

# Predictors of Neoadjuvant Chemotherapy Response in Breast Cancer: A Review

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**Abstract:** Neoadjuvant chemotherapy (NAC) largely increases operative chances and improves prognosis of the local advanced breast cancer patients. However, no specific means have been invented to predict the therapy responses of patients receiving NAC. Therefore, we focus on the alterations of tumor tissue-related microenvironments such as stromal tumor-infiltrating lymphocytes status, cyclin-dependent kinase expression, non-coding RNA transcription or other small molecular changes, in order to detect potentially predicted biomarkers which reflect the therapeutic efficacy of NAC in different subtypes of breast cancer. Further, possible mechanisms are also discussed to discover feasible treatment targets. Thus, these findings will be helpful to promote the prognosis of breast cancer patients who received NAC and summarized in this review.

**Keywords:** breast cancer, neoadjuvant, chemotherapy, response, predictor

## Introduction

Breast cancer is the most prevalently diagnosed cancer and the leading cause of cancer deaths for females.<sup>1</sup> Apart from the traditional surgical plus adjuvant therapies, neoadjuvant chemotherapy (NAC) has been increasingly applied. Patients, especially the cohort of triple negative breast cancer ones who have undergone NAC turn out to have incredibly well pathologic complete response (pCR) rates. But those who reach to chemoresistance after NAC could suffer from a much harder time for survival, particularly in the first 3 years.<sup>2</sup>

In order to assess early responses to NAC of primary breast cancers, quantitative ultrasound (QUS), texture and molecular features alter in the first place, which are hopefully used to guide the treatment planning of refractory patients.<sup>3</sup> Several studies indicated that the presence of tumor after NAC drawing support from histopathological examination of the tumor bed could be the golden standard as well as pCR rate. Further surrogate biomarkers could be applied for evaluating the outcomes defined by Chevallier's system following neoadjuvant settings.<sup>4</sup>

Fine-needle aspiration cytology is considered as an accurate technique performed by experienced cytologists to assess the existence of breast cancer.<sup>5</sup> The core breast biopsy used to be a traditional examination technique to identify the initial diagnosis of breast lumps. Fortunately, this critical technique is able to accurately predict pathologic responses after NAC.<sup>6</sup>

In previous studies, biomarker changes before and after NAC were claimed to have great clinical relevance to age or grade impacts.<sup>7</sup> For example, ER and Ki-67 status were reported to possess obvious changes after NAC treatments in breast

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cancer patients. CYP1B1 was reported to be associated with taxane hypersensitivity.<sup>8</sup> In locally advanced breast cancer, carbonic anhydrase IX (CAIX) significantly reacted to the paclitaxel plus sunitinib therapy.<sup>9</sup>

However, there was a report noted that the expression of  $\beta$ III-tubulin protein, MDR1 protein, TACC3 and CAPG gene, multigene models (20- and 26-gene), and mRNA were not predictive markers for differentiating treatment benefits between ixabepilone and paclitaxel in early-stage breast cancer.<sup>10</sup> Few circulatory molecules were found to be probable biomarkers to forecast the effects and efficacy of NAC systemically.<sup>11</sup> Therefore, we focus on the alterations of tumor tissue-related to microenvironments such as stromal tumor-infiltrating lymphocytes status, cyclin-dependent kinase expression, non-coding RNAs transcription or other small molecular changes, to detect potentially predicted biomarkers reflecting the therapeutic activities of NAC in different subtypes of breast cancer (Table 1).

## Imaging Examination as One of the Criteria for Evaluating Treatment Outcomes

Previous evidences investigated the accuracy of MRI in evaluating residual tumor sizes in breast cancer patients after NAC, and the results supported the use of MRI to guide the following surgical planning, especially in HR-subtype of breast cancers.<sup>12,13</sup>

It is obvious that after NAC, the inner microenvironment of breast cancer patients will develop several changes which could be seen by traditional anatomical imaging or the newly improved MRI method. Besides, assessments of responses to NAC in breast cancer patients is helpful to early identification of non-responders,<sup>14</sup> thus providing alternative treatment options to those patients suffering from poorer prognosis.<sup>15</sup>

## Dynamic Contrast Enhanced MRI (DCE-MRI)

The breast DCE-MRI, with its high sensitivity and specificity, shows greater values in mammography than ultrasound. The principle of this approach is that the feature of having an enhancing curve, together with being morphologic, helps to differentiate malignant lesions from the benign ones.<sup>16</sup> Vignati and al., applied breast DCE-MRI to 24 breast cancer patients receiving NAC (8 responders and 16 non-responders) and discovered that the vascular volume of breast cancer had

significant differences between the situations before and after NAC for responders (median=1.71cc) and non-responders (median=0.41cc) by calculation from automatic vascular maps ( $P=0.003$ ).<sup>17</sup> Meanwhile, a study of 38 breast cancer patients with NAC demonstrated that tumor heterogeneity changes measured by quantitative DCE-MRI had potentials to predict pathologic responses of breast tissues to NAC.<sup>18</sup>

## Diffusion-Weighted MRI

In contrast with DCE-MR, DW-MRI is more sensitive to the changes of cell density, membrane integrity and tissue microstructure caused by the changes in water motions. Breast cancers present high signal intensity images in DW-MRI, for the inflexibility of cancer lumps with subdued signal loss from Brownian motion. Besides, a breast cancer mice model evaluated the application of DW-MRI as a reliable approach for the early measurement of response to chemotherapy.<sup>19</sup> To further confirm the advantages of DW-MRI, Galban and al., collected 39 locally advanced breast cancer patients with NAC and proved DW-MRI to be a predictive biomarker of NAC assessments.<sup>20</sup> MRI could be fully used to measure the shrinkage of tumor,<sup>21</sup> therefore, in addition to distinguishing its density, DW-MRI is also an alternative choice to measure its sizes with repeatable and reproducible analysis of apparent diffusion coefficient (ADC).<sup>22</sup> Pickels and al., emphasized the significance of DW-MRI in predicting NAC responses from data of 10 patients, and found that DW-MRI delivered obvious increases or reductions in the mean (normalized) ADC at the first cycle time ( $P=0.005$ ) or the second cycle time ( $P=0.004$ ) of NAC treatments.<sup>23</sup>

## 18F-FDG PET/CT

PET/CT may trace tumor perfusion and angiogenesis in response to chemotherapy treatments. Previous studies have investigated 46 patients and demonstrated that early changes in blood flow detected by a short dynamic 18F-FDG PET/CT could be a biomarker of prognosis of triple-negative breast cancer with NAC.<sup>24</sup> Simultaneously, in HER2 negative breast cancer subtype, a multicenter randomized Phase II neoadjuvant trial (n=59) confirmed that the early reduction in SUVmax (63.0% in pCR group comparing to 32.9% in non-pCR group;  $P=0.003$ ) on 18F-FDG PET/CT 15 days after NAC was probably a potential predictor to the pCR rate in patients.<sup>25</sup>

**Table I** Potential Predictors of Neoadjuvant Chemotherapy Response for Breast Cancer Patients

NAC Strategy	Subtypes of Breast Cancer	Potential Predictors	Effects	Outcomes
NA	NA	IL-6,IL-8,MMP9	positive	clinical response
NA	NA	tPAI-I	negative	clinical response
NA	NA	CD34+ CECs	positive	clinical response
NA	early stage	HMGB1	positive	clinical response, prognosis
NA	ER+	IGF-1R	negative	pCR
taxane-based	stage II-III	NCS-1	positive	pCR
NA	locally advanced	KLF4	negative	pCR
anthracycline-based	NA	serpinB3	positive	survival
NA	early	PKCeta	negative	prognosis
NA	locally advanced	osteopontin	positive	prognosis
anthracycline-based	NA	Smac	positive	DFS and OS
NA	stage II-III	HGF	positive	RFS
NA	NA	threonine, glutamine, isoleucine and linolenic acid	positive	response
TAC or TAC-NX	TNBC	SPARC,MMP9,VEGF	positive	pCR,prognosis
docetaxel	TNBC	IMP3+, AKT/KIF14	negative	chemosensitivity
NA	NA	miR-222, miR-29a, miR-34a, miR-744	negative	chemosensitivity
NA	HR-	miR-221	positive	chemosensitivity
NA	TNBC	miR-21 with miR-155	negative	prognosis
cisplatin/doxorubicin-based	TNBC	miR-145-5p/TGFβR2	negative	pCR,prognosis
NA	TNBC	TP53, PIK3CA, CDKN2A mutations	negative	DFS,recurrence
docetaxel/capecitabine	ER-/PR-	Ki-67	negative	response
anthracycline-taxane-based	NA	SIRT5	positive	prognosis
NA	NA	SPAG5	negative	prognosis
NA	TNBC	JAK2-JAK1/STAT3	negative	prognosis
NA	leaner patients	γ-H2AX	negative	pCR
NA	GS+ TNBC	TNFalpha	positive	pCR
platinum	TNBC	BLM, FANCI	positive	pCR
anthracycline and cyclophosphamide	basal	CK5/6	negative	chemosensitivity

(Continued)

Table I (Continued).

NAC Strategy	Subtypes of Breast Cancer	Potential Predictors	Effects	Outcomes
anthracycline and cyclophosphamide	luminal	CK18	negative	chemosensitivity
NA	residual	CDK9	positive	OS
paclitaxel followed by 5-fluorouracil, epirubicin and cyclophosphamide	NA	C2P-RS based on CDK1 and CDK2	positive	pCR
anthracycline and taxane	NA	the ratio of CDK1 transcript to HSP90AA transcript	positive	pCR
epirubicin/docetaxel-based	NA	inter-a-trypsin inhibitor, a-1-antichymotrypsin and a-2-HS glycoprotein, N-glycoproteome profile (AHSG, APOB, C3, C9, CP and ORM1	positive	RFS
NA	stage II–III	gamma-synuclein	positive	response
taxane	ER-	$\beta$ III-tubulin, CIP2A	positive	response
NA	ER+	FOXA1	negative	response, chemosensitivity
NA	NA	pS6, pJAK2–mTOR, JAK/STAT	negative	chemosensitivity
NA	NA	TILs	positive	pCR, DFS, OS

**Abbreviations:** NAC, neoadjuvant chemotherapy; CECs, circulating endothelial cells; IGF-1R, insulin-like growth factor receptor 1; NCS-1, neuronal calcium sensor-1; HGF, hepatocyte growth factor; SPAG5, sperm-associated antigen 5; BLM, Bloom helicase; FANCI, Fanconi anemia complementation group I; RFS, relapse-free survival, NA, not available.

## Other Factors

The performance of MRI in breast cancer with NAC partly depends on the molecular subtypes, which tends to be more accurate under the circumstance of more aggressive cancer types than those less aggressive ones.<sup>26</sup> While in HER2 negative cancers, it is worse in HR positive cancers than the negative ones.<sup>27</sup> Plenty of studies were conducted to investigate other parameters which were correlated with NAC responses. Background parenchymal enhancement (BPE) on breast MRI,<sup>28</sup> Diffuse optical spectroscopic imaging (DOSI) parameters of MRI,<sup>29</sup> chemical exchange saturation transfer (CEST)<sup>30</sup> were all associated with tumor responses to NAC in breast cancer patients. Furthermore, a study of 64 patients undergoing NAC for breast cancer proved that functional tumor volume (FTV) by breast MRI was a potential assessment for recurrence-free survival (HR=8.71, 95% CI: 2.86–25.5;  $P \leq 0.00015$ ).<sup>31</sup> Besides, thanks to the property of the high speed of the computation, the in silico Pathway Activation Network Decomposition Analysis (iPANDA) introduced by Ozerov and al., could be a scalable and robust method

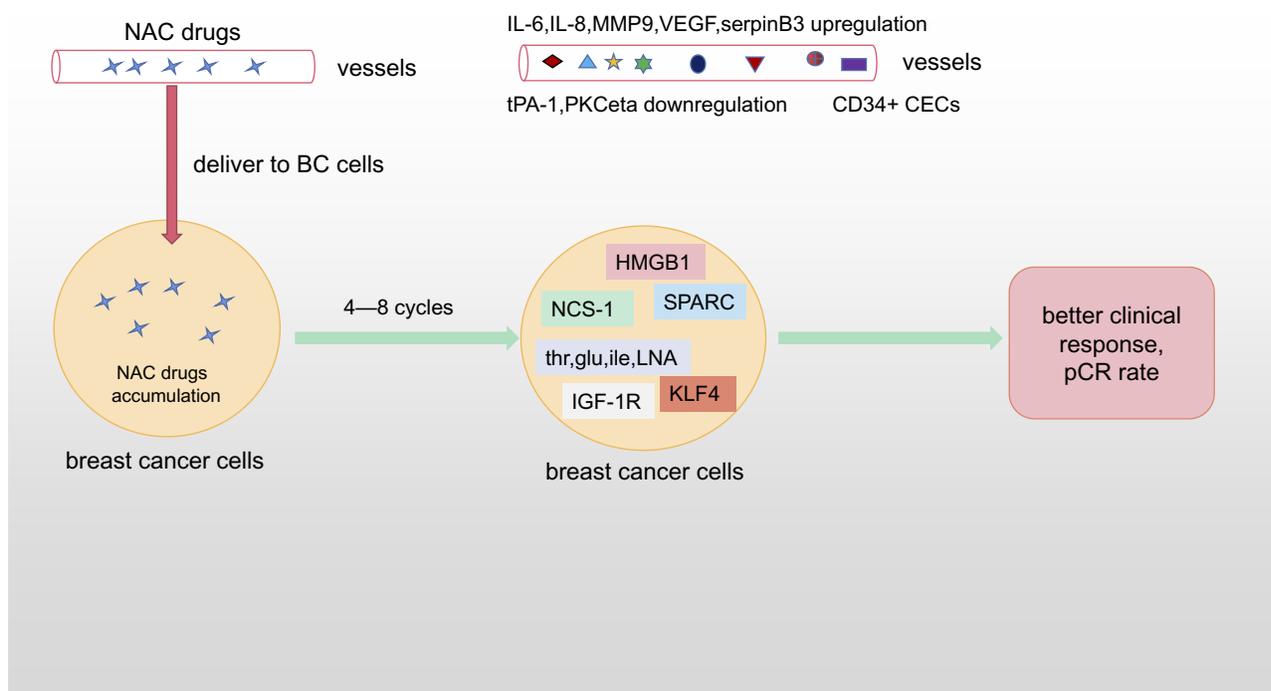
for stratifying breast cancer patients based on sensitivity to NAC.<sup>32</sup>

## Small Molecular Changes with the Use of NAC

### Changes in Subtypes

In the process of neoadjuvant therapy, small molecule changes may provide new breakthroughs in researching how to acquire better prognosis and survival (Figure 1).

Nolen and al., demonstrated that elevated serum levels of IL-6, IL-8, MMP-9 ( $P \leq 0.05$ ) and reduced serum level of tPAI-1 ( $P \leq 0.05$ ) before the initiation of NAC were associated with improved clinical response.<sup>33</sup> The study by Ali and al., also showed that CD34+ circulating endothelial cells (CECs), in relation to tumor angiogenesis, might predict preoperative chemotherapy response in breast cancer patients.<sup>34</sup> The chemo-induced increase HMGB1, generally considered to be released by dying cells, in plasma observed in surviving patients might be associated with a higher degree of cell death in response to therapy than in non-surviving patients. Changes of plasma HMGB1 could



**Figure 1** Possible responses to neoadjuvant chemotherapy in breast cancer cells and serum. After standardized NAC regimens, serum IL-6, IL-8, MMP9, VEGF, serpinB3 upregulation and tPAI-1, PKCeta downregulation with CD34+ CECs accumulation are positive predictors for better clinical responses. IGF-1R, KLF4 reduction and NCS-1, SPARC, threonine, glutamine, isoleucine and linolenic acid alteration will predict fine pCR rate.

**Abbreviations:** NAC, neoadjuvant chemotherapy; BC, breast cancer; CEC, circulation endothelial cells; pCR, pathologic complete response.

be a potential biomarker to predict clinical responses to NAC in breast cancer.<sup>35</sup> Wachter and al., analyzed the association between pCR and CK5/6 or CK18 in a group of breast cancer patients undergoing NAC containing anthracycline and cyclophosphamide, and indicated that CK5/6 mainly predicted resistance to NAC in a basal subtype while CK18 predicted resistance to NAC in a luminal phenotype.<sup>36</sup>

In HR± breast cancers, a viewpoint claims that reduced insulin-like growth factor receptor 1 (IGF-1R) was related to pCR rate of NAC treatments, and thus therapies targeting IGF-1R would be an alternative choice to those who express IGF-1R.<sup>37</sup> For stage II–III breast cancer patients, the high surviving expression was associated with pCR of NAC.<sup>38</sup> As to the pCR of taxane-based NAC, the role of the elevated neuronal calcium sensor-1 (NCS-1) was valued.<sup>39</sup> For locally advanced breast cancer patients, pCR rate of NAC was inhibited by an overexpression of KLF4.<sup>40</sup>

Collie and al., described that serpinB3 status might predict survival in breast cancer patients with anthracycline-based NAC.<sup>41</sup> Studies suggested that an early increased HMGB1<sup>42</sup> or reduced PKCeta levels<sup>43</sup> indicated better prognosis in early breast cancer patients receiving NAC. Prognosis of locally advanced breast cancer patients

undergoing NAC appeared to be significantly related to osteopontin.<sup>44</sup> Evidences also indicated that low surviving or high Smac expression in breast cancer patients treated with anthracycline-based NAC was obviously related to longer DFS and OS.<sup>45</sup> Meanwhile, high serum hepatocyte growth factor (HGF) levels were related to longer relapse-free survival in stage II–III breast cancer receiving NAC.<sup>46</sup>

Identifying the small-molecular metabolites that are sensitive to pathological modifying by means of Metabolomics (or metabolite profiling), integration nuclear magnetic resonance spectroscopy (NMR) with liquid chromatography-mass spectrometry (LC-MS). Wei and al., observed altered metabolites of threonine, glutamine, isoleucine and linolenic acid in serum for predicting response to NAC.<sup>47</sup>

Triple negative breast cancer is not an unfavorable breast cancer because the rate of pCR after NAC is approximately 40%. This type of breast cancer has a high chemosensitivity. Regarding this subtype, the findings by Lindner and al., indicated that high expression of SPARC in the primary tumor induced a higher possibility of achieving a pCR after TAC or TAC-NX treatments.<sup>48</sup> Moreover, IMP3+ (an oncofetal protein) along with KIF14 expression in tumors contributed to poor outcomes for the occurrence of chemoresistance to NAC in TNBC.<sup>49,50</sup>

Serum MMP-9, VEGF and secreted protein acidic and rich in cysteine (SPARC) were promising biomarkers to predict responses to NAC and prognosis of TNBC patients.<sup>51,52</sup>

## miRNA Alternation

MicroRNAs (miRNAs) are 20–25 nucleotides single-stranded, non-coding RNAs that involve numerous biological processes in various cancers. Hopefully, changes of miRNAs resulted from NAC treatments in breast cancer patients may play a promising role in future precise medicine for breast cancer.<sup>53</sup>

RNA disruption is a reduction of tumor RNA integrity followed by the application of NAC in breast cancers. It has a positive relevance to elevated DFS as well.<sup>54</sup> The study conducted by Toomey and al., investigated the use of RNA Disruption Assay (RDA) score and they found that RDA score would be a novel, early, on-treatment approach to guide subsequent system therapies after NAC, owing to its specially speculative and predictive role in pCR rates and prognosis of HER2+ breast cancer.<sup>55</sup>

Previous data presented that several chemo-resistant miRNAs including miR-222, miR-29a, miR-34a, miR-744 and so on exhibited significantly higher expressions in post-NAC breast tumor cells than pre-NAC tumors. Simultaneously, relatively high expressions of miR-222, miR-29a and other 5 miRNAs were associated with non-responders to NAC therapy.<sup>56</sup> Moreover, for breast cancer patients receiving previous NAC with different levels of plasma miR-221, their overall response rates varied. And higher miR-221 level, as a chemosensitivity biomarker, was more frequently found in HR- patients.<sup>57</sup> The serum miR-21 together with miR-155 which were poor prognostic predictors, endured obvious suppressions by NAC therapy especially in TNBC, thus being potential biomarkers for outcomes of patients with NAC.<sup>58,59</sup> Besides, miR-145-5p was reported to discriminate between pCR and non-pCR TNBC patients with cisplatin/doxorubicin-based NAC, and miR-145-5p was proven to impair cell proliferation partly by targeting TGF $\beta$ R2.<sup>60</sup>

Besides, some researches explored the specific function of circulating tumor DNAs in TNBC patients with residual tumors after NAC. TP53 mutations, PIK3CA mutations, CDKN2A mutations were the three most prevalent predictors for inferior DFS and rapid recurrence in breast cancer patients.<sup>61</sup>

## Ki-67

Ki-67 is a well-known proliferation marker, even reported as a continuous marker,<sup>62–64</sup> in breast tumors or even locally

advanced breast cancer.<sup>65</sup> With the development of treatment strategies such as NAC, endocrine therapy and chemo-endocrine therapy, the Ki-67 index presents a significant reduction to estimate the decreased proliferation index of individual tumors.<sup>66,67</sup> Interestingly, Enomoto and al., found Ki-67 suppression only in those patients who attained clinical response and who were ER positive subgroup after NAC.<sup>68</sup> Ohno and al., observed that Ki-67 may be useful in identifying responses to preoperative docetaxel/capecitabine therapy in early-stage breast cancer.<sup>69</sup> Also, with the help of Ki-67 status, NAC was reported to be more effective in ER-/PR- and high Ki-67 breast cancer patients.<sup>11</sup> Therefore, reexamining the Ki-67 level after NAC might be useful to optimize the appropriate following systemic therapy and achieve better prognosis.<sup>70</sup>

## Gene-proteins in the prediction to NAC response

### Gene

Although with increasing effects of recent therapies, Toi and al., recognized the necessity to incorporate biomarkers, which enables researchers to further classify conventional subtypes by methods including genetic mutations and epigenetic phenotypes in order to realize better planning of treatment. It is also crucial to analyze tumor biology particularly the tumor development in the metastasis process and the clonal selection by the treatment in clinical settings.<sup>71</sup>

The researchers exhibited that the response of anthracycline-taxane-based chemotherapy may be influenced by SIRT5 through Rho pathway. SIRT5 upregulation in various degrees may be specific to certain histological subtypes, and SIRT5 mRNA in high level may imply the good prognosis.<sup>72</sup> The findings by Abdel and al., showed that gene copy number aberration, transcript and protein on sperm-associated antigen 5 (SPAG5) were connected with poor prognosis, such as TP53 mutation, PAM50-LumB phenotype, and PAM50-HER2 phenotype. As predictive markers in breast cancer, both SPAG5 transcript and protein may be the key point for chemo-response.<sup>73</sup>

Compared to TNBC untreated with chemotherapy, the treated group showed greater frequency of amplification on JAK2. Balko and al., reported that combining JAK2-specific inhibitors with chemo-agents could delay the progression in TNBC with the aid of JAK1/STAT3-independent signaling program derived by JAK2.<sup>74</sup> Barba and al., found that the predictive meaning of  $\gamma$ -H2AX might be different based on the Body Mass Index

(BMI) status in TNBC. In leaner patients,  $\gamma$ -H2AX upregulation seems to be correlated with lower pCR rate, while, in heavier patients, the differences in pCR rates based on  $\gamma$ -H2AX levels did not make significant senses.<sup>75</sup> Bardia and al., explored a TNF $\alpha$ -based gene expression signature associated with pCR and confirmed a biomarker-driven targeted therapy approach for selected patients with GS-positive TNBC.<sup>76</sup>

Both of the genes, which are Bloom helicase (BLM) and Fanconi anemia complementation group I (FANCI), could increase the amount of DNA and expressed in the platinum-sensitive with TNBC. Among them, BLM overexpression promoted DNA damage and upgraded sensitivity to cisplatin.<sup>77</sup>

## Cyclin-Dependent-Kinase Expression

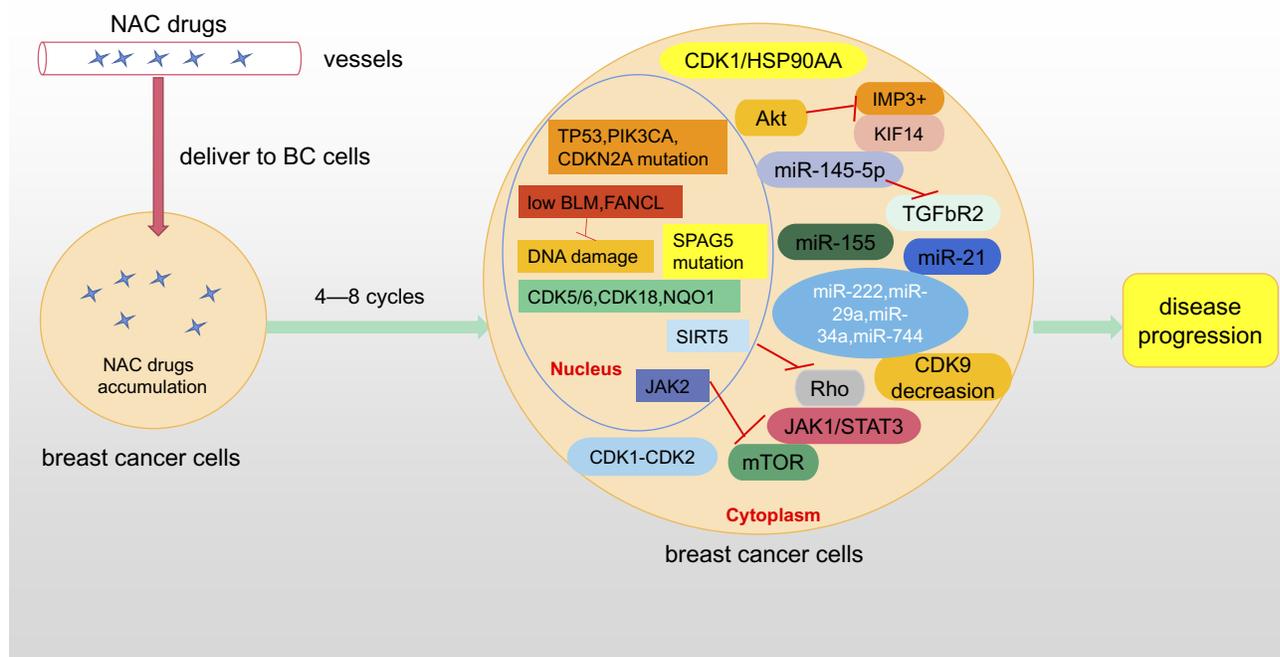
It is well known that CDK4/6 inhibitors block the phosphorylation of retinoblastoma tumor suppressor proteins, thereby preventing the progress of the cell cycle. Nowadays, there are three selective CDK4/6 inhibitors (Palbociclib, Ribociclib and Abemaciclib) approved by the FDA and EMA for the treatment of breast cancer with HR+/HER2-.<sup>78</sup> With the help of CDK1 and CDK2 to establish the cell cycle profiling risk score (C2P-RS),

Kim and al., indicated a positive association pCR and the predictive model in breast cancer patients received NAC by paclitaxel followed by 5-fluorouracil, epirubicin and cyclophosphamide (P-FEC).<sup>79</sup> Schlafstein and al., analyzed the residual breast cancer after NAC and found that the expression of CDK9 was discovered to be a promising positive indicator to the improved 3 years OS.<sup>80</sup> Moreover, the ratio of CDK1 transcript to HSP90AA transcript was significant in the predictor of pCR for patients receiving NAC.<sup>81</sup> Besides, quinone oxidoreductase 1 (NQO1) was observed to rise in terms of the residual breast tumor tissues after NAC.<sup>82</sup>

## Serum Proteins

The role of serum proteins pattern to predict chemo-sensibility has been extensively studied in the field of breast cancers. Prediction of the responses to NAC tends to improve effective treatment strategies of advanced breast cancer patients.

It was the very first time for Michlmayr and al., to study the complement cascade alterations by NAC in breast cancer. When patients were treated by epirubicin/docetaxel-based NAC, activation of complement component C3 occurred, followed by modulations of protein spots 195 and 529 in C3, as well as inter-a-trypsin inhibitor, a-1-antichymotrypsin



**Figure 2** Several genetic, miRNA changes and pathways in breast cancer cells after neoadjuvant chemotherapy.

**Abbreviations:** NAC, neoadjuvant chemotherapy; BC, breast cancer.

and a-2-HS glycoprotein.<sup>83</sup> N-glycoproteome profile (AHSG, APOB, C3, C9, CP and ORM1) were confirmed to identify sensitive responders to DC+AC NAC in breast cancer and to predict RFS.<sup>84</sup> In stage II to III locally advanced breast cancers, combination of gamma-synuclein and other biomarkers may speculate responses to NAC.<sup>85</sup> At the same time, overexpression of class III  $\beta$ -tubulin ( $\beta$  III-tubulin) and CIP2A may serve as a positive prediction to responses in taxane-based NAC for ER- breast cancer patients.<sup>86,87</sup>

FOXA1 expression before NAC was correlated with poor chemo response in ER $\pm$  as well as luminal A and B breast cancer patients ( $P=0.002$ ,  $0.001$ , and  $0.049$  respectively). There is also a significant correlation between the change in FOXA1 staining position and chemo-sensitivity after NAC ( $P=0.024$ ). Thus it was decided that FOXA1 expression might independently predict chemosensitivity to NAC in ER $\pm$  breast cancer patients.<sup>88</sup>

## Signal Pathways

In the study of the prognosis of NAC for breast cancer, signaling pathways are a new choice and the key point for many researchers.

The phenomenon of chemo-sensitivity in patients treated with docetaxel mediated by increasingly low expression of KIF14, which might be descended with AKT activity, finally led to pro-survival pathways downgraded.<sup>50</sup>

The study by Jhaveri and al., exhibited that the increase in the expression with pS6, pJAK2, pSTAT3 and IL6 existed in IBC and IDC treated with NAC. Both pS6 and pJAK2 active status in IBC may imply dual targeting of mTOR and JAK/STAT pathways, and these findings inferred a potential mechanism following NAC.<sup>89</sup> (Figure 2)

## Tumor-Infiltrating Lymphocytes (TILs)

The number of circulating endothelial progenitor cells is correlated with NAC response.<sup>90</sup> In details, reports discovered that the high peripheral lymphocyte count was a positive predictor of NAC effectiveness, while low peripheral neutrophil counts might result in a favorable DFS.<sup>91</sup>

Among breast cancer patients who received NAC, immune responses like tumor-infiltrating lymphocyte (TIL) counts was associated with high-grade, ki67, and HR- breast cancer.<sup>92,93</sup> High levels of TIL were observed in TNBC patients and were associated with pCR in ER- breast cancers.<sup>94-97</sup>

TILs can be classified into two subgroups: lymphocytes infiltrating the tumor stroma (stromal TILs) and lymphocytes infiltrating the tumor epithelial cells (intra-tumoral).<sup>98</sup> Both of them were associated with pCR in HER2+ and

TNBC breast cancers.<sup>95,99,100</sup> The Breast International Group 02-08 trial indicated that each 10% elevation in intra-tumoral and stromal TILs was respectively related to 17% and 15% reduced relapse risk (adjusted  $P=0.1$  and  $P=0.025$ ), 27% and 17% reduced death risk (adjusted  $P=0.035$  and  $P=0.023$ ) in node-positive, ER-/HER2- breast cancer patients.<sup>101</sup> Interestingly, sTILs alone may be an essential evaluation in the assessment of pCR rates to NAC and prognosis in HER2+ breast cancers.<sup>100,102</sup>

The majority of TILs are T lymphocytes, and B lymphocyte infiltrations are less common.<sup>103</sup> Abundant counts of CD8+ TILs were verified to be associated with improved prognosis and prolonged survivals of less aggressive breast cancer subtypes with over 1300 cases.<sup>104</sup> The presence of FOXP3+ sTILs, instead of the intra-tumoral FOXP3+ TILs, was reported to be able to forecast a poor prognosis, and the CD8+/FOXP3+ TIL ratio (CFR) can be invented to identify well responders to NAC in breast cancers, especially in TNBC.<sup>95,105</sup> The increasing pCR rates and better RFS were obviously relevant to high changes of CFR in breast cancer patients with NAC,<sup>106</sup> especially in HR+/HER2-subgroups.<sup>107</sup>

In contrast,  $\gamma\delta$  TILs were responsible for poor prognosis in another study.<sup>108</sup> Similarly, programmed death (PD)-1+ TILs were observed to result in inferior OS in luminal B and basal-like breast cancer types.<sup>109</sup>

Therefore, lymphocyte-predominant breast cancer (LPBC) mainly had an increased pCR rates in HER2+ and TNBC cases undergoing anthracycline and taxane based NAC treatments.<sup>110,111</sup>

Besides, a profile including 7270 samples reflected that higher fraction of M0 macrophages and activated mast cells were independently associated with worse DFS (HR=1.66, 95% CI: 1.18–2.33) or OS (HR=1.71, 95% CI: 1.12–2.61) in ER+ or ER+/HER2- tumors and worse DFS (HR=5.85, 95% CI: 2.20–15.54), OS (HR=5.33, 95% CI: 2.04–13.91) in HER2+ tumors.<sup>112</sup>

Despite of the helpful role of TILs in stratifying prognostic breast cancer subgroups and in guiding future therapy decisions, a standard definition of TILs is still under confirmation. There is a lot to solve until they are applied in routine clinical practices. Therefore, TILs are emerging biomarkers mediating tumor response to NAC treatments.

## Discussion

Surgery was the vital therapy for breast cancer patients in the past decades. With the development of technologies, NAC raises its significant power in the treatment of breast cancer.

If breast cancer patients have one of the following conditions, neoadjuvant therapy is usually recommended: 1) the mass is larger than 5cm;2) being axillary lymph node metastasis;3) Her-2± subtype breast cancer;4) triple negative breast cancer;5) the proportion of primary tumor to breast is large but patients who wish to retain the breast. The positive lymph node after NAC was used to be considered as the predictor for the development of metastasis in breast cancer patients and for the following choices for therapy strategies.<sup>113,114</sup> Unfortunately, no specific biomarker for predicting the clinical response to NAC has yet been defined.

Background parenchymal enhancement (BPE) on breast MRI was described as an independent marker for breast cancer risk assessment, diagnosis, and treatment. However, BPE is influenced by endogenous and exogenous hormone levels, so its application in breast cancers may be somehow limited.<sup>115</sup> Therefore, researches tried to find that PET/CT imaging features might be potential predictors of pCR rate of NAC in locally advanced breast cancer patients,<sup>116</sup> but the cost and inconvenience hindered its way to be used broadly. Simultaneously, an increasing number of scientists are endeavoring to find the breaking points in cancerous treatments by investigating the tumor microenvironments, such as surrounding immune cells, adipocytes, secreted small molecules and so on.<sup>117</sup>

Therefore, we summarized the alterations of microenvironments related to tumor tissue to reflect the NAC response, such as the changes in the stromal tumor-infiltrating lymphocytes status, cyclin-dependent kinase expression, non-coding RNAs transcription or other small molecular. We aim to detect potentially predicted biomarkers to reflect the therapeutic activities of NAC in different types of breast cancer. Therefore, it will be possible to promote the prognosis of breast cancer patients who received NAC by monitoring the response predictors.

## Conclusion

After overviewing relevant studies, it is concluded that cellular and molecular changes (such as stromal tumor-infiltrating lymphocytes status, cyclin-dependent kinase expression, non-coding RNAs transcription) in tumor microenvironments are potential predictors to reflect the NAC response of breast cancer patients, which will be helpful to optimize the therapeutic strategy of breast cancer patients.

## Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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## Disclosure

The authors report no conflicts of interest in this work.

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