Characterization of FOLR2 Expression on Tumor-Associated Macrophages (TAMs) Across Breast Cancer Molecular Subtypes in Bandung

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Abstract. Breast cancer is a heterogeneous disease and a leading cause of death in women worldwide. The tumor microenvironment (TME), which includes tumor-associated macrophages (TAMs), plays a key role in its progression. Folate Receptor 2 (FOLR2) is a marker of M2 macrophages and is associated with pro-tumor activity. Previous studies have shown increased FOLR2 expression on TAMs in various cancers, including breast cancer, which has been linked to poor clinical outcomes. This study aimed to characterize FOLR2 expression on TAMs in breast cancer subtypes and evaluate its potential as a diagnostic and prognostic marker. Immunohistochemistry (IHC) results of $FOLR2^+$ TAMs, which are expressed as the immunoreactive score (IRS), were analyzed across three molecular subtypes of breast cancer (TNBC, Luminal, and HER2-enriched). Kruskal–Wallis analysis demonstrated significant differences in FOLR2 expression among the subtypes. The mean ± SD IRS values were TNBC = 3.81 ± 1.16, HER2-enriched = 2.42 ± 1.73, and Luminal = 2.18 ± 1.54. Post hoc Dunn's test revealed that the difference was statistically significant between TNBC and Luminal subtypes ($p < 0.05$), whereas no significant difference was observed between TNBC and HER2-enriched, or between Luminal and HER2-enriched subtypes. Fisher's exact test revealed a statistically significant association between molecular subtype and FOLR2 expression in breast cancer (p-value < 0.05). Spatial analysis further showed that FOLR2 was predominantly expressed in peritumoral areas, particularly around blood vessels and adipose tissue, while its expression in the intratumoral stroma was relatively lower. These findings suggest that FOLR2 expression on TAMs varies among breast cancer molecular subtypes, with TNBC showing the highest levels, and that its spatial distribution within the TME may contribute to tumor progression, therefore highlights the potential of FOLR2 as a diagnostic and prognostic biomarker in breast cancer.

Keywords: *FOLR2, breast cancer, tumor microenvironment, tumor-associated macrophages (TAMs), molecular subtypes.*

A. Introduction

Breast cancer is the most common type of cancer affecting women worldwide, with an estimated 2.3 million new cases and approximately 670,000 deaths reported in 2022 (1). In Indonesia, data from the Global Cancer Observatory (Globocan) in 2020 showed that breast cancer was the most frequently diagnosed cancer, accounting for 68,858 new cases (16.6%) out of a total of 396,914 new cancer cases. The mortality reached more than 22,000 cases (2). Breast cancer is a genetically and clinically heterogeneous disease and is classified into several distinct subtypes. These subtypes are generally grouped into four categories based on hormone receptor expression: Luminal A, Luminal B, HER2-positive, and Triple-Negative Breast Cancer (TNBC) (3). Molecular classification is essential for identifying patient groups that may benefit from targeted therapy, thereby improving treatment effectiveness and patient clinical outcomes (3,4).

One crucial aspect of breast cancer progression is the tumor microenvironment (TME), which consists of various cellular components. From the early stages of tumor growth, reciprocal interactions

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between cancer cells and components of the TME form an ecosystem that supports survival, local invasion, and metastatic spread of tumor cells (5). Tumor-associated macrophages (TAMs) are among the key components within the TME. In primary tumors, macrophages can stimulate and enhance tumor cell invasion, motility, and intravasation (6). TAMs also exhibit immunosuppressive properties, preventing tumor cell elimination by natural killer (NK) cells and T cells during tumor progression, even after recovery from chemotherapy or immunotherapy (7). High infiltration of TAMs has been associated with unfavorable clinicopathological features and reduced overall survival in patients with primary invasive breast cancer (8). Tumor-associated macrophages (TAMs) comprise two main subtypes, M1 and M2, which play opposing roles in breast cancer progression, with M1 exerts pro-inflammatory while M2 has anti-inflammatory effects (8). The transformation from the M1 to the M2 subtype can impair the intrinsic recognition and phagocytic capacity of macrophages, as well as the tumor-killing functions of CD4+ and CD8+ T cells that act in cooperation with them (9).

One marker of M2 macrophages in tumors is Folate Receptor 2 (FOLR2), whose expression has been linked to pro-tumor activity (10). FOLR2 is a glycoprotein associated with folate metabolism and is detected at higher levels on the membranes of cancer cells (11). TAMs expressing FOLR2 contribute to the formation of immunosuppressive TME. For example, FOLR2 is expressed in macrophages with anti-inflammatory properties (12). Moreover, FOLR2-positive TAMs have been reported to suppress cytokine secretion and proliferation of tumor-specific T cells (13). Previous studies have shown significantly increased expression of FOLR2 in TAMs within breast cancer (14). Elevated FOLR2 expression has also been reported in other cancers, including liver and lung cancers (15,16)

According to Qiu et al. (2018), the polarization, localization, and relative abundance of TAMs within tumor lesions may play a more critical role than their mere presence (8). Therefore, immunohistochemistry (IHC) approaches to evaluate the distribution and characteristics of FOLR2 in TAMs across tumor tissues are of significant importance. Furthermore, the expression of FOLR2 in TAMs across different molecular subtypes of breast cancer remains poorly explored. Such characterization could provide distinct diagnostic, prognostic, and therapeutic insights among subtypes. Hence, this study aims to investigate the potential of FOLR2 as a diagnostic marker and therapeutic target, particularly in the context of breast cancer molecular heterogeneity, to support prognosis determination and the development of more precise treatment strategies.

B. Method

Research Subjects

This study employed an observational design with a descriptive-analytical approach to characterize FOLR2 expression on the membranes of tumor-associated macrophages (TAMs) in tumor tissues of Luminal, HER2-positive, and Triple-Negative Breast Cancer (TNBC) subtypes. The samples consisted of thirty (30) breast cancer tissue specimens obtained from patients diagnosed with breast cancer at several hospitals in Bandung. All samples were formalin-fixed and paraffin-embedded (FFPE). Subtype confirmation of the paraffin blocks were conducted through immunohistochemistry (IHC), identifying Luminal, HER2-enriched, and TNBC. Samples were included if tissue adequacy was greater than 50 µm and excluded if less than 50 µm. Clinical data and the use of sample was approved by the Health Research Ethics Committee of RSUD Cibabat, Cimahi (Approval No. 070/38/Ethical Clearance/RSUD Cibabat/V/2025) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Patient confidentiality was strictly maintained by ensuring that all identifiable information remained anonymous.

Immunohistochemistry (IHC)

Immunohistochemical analysis was carried out to characterize FOLR2 expression on TAM membranes within breast cancer tissues. The IHC procedure included the following steps: tissue sectioning at 3–5 µm thickness, mounting on glass slides, deparaffinization with xylol, followed by gradual rehydration through graded alcohol concentrations (100%, 95%, 80%, 70%). Protein blocking was then performed, followed by incubation with a primary antibody against FOLR2 (Genetex Folate Receptor beta antibody, Cat. No. GTX105822, dilution 1:500), which specifically binds to the target antigen. A biotinylated secondary antibody was then applied. Detection was performed using DAB

(3,3′-diaminobenzidine) chromogen, and counterstaining with hematoxylin was used to visualize cell nuclei, followed by neutralization with lithium carbonate. The slides were dehydrated and mounted with cover glass. Human tonsil tissue was used as a positive control. Completed preparations were observed microscopically to evaluate FOLR2 expression and localization.

Immunoreactive Scoring and Statistical Analysis

IHC analysis was performed using a Pro Histo Biological Microscope Pro 31W and documented with SunnyScope software. Quantification of distribution and intensity was carried out using QuPath, which was analyzed selectively to tumor-associated macrophages (TAMs) rather than the entire tissue section. Immunoreactive scoring was determined by multiplying the distribution score by the intensity score as described by Remmelle & Stegner (1987) (17).

Table 1. Immunureactive scoring (IRS)

A (percentage of positive cells)	B (intensity of staining)	Final IRS score (A × B): 0–12 & interpretation
0 = no positive cells	0 = no color reaction	0–1 = Negative
1 = <10% positive cells	1 = mild reaction	2–3 = Mild
2 = 10–50% positive cells	2 = moderate reaction	4–8 = Moderate
3 = 51–80% positive cells	3 = intense reaction	9–12 = Strongly positive
4 = >80% positive cells		

Data normality was assessed using the Shapiro–Wilk test. Parametric statistical analysis was performed using analysis of variance (ANOVA) for normally distributed data, while the Kruskal–Wallis test was applied for non-normally distributed data. Post-hoc comparisons between groups were conducted using Tukey's test or Dunn's test. Categorical data were analyzed using the Chi-square test for normally distributed data and Fisher's exact test for non-normally distributed data. Statistical analysis and visualization was performed using Graph Pad Prism.

C. Result and Discussion

Initial Findings

Immunohistochemistry result as immunoreactive score (IRS) of $FOLR2^{+}$ tumor-associated macrophages (TAMs) was analyzed across three molecular subtypes of breast cancer (TNBC, Luminal, and HER2-enriched) (Figure 1). The highest expression was observed in TNBC (3.81 ± 1.16), followed by HER2-enriched (2.42 ± 1.73) and Luminal (2.18 ± 1.54). Kruskall-wallis analysis demonstrated significant differences in FOLR2 expression among the subtypes. Post hoc Dunn's test revealed that the difference was statistically significant between TNBC and Luminal B subtypes (p-value = 0.02035), whereas no significant difference was observed between TNBC and HER2-enriched, or between Luminal and HER2-enriched subtypes.

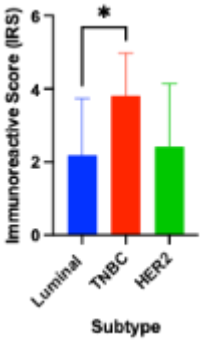

Figure 1. IHC expression using Immunoreactive score (IRS) of FOLR2+ TAMs across across three molecular subtypes of breast cancer, * = p-value < 0.05, post hoc comparison analysis using Dunn's test

The IRS score, derived from the combination of intensity and distribution scores, was subsequently interpreted into categorical expression levels (negative, mild, moderate, and strongly positive). In our study, FOLR2 expression was identified within the categories of negative, mild, and moderate, while no cases demonstrated a strongly positive expression (Figure 2). The IRS categorical expression levels of FOLR2+ TAMs IHC results were subjected to statistical analysis using Fisher's exact test to evaluate their association with molecular subtypes (Table 2). The analysis revealed a statistically significant association between molecular subtype and FOLR2 expression in breast cancer, with a p-value of <0.0001 (p-value < 0.05).

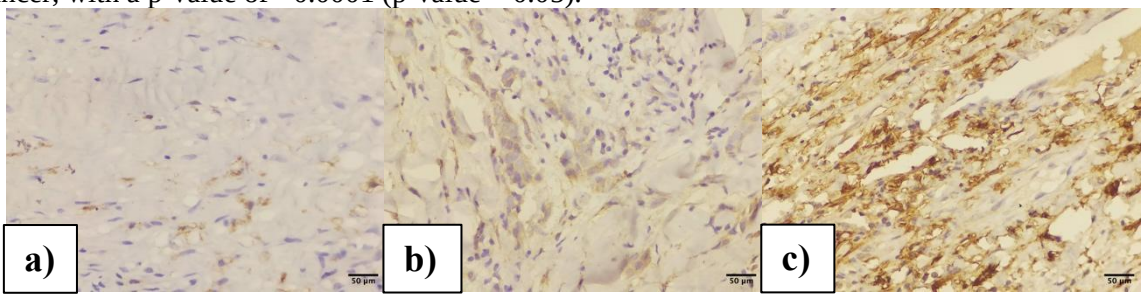

Figure 2. Representative immunohistochemical staining of FOLR2 expression in breast cancer tissues showing (a) negative, (b) mild, and (c) moderate expression levels (magnification 40x objective × 10x ocular)

Table 2. Association between FOLR2 IHC expression levels and molecular subtypes of breast cancer, association analysis using Fisher's exact test

Categories	Molecular Subtypes N (% within subtype)			
	Luminal (n= 15)	**HER2 (+) (n= 3)**	**TNBC (n= 12)**	**p value**
FOLR2 Expression				
Negative	5 (33.33%)	1 (33.33%)	1 (8.33%)	P < 0.0001
Mild	6 (60%)	1 (33.33%)	4 (33.33%)	
Moderate	1 (6.67%)	1 (33.33%)	7 (58.33%)	
Strongly positive	0 (0%)	0 (0%)	0 (0%)	

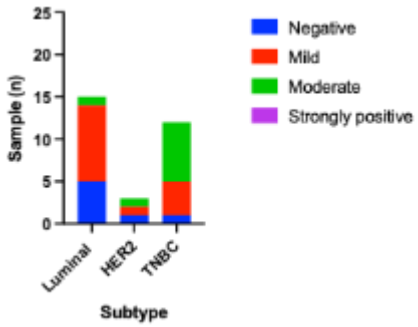

Figure 3. Distribution of FOLR2 IHC expression levels within molecular subtypes of breast cancer

Spatial analysis (Figure 4) showed that FOLR2 was predominantly expressed in peritumoral areas, particularly around blood vessels and adipose tissue, while its expression in the intratumoral stroma was relatively lower. In addition to tumor-associated macrophages (TAMs), FOLR2 was also detected in other inflammatory cells, such as neutrophils.

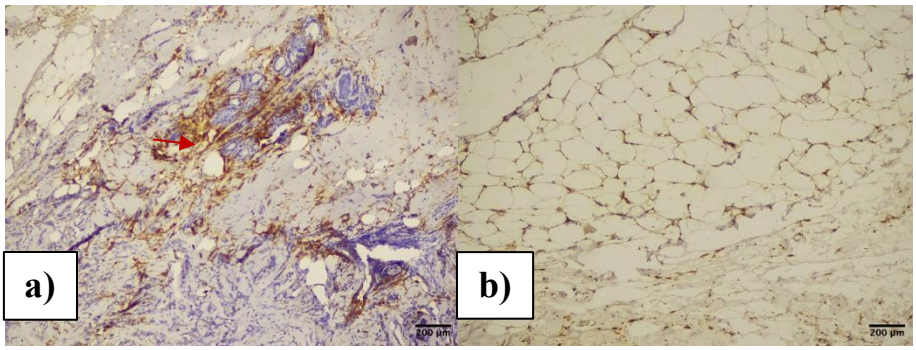

Figure 4. Positive FOLR2+ Tumor associated macrophages (TAMs) a) around blood vessels; b) within adipose tissues (magnification magnification 10x objective × 10x ocular); red arrow showing blood vessel

In this study, we analyze the expression of FOLR2 in the TAM across breast cancer molecular subtypes, which are TNBC, HER2-enriched, and Luminal. We found the highest FOLR2 expression was observed in the TNBC molecular subtype, with an average IRS score of 3.81 ± 1.16. Triple-negative breast cancer (TNBC) is a clinically aggressive subtype characterized by the absence of estrogen receptor, progesterone receptor, and HER2 expression. TNBC accounts for 15–20% of breast cancers and is associated with poor prognosis, high recurrence rates, and limited targeted therapy options (18). Previous studies have reported that high abundance of TAMs in TNBC correlates with unfavorable prognosis and reflects an increased likelihood of metastatic spread (19). Moreover, TAMs predominantly shift toward the M2 phenotype in TNBC, which contributes to immune suppression and supports tumor progression (20). This is consistent with the findings of Rodriguez-Garcia et al. in FRβ^{+} TAM subsets, who found upregulation of IL-10 and PD-L1 (Cd274) genes, which are consistent with an immunosuppressive M2 phenotype (13). In murine models, knockout of FRβ (FOLR2) resulted in increased activation of T cells (CD69^{+}), lower PD-1 expression on T cells, and reduced PD-L1 on TAMs, which indicates a functional role for FRβ in promoting immune suppression (21).

In the HER2-enriched subtype, FOLR2 expression was also relatively high and did not differ significantly from TNBC. HER2-positive breast cancers are characterized by overexpression of the HER2 oncogene and are typically associated with aggressive clinical behavior and poorer prognosis if left untreated (22). Although direct evidence of FOLR2^{+} TAMs in HER2^{+} breast cancer remains limited, several studies support a role for TAMs in modulating HER2-targeted therapy. For example, Jääskeläinen et al. reported that high numbers of CD163^{+} TAMs are independently associated with poorer outcomes in HER2^{+} breast cancer, even in patients receiving trastuzumab, which is anti-

HER2+ therapy (23). A preclinical study also suggest that TAM accumulation in $HER2^+$ breast cancer can impair antibody-dependent cellular cytotoxicity (ADCC) mediated by anti-HER2 antibodies. This suggests that immunosuppressive macrophage populations contribute to resistance in $HER2^+$ tumors.

In the Luminal subtypes (A and B), FOLR2 expression was found to be significantly lower compared with TNBC, even when luminal B HER2+ are included in the cohort. This finding is consistent with previous reports showing that Luminal breast cancers harbor fewer macrophages, particularly the $CD163^+$ subset that represents immunosuppressive TAMs. Previous research demonstrated that the Luminal A subtype exhibits lower infiltration of $CD163^+$ TAMs compared with TNBC (24). A local study from Korea also reported that Luminal A harbors significantly fewer macrophages ($CD68^+$, $CD163^+$) than TNBC. CD163 is an optimal marker for M2, while CD68 is known as a pan-macrophage marker. They also found that high numbers of macrophages (CD68+, CD11+, or CD163+) were associated with higher histologic grade, higher Ki-67 proliferating index, estrogen receptor negativity, and progesterone receptor (25). FOLR2 is also preferentially expressed in subsets of immunosuppressive macrophages, often overlapping with $CD163^+$ TAMs (12,26). Collectively, these observations indicate that Luminal tumors possess a less immunogenic microenvironment and are more driven by hormonal signaling (ER/PR) rather than immune–stromal interactions in supporting tumor progression (27). Thus, the relatively low FOLR2 expression in Luminal subtypes can be interpreted as a less contribution of TAMs within the TME of Luminal tumors compared with TNBC.

Spatial analysis of FOLR2 in TAM indicates that expression of FOLR2+ TAMs was predominantly expressed in the peritumoral area, particularly around blood vessels and adipose tissue, while expression within the intratumoral stroma was relatively lower. This finding is consistent with previous studies that have also consistently reported the presence of FOLR2+ TAMs located adjacent to blood vessels within the tumor stroma across multiple cancer types, including pancreatic cancer (15), hepatocellular carcinoma (HCC) (4), breast cancer, colorectal cancer, and lung cancer (20,28). Moreover, Bulk RNA-seq and CyTOF analysis of FOLR2+ macrophages show that FOLR2+ macrophages specifically express LYVE1 and MRC1/CD206, both markers of perivascular (PV) macrophages (20,29). This pattern indicates that FOLR2-positive cells, especially tumor-associated macrophages (TAMs), tend to accumulate in locations associated with nutrient and oxygen supply as well as immune cell migration pathways, aligning with the ability of cancer cells to co-opt or induce the formation of new blood and lymphatic vessels to meet their metabolic demands (30). The localization of TAMs around blood vessels contributes to the establishment of a perivascular niche that functions as a cellular hub, where complex and dynamic interactions among cells foster cancer stemness, immune escape, dormancy, and metastatic progression. (9, 20). Sharma et al. reported that tumor-associated macrophages contribute to shaping an immunosuppressive perivascular niche by modulating the angiogenic switch, which is a key process in the transition of tumors from dormancy to malignancy (7).

Furthermore, we detected high FOLR2 expression in adipose tissue within peritumoral area. This observation aligns with the findings of Petit et al., who identified adipose tissue macrophages (ATMs) co-expressing FOLR2 along with TIM4, CD163, CD206, and LYVE-1, indicating a core profile of fat-associated macrophages (31). In addition, Liu et al., reported interactions between FOLR2+ macrophages and adipocytes, although the intensity of these interactions differed (32). Adipocytes represent the major cellular component of the TME, where tumor cells induce their transformation into cancer-associated adipocytes (CAAs) (33). In breast cancer, CAAs support tumor progression by secreting various adipokines, including leptin and adiponectin (34). Adipokines functions to enhance tumor cell adhesion, migration, and invasion. CAAs also release fatty acids which can be transported to tumor cells where it is utilized for energy production via β-oxidation (35). Furthermore, immunomodulatory molecules released by adipocytes during lipolysis can drive tumor cell proliferation, stimulate macrophage activation and polarization, and influence the course of cancer progression. Through reciprocal regulation, adipocytes and macrophages shape an anti-inflammatory tumor microenvironment that prevents the infiltration of antitumor immune cells into the tumor site (36).

From a therapeutic perspective, FOLR2 represents a promising biomarker target to selectively modulate TAMs without broadly depleting the entire macrophage population. In preclinical models, CAR-T cells specific for FRβ have selectively eliminated $FOLR2^+$ TAMs, led to enrichment of pro-

inflammatory monocytes, an influx of endogenous tumor-specific CD8+ T cells, delayed tumor progression, and prolonged survival. However, potential on-target toxicity in non-tumor sites (e.g., inflamed joints) with FOLR2 expression and the in vivo persistence of FOLR2-specific CAR-T cells remain important challenges to translate it into clinic application (37). Additionally, nanoparticle and liposome platforms modified with folate ligands have been used to deliver cytotoxic or immunomodulatory agents into $FOLR2^+$ macrophages. However, rapid liver uptake by macrophages still limits tumor targeting efficiency (38). Targeting $FOLR2^+$ TAMs may reprogram the TME toward an immunostimulatory state, thereby enhancing the efficacy of immune checkpoint inhibitors and conventional therapies (39). This study highlights that its increase expression in TNBC indicate that FOLR2 could be a potential biomarker for its therapeutic target, and it is particularly relevant given the limited treatment options for this subtype, where FOLR2-based strategies may help overcome immune evasion and enhance patient survival.

This study has several limitations. First, the sample size was relatively small, as only 30 breast cancer tissue samples were analyzed. Consequently, the generalizability of the findings to a broader population remains limited and requires validation in larger cohorts. Second, the distribution of molecular subtypes (TNBC, Luminal, $HER2^+$) was not entirely balanced, which may have affected the statistical power of intergroup comparisons and the robustness of the conclusions. Future studies should address these limitations by incorporating a larger sample size and ensuring a more balanced representation of molecular subtypes. In addition, subsequent research should aim to link FOLR2 expression with clinical outcomes such as patient survival, therapeutic response, and metastatic potential. Since the present study did not evaluate these associations, the clinical applicability of FOLR2 as a prognostic or predictive biomarker remains limited. Integrating molecular findings with patient outcome data in larger, longitudinal cohorts will be essential to establish the translational relevance of FOLR2 in breast cancer.

D. Conclusion

This study demonstrates that FOLR2 expression in tumor-associated macrophages varies across breast cancer molecular subtypes, with the highest expression observed in TNBC compared with Luminal tumors. The preferential increase expression of $FOLR2^+$ TAMs in TNBC supproted by its preferential expression location adjacent to blood vessels and within adipose tissue in peritumoral area suggests their involvement in promoting an immunosuppressive tumor microenvironment, which potentially contributing to the aggressive clinical course and limited therapeutic responsiveness of this subtype. These findings support FOLR2 as a promising biomarker and therapeutic target to selectively modulate TAMs, providing opportunities to improve treatment strategies, particularly in TNBC where current options remain limited.

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