation of let-7b microRNA precursors [30-31] which promotes genomic instability, cell proliferation and metastasis [32]. In normal tissues, reduced Phosphatase and tensin homologue (PTEN) expression is adduced to epigenetic events such as promoter methylation [33-34], phosphorylation and ubiquitination, while oxidation and acetylation reduce PTEN activity [35]. Overexpressions of PTEN via downregulation of Let-7b in TPC have been reported in literature (Table 1). Several studies revealed that let-7b is underexpressed in TPC; ovarian cancer [36-38], cervical cancer [39] and breast cancer [40-41].

2.2. Plasticity of miR-125b in Cancer Tissues

Precursors of mature miRNA-125b which include pre-miR-125b-1 and pre-miRNA-125b-2 are located at chr11q24.1 and chr21q21.1, respectively [42]. More importantly, miR-125b is located at chromosome 11q23-24,

a region recurrently identified and downregulated in breast, ovarian, and lung tumors [43-44]. In normal tissues, miR-125b reduces cell proliferation, motility, invasiveness and anchorage-dependent cell growth [45]. Its upregulation promotes cell proliferation, de-differentiation, and inactivation of apoptosis in cancers [46]. Interestingly, variation in miR-125b expression has been reported in different cancers under pathophysiological conditions [47-49]. This suggests that some miRNAs are tissue-specific or even cell-type-specific. This information explains, in part, the discordant reports in miRNA expression in some type of cancers [50]. MiR-125b is overexpressed in papillary thyroid cancer and underexpressed in anaplastic thyroid carcinomas, hepatocellular carcinoma (HCC) tissues and HCC cell lines [48] when compared with normal thyroid tissue [51]. Its levels are more reduced in oral squamous cell carcinoma (OSCC) tissues and cell lines compared with oral keratinocyte (NHOK) controls [49]. MiRNA-125b is regulated by transcriptional control of nuclear factor-kB [52-53]. Normally, activation of p53 during DNA damage or oncogene activation leads to cell cycle arrest or apoptosis [54]. Underexpression of miR-125b upregulates p53 and induces cell apoptosis (Le et al., 2009) while its over-expression inhibits the endogenous level of p53 and p21 resulting in malignant cell immortality.

According to Guan et al. [56], miR-125b decreases the proliferation of human ovarian cancer (OC) cells, and suppresses the growth of OC cells by targeting BCL3. MiR-125b, as a tumour suppressor, is down-regulated in biopsy specimens [57-58] through the ERBB2 and ERBB3 signaling [59] or by targeting the ETS1 gene [60]. It has also been reported to reduce the expression of MUC1 oncoprotein [61]. Mounting evidences suggest that it increases the resistance of cancer cells to anticancer drug [62], with resultant recurrence and metastasis (by targeting STARD13), particularly in triple negative breast cancer [63]. The observed metastasis could be due to the molecular interaction of miR-125b and mutant BRCA genes in complex genetic pathways (figure 1). MiR-125b has also been shown to be downregulated by approximately 30% in endometrioid endometrial cancer resulting to increased cell invasiveness, possibly through ERBB2 signaling [64]. The down-regulation of miR-125b in the endometrial cancer and TPC suggests that these cancers occur by a single pathway with the involvement of the female reproductive hormones. The dysregulation of miR-125b may be linked to some cases of infertility. According to Banzhaf-Strathmann and Edbauer [65], downregulation of miR-125b through ERBB2/3 signaling induces cell proliferation by Ras-mitogen activated protein kinase (MAPK) pathway which ultimately stalls apoptosis via the mammalian target of rapamycin (mTOR) pathway. In TPC, underexpression of miR-125b was observed; ovarian cancer [36,37,66], cervical cancer [39,67-73] and breast cancer [58,67,68,74].

2.3. Modulation of miR-143/145 in Cancer

Transcription factor, p53, controls cellular response to DNA damage by regulating cell cycle and apoptosis. Half of human cancers possess the mutated form of this transcription factor which regulates the transcription of several miRNAs [75]. In the event of DNA damage, interaction of p53 and p68 promotes the posttranscriptional maturation of several miRNAs such as miR-143 and miR-145 with growth-suppressive function [76]. MiRNAs, miR-143 and miR-145, develop a bicistronic cluster in 5q33.1 and are known to be inhibit cell proliferation and angiogenesis, and promote apoptosis [32,77]. Undetectable levels of MiR-143 and miR-145 in epithelium-derived cancer cell lines has been reported with detectable levels in normal human tissue. Due to their tumour suppressive capability of these miRNAs, the loss of posttranscriptional action via denaturation or mutation of p53 promotes malignancies in epithelial cell [78-80]). Repression of miR-143 or miR-145 leads to activation of the Ras oncogene in KRAS mutant pancreatic and colorectal cancers via Ras-responsive element-binding protein (RREB1) cleaving to miR-143/145 promoter [81]. The latter signaling pathway is supported by the findings of Hingorani et al. [82]. Despite the fact that modulation of K-RAS by miR-143 was detected in an epithelial cell type, miR-143 may also modulate K-RAS in mesenchymal cells. MiR-143 has been reported to be underexpressed in TPC; ovarian cancer [38], cervical cancer [67,68,83-89] and breast cancer [90,91]. More so, miR-145 is underexpression in ovarian cancer [69,90,93], cervical cancer [83,85-89] and breast cancer [4,40,91,92,95].

3. Dual Activity of over miR-214 Expression in TPC

Chemoresistance, tumor progression, and metastasis have been observed in many malignancies (such as pancreatic, prostate, gastric, breast, cervical and ovarian cancers including malignant melanoma) which had overexpressions of miR-214 and downregulation of tumour suppressors target genes such as FAP2C, PTEN and p53 [96-103,108]. MiR-214 was also reported to be overexpressed in cervical and hepatocellular cancers by Sharma et al. [104]. Contrary to these reports, down-regulation of miR-214 was observed in human breast cancer tissues [105-111], ovarian cancer [38], and cervical cancer [68,84,87,105]. These contradicting reports might be due to the fact that miRNAs expressions vary in different tumor cells and sites even in the same organ, as also reiterated by Okoye [50]. More so, depending on the tumour stimulating factor, miRNA may function as a tumor suppressor in a neoplastic disease and oncomir in others. MiR-214 underexpression was suggested to upregulate RAS in ovarian cancer [112]. Deactivation and activation of Ras family members are antagonistically regulated by GTPase activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs) [113,114]. Downregulation of miR-214 and upregulation of GALNT7

in cervical cancer was also reported by Peng et al. (2014). Other modulated regulons in ovarian cancer targets include: PTEN, RAS, SRC, BCL-2 [112] CCNL2; WDR8; WDR8 [73] and IKK [38], while that of cervical cancer include GALNT-7 [105,115] Plexin-B1 [96,115]. Targets such as PTEN and FAP2C are also modulated in breast cancer [105].

4. Oncogenic miRNAs in TPC

In TPC, upregulated oncogenic miRNAs include miR-21, miR-146a, miR-155, miR-182 and miR-200c (Table 2). Their roles in tumorigenesis in respect to cancers, especially TPC, are discussed below. More so, the interaction of these miRNAs and tumour suppressor equivalents and their target oncogenes in the emergence of TPC is shown in figure 1.

4.1. Bi-Functional Activity of Mir-146a

In humans, miR-146a resides on chromosome 5q33.3 [132]. It promotes cell proliferation and cell cycle progression [32]. It is up-regulated in LPS-stimulated macrophages and negatively modulates the Toll-like receptor-mediated immune response to forestall undue cell activation [133-135]. Overexpression of miR-146a is suggested to occur through by transcriptional repression of NF- κ B family members [133,136]. Upregulation of miR-146a is not only observed in cervical cancer [71,83,89,137], but also upregulated in ovarian cancer [138], and breast cancer [139,140]. Upregulation of miR-146a in TPC activates cell cycle progression and proliferation via repression of NF κ B activators IRAK1/ TRAF6 [133,141]. The TRAF6 signaling in TPC in turn recruits IKK complex which results in phosphorylation and degradation of the i κ B inhibitor that ultimately activates NF κ B dimmers [142-144] which suppresses BRCA 1 [145]. Suppressed BRCA1 expression is also associated with upregulated expression of high-mobility group proteins type A1 (HMGA1) and inhibitor of differentiation 4 (ID4) which regulates gene transcription and DNA conformation [146-148]. Inactivation of the BRCA1 gene in TPC may occur through a combination of complex mechanism or single mechanism such as somatic mutation, promoter methylation, haploinsufficiency, transcriptional inhibition and impairs homologous recombination [145]. More so, upregulation of miR-146a downregulates p53, tumor necrosis factor, FADD and TRADD which results in increased proliferation in both luminal and basal-like breast cancer cell lines [149].

Tumor cells exhibit morphological and phenotypical changes during cancer progression by a phenomenon known as epithelial-mesenchymal transition [153]. This phenomenon is observed in miR-146a activity. Just like miR-125b, miR-146a expression is suggested to differ in varied cancer tissues. For example, in Burkitts lymphoma lines, elevated level of miR-146a was seen with EBV-LMP1 expression [150,151], whereas reduced levels were

observed in hormone-refractory prostate cancer [152], papillary thyroid carcinoma [154] and mesenchymal-like lung cancer cell lines [153]. MiR-146a upregulation reduces mesenchymal marker and elevates the epithelial marker in lung cancer cell lines which leads to reduction in migration and invasion of cancer cells, possibly by directly targeting the insulin receptor substrate 2 (IRS2) [153]. The reason for this varied expression is yet unclear.

4.2 Mir-21 Activity in Malignancy

MiRNA-21 possesses tumorigenic activity which are elevated in different types of cancers including glioblastoma [155], glioma [156] brain, breast, cervix (table 1), lung, liver, prostate, pancreas, and colon [37,58,99,157-160] where it promotes cell proliferation, angiogenesis, metastasis, escape from surveillance and inactivates apoptosis [32,158]. Haverty et al. [161] suggests that miR-21 is upregulated by gene amplification, a non-transcriptional mechanism, rather than promoter hyper-activation. However, some studies suggest that miR-21 expression is controlled by transcriptional and post-transcriptional modulation [161]. According to Hayashi et al. [162], miR-21 promotes branching morphogenesis possibly by regulating MMPs and targeting RECK and PDCD4. Some findings revealed over-expression of miR-21 in ovarian cancer [38,66,93,163], cervical cancer [67,83,85-87,99,164] and breast cancer [36,40,57,58,93,99,158,165-168] through PTEN signaling (table 2).

4.3. Regulation of Mir-155 in Cancer

Overexpression of miR-155 has been reported in several neoplastic diseases such as hematopoietic cancers, breast, lung and colon cancer [169], especially through the downregulation of mutant p53 and tumor protein 53-induced nuclear protein 1 (TP53INP1) in breast tumours which promotes metastasis [170,171]. MiR-155 suppresses apoptosis and inhibits cell cycle arrest through a blockade of caspase-3 activity [172,173]. Its upregulation represses the RHOA gene, which serves a vital function in cell junction formation and sustenance. The RHOA gene, though yet to be validated in ovarian cancer, when underexpressed, results in lack of cell adhesion among mutated cells [32]. Interestingly, miR-155 is overexpressed in ovarian cancer [66,174], cervical cancer [39,69,70-72,83,89,99] and breast cancer [40,58,93,99,175].

4.4. Oncogenic Activity of miR-182

miR-182 is frequently overexpressed in human breast, ovarian and endometrial tumor tissues and cell lines [176-179] compared with that of healthy controls. Its oncogenic activity was revealed following the repression of FOXO1, which promotes proliferation of malignant cells and metastasis [176,180]. It represses the expression BRCA1 gene in the event of DNA damage response, thereby inhibiting DNA repair via poly adenosine diphosphate ribose polymerase 1 (PARP1) inhibition [181]. Evaluation of breast cancer cell lines revealed that miR-182 downregulates the metastasis suppressor missing-in-metastasis (MIM/MTSS1) which also inhibits cancer cell motility, invasiveness through inactivation of the cytoskeleton regulator RhoA. Additionally, miR-182 has been implicated in malignancies involving TGF β and NF κ B, pathway [182]. According to recent findings, miR-182 is overexpressed in ovarian cancer [183-186], cervical cancer [67,84,68] and breast cancer [187].

4.5. Clonogenic and Tumorigenic Activity of Mir-200c

Downregulation of miR-200c is observed in breast cancer stem cells, normal mammary stem or progenitor cells [188]. Its overexpression reduces clonogenic and tumour initiation activities in breast cancer stem cells which inhibits formation of mammary ducts through BMI-1 modulation [189]. The findings of Kan et al. [190] revealed that the expression of miR-200c is significantly overexpressed in serous epithelial ovarian cancer. According to Bendoraite et al. [191], miR-200c determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressor proteins ZEB1 and ZEB2, and controlling oxidative stress via p38 α [192]. Snowden and his colleagues [193] also reported up-regulation of miR-200c in both endometrioid endometrial adenocarcinoma and complex atypical hyperplasia compared to normal control endometrium. Their work is in line with that of Lee et al. [194] and Park et al. [195] which revealed similar findings in cancerous tissues as well as endometrial adenocarcinoma cell. Upregulation of miR-200c in tri-reproductive cancer occur through the ZEB1/ZEB2 pathway. Other likely pathways may include targets genes such as TARDBP, PTEN and ZEB1. In literature, miR-200c was suggested to be overexpressed in ovarian cancer [37,38,69,93,184,185], cervical cancer [71,84,196] and breast cancer [40,41].

Table 1. Antitumorigenic miRNAs and their targets in TPC.

miRNAs	Ovarian cancer	Cervical cancer	Breast Cancer
Let 7b	RAS, HMGA2 [38], c-Myc [116]	RAS, NFκB, [117], XIAP [115]	RAS, HMGA2, LIN28, PEBP1 [117-121]
miR-125b	CSNK2A1 [36,37], FAM169B [73], HIF-1α, VEGF [38], BCL3, ERBB2, ERBB3 [65].	PIK3CD, PI3K, P-Akt, P-mTOR [87], BAK-1 [117], ERBB2, ERBB3 [65].	BMPRI1B [74], ENPEP, CK2-α, CCNJ, MEGF9 [45], ERBB2, ERBB3, ETS1, MUC1, STARD13, Bcl-2, p53, TP53INP1, TNFAIP3, BAK-1, CBFβ, ABTB1 [120], E2F3 [121].
miR-143	ENO1; KIF1B; KRAS [73].	Bcl-2, ERK5/ MAPK7 [67,123], KRAS, PIK3CA [124].	ERK5, KRAS [125,126], ERBB3 [91].
miR-145	RERE; CTNNBIP1; FSCN1 [158], HIF-1, VEGF [38], P70S6K1, MUC-1 [127].	HLTF [128], MUC-1, IRS-1 [115].	Muc-1 [129], RTKN [130], EGFR [131], c-Myc [129], ERBB3 [91], PTEN, ZEB1, ZEB2 [120].

In table 1 above, common target genes for the tumour suppressor miRNAs in TPC include RAS, HMGA2, ERBB2, ERBB3, BAK1, KRAS, ERK5/MAPK7, MUC-I, Bcl-2 and c-Myc. Crosstalk is suggested to exist through this target genes.

Table 2. Tumorigenic miRNAs and their targets in TPC

miRNAs	Ovarian cancer	Cervical cancer	Breast Cancer
miR-21	PTEN, E2F1 [192,197], YOD1, LOC150786, GPR64, PLAG1, RP2, ADNP [13], CLCA3P, SATB1 [13,36,37]	PTEN [196], MMPs [155,199,200], PDCD4,TPM1 [201,202], CCL20 [203].	BCL-2, TPM1, PDCD4, PTEN, MASPIN [204,205-207]. SEPINB5, Bcl2, TPM1, NCAPG, OXSR1, SEC23A [208].
miR-146a	IRAK1 and TRAF6 [138]	NFκB [83]	EZH2 [120], NFκB [136], p53 [149]
miR-155	BACH1, ZNF652, RAB11FIF2, ZNF537 [13], CLDN1 [209].	RhoA, TGFβ1, R-SMAD, SMAD4 [32] RHEB, mTOR, Cyclin D, RPS6KB2 [115].	RHOA [210] RAD51[211] SOCS1 [3] FOXO3a, APC [120], HK2 [209]
miR-182	NRCAM; RGS17 [183,184]	DNMT3a [212]	FOXO1 [187], PFN1 [3], TCEAL7 [213]
miR-200c	TARDBP [37,92,184,185], ZEB1; ZEB2; TARDBP [101], TUBB3 [38].	ZEB1 and ZEB2 [115,192]	BMI1,ZEB1,ZEB2 [188,214,216,217] PLC1, SUZ12, FN1, LEPR, NTRK2, ARHGAP19, EphA2 [3], ZEB1, CDH1, PTEN [121]

In table 2 above, common targets of oncogenic miRNAs in TPC include: TPM1, PDCD4, PTEN, NFκB, ZEB1, ZEB2, and RHOA.

Figure 1. Cross-talk signaling pathways involving miRNA and target gene in tri-positive cancer

5. Inflammation and Mirna Expression

Universally, chronic inflammatory conditions are believed to create the favourable microenvironment for malignancy initiation through a cascade of events. Examples include the link between: gastroesophageal reflux disease and esophageal cancer, atrophic gastritis and stomach cancer and inflammatory bowel diseases and colon cancer [217]. The chronic inflammatory due to infection (such as in Human papilloma virus) and irritation (radiation and mutagens) may encourage genomic lesions and tumor initiation. An efficient system through which immune cells and enzymes attack microbial infection is the synthesis of free radicals such as reactive oxygen intermediated (ROI), hydroxyl radical, superoxide and reactive nitrogen intermediates (RNI), nitric oxide and peroxynitrite. Interestingly, ROI and RNI result in oxidative damage and nitration of DNA bases which increases the risk of DNA mutations [218]. Mutagen induced DNA damage or oncogenic activation may either initiate cell DNA repair or death of initiated cells. In the event of enormous cell death as a result of repeated exposure to microbial infection or tissue trauma, lost cells must be replaced by undifferentiated reserve cells such as tissue stem cells through proliferation [219,220]. Concurrent DNA damage and cell division in chronic inflammation, in a bid to maintain homeostasis, may result in cancer due to the fact that cells that are dividing are more susceptible to mutations caused by DNA damage [221]. This is supported by the fact that miR-155 and miR-146a have been reportedly dysregulated in cases of chronic inflammation [222-226]. Hypothetically, dysregulation of seven out of the ten discussed miRNAs may be a strong indication of imminent TPC. Thus, their expressions can be used to predict cancer in high risk individuals with chronic inflammation. These miRNAs might be responsible for the metastasis of the individual cancers to other sites.

6. Functional Patterns of Tumour Initiating Cells

The cancer stem cells, also referred to as tumour initiating cells (T-ICs), are described as cancer cells that have the ability to self-renew and differentiate into other malignant stem cells, including cells that will lead to the emergence of diverse phenotypes of cancer cells called transient amplifying cells [227-230]. These cells are left behind and intact following conventional therapy, which according to cancer stem cell hypothesis, eventually repopulate the tumor [231] and resulting in tumor heterogeneity, progression and metastasis [232]. The cancer stem cells are thought to be resistant to conventional therapy through mechanisms including drug efflux and resistance to DNA damage [232,233]. Though, the source of cancer stem cells is largely unknown, some studies suggest that they originate from either adult tissue stem cells or

tumorigenic progenitor cells [234]. Cancer stem cells can be identified from solid human cancers such as breast, brain, bone, lung, melanomas, prostate, colon, pancreas, liver, and head and neck [235-245]. According to the current cancer stem cell hypothesis, tumors are organized in cell hierarchies composed of T-ICs, cancer cells and differentiated cells [246]. Furthermore, the hypothesis also posits that tumor cells are structured in a hierarchy and that only cells that exist at the apex of the hierarchy can regenerate the tumor when implanted into immunocompromised mice and in so doing reproduce the heterogeneity of the original patient tumor [247]. Stem cells live longer than many differentiated cells and may therefore be exposed to damaging agents for a longer time, allowing accumulation of mutations that can result in transformation [248,249].

7. Mirna Regulation in Tumour Initiating Cells and Tumour Cells

Tumor - initiating cells (TICs) display characteristics of normal adult stem cells such as the capability for self-renewal and differentiation [232]. Although pathways that regulate self-renewal are tightly controlled in normal stem cells, in tumour-initiating cells they may be constitutively activated or improperly regulated through genetic and/or epigenetic changes, leading to uncontrolled growth [250]. This is further supported by the fact that knockout of Dicer (the enzyme that controls the maturation of pre-miRNAs) in mice is embryonically fatal [251] due to failure in cell differentiation [252]. Reports show that miRNAs modulate the properties of embryonic stem (ES) and tissue stem cells in a variety of eukaryotic organisms [253,254]. MicroRNA expressions vary between normal tissues and tumor tissues and among tumor types [99,170,255-258]. This is buttressed by the fact that BRCA cells with a higher prevalence of T-ICs have been revealed to possess distinct miRNA expression profiles that may contribute to the maintenance of stem cell properties. Mammalian let-7 expression is underexpressed in human BRCA T-ICs and significantly overexpressed in differentiated cells. Let-7 represses self-renewal by targeting H-RAS and promotes differentiation by targeting HMGA2 [259]. More evidence of miRNA involvement in cancer stem cell activity was revealed when high and low expressions of miR-22 and miR-205, and miR-93 and let-7 were observed in progenitor cells compared to differentiated cells [260], respectively. The findings of Wang et al. [261] suggest that the function of leukemia-initiating cells are PTEN dependent while normal HSCs function are PTEN independent [261].

Recent findings reveal some variation in miRNA expression between T-ICs and tumour cells. For example, under-expression of miR-200c was observed in T-ICs [188] when compared with tumours cells which had over-expression of the miRNA [190-196]. MiR-200c

under-expression in T-ICs induces down-regulation of target genes such as FN1 and ZFH1B [188]. Tumour initiating cells also exhibit under-expression of miR-21 [262] when compared with other cancers [155-160]. More so, miR-125b is upregulated in T-ICs with concurrent down-regulation of target genes such as U251 GPC4, TAZ, MSI1 [263] when compared with other cancers, particularly TPC (Table 1). The variation in miR-125b between T-ICs and normal cancer cells may be responsible for the reported cancer resistance to therapy, especially among patients with Triple Negative Breast Cancer (TNBC) [62,63]. Let-7b is over-expressed in some solid tumours [20-26], but under-expressed in T-ICs [16,17] and TPC [36-41]. The similarity in let-7b expression in T-ICs and TPC accounts for the lower number of cancer relapse among TPC patients undergoing let-7 directed therapy. This is due to the fact that the destruction of tumour cells by some anti-cancer drugs also eliminates the T-ICs. Despite the similarity in Let-7b expression, the target genes involved in T-ICs self-renewal and proliferation (COL2A1, GLI3, KLF4) [264] vary from that observed target genes in TPC (Table 1).

8. Conclusions

MiRNA crosstalk occurs through a number of target genes leading to a complex regulating network which could result in tri-positive cancer. In TPC, upregulated oncogenic miRNAs includes: miR-21, miR-146a, miR-155, miR-182 and miR-200c while the downregulated tumour suppressor miRNAs includes: let-7b, miR-125b, miR-143 and miR-145. The dual activity (controversial reports) of miR-214 in TPC suggests that it can function both as a tumour suppressor and oncogene, thus its tight regulation. MiRNAs interact with each other through a range of target genes such as ERK5, BRCA1, PTEN, Muc-1, ERB2/3, ZEB1/2, RAS, Bcl-2 and c-Myc among others, mostly through the PI3k/Akt signaling pathway. Furthermore, upregulation of miR-146a and miR-182, and downregulation of miR-125b were observed in the repression of BRCA expression in TPC. Furthermore, an understanding of the variation in miRNA and target genes expression between T-ICs and other cancers or tumour cells may provide solutions to the observed failure in therapy during patient management. Thus, proper investigation of these miRNAs and target genes in high risk individuals may aid cancer prediction and early diagnosis of cancer which will in turn reduce mortality due to cancer.

Abbreviations

Bak1: Bcl-2 antagonist killer 1, Bcl-2: B-Cell lymphoma 2, CLDN1: claudin-1, c-Myc: Myelocytomatosis, E2F3: E2F transcription factor 3, ERB2/EGFR: epidermal growth factor receptor, FOXO 1/3: Forkhead box protein 1/3, HMGA2: High mobility group A2, HMGB3: High mobility

group box 3, IKK: ikB kinase Ch11, JNK: c-Jun N-terminal kinase, MAPK/ERK: Mitogen-activated protein kinase/Extracellular signal-regulated kinase, Muc-1: Mucin-1, NCAPG: non-SMC condensin I complex subunit G, NFkB: Nuclear Factor-kappa B, OXSR1: oxidative-stress responsive 1 (OXSR1), PDCD4: Programmed cell death 4, PTEN: Phosphatase and tensin homolog, RAS: Rat sarcoma, RHEB: Ras homolog enriched in brain, RHOA: Ras homolog gene family member A, SMAD: Mother against decapentaplegic homolog, TGFβR2: transforming growth factor-β receptor II, TPM1: Tropomyosin 1 VEGF: vascular endothelial growth factor, XIAP: X-linked inhibitor of apoptosis, ZEB 1/2: zinc finger E-box 1/2.

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