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Original Article

Exosomal *ITGB2* Mediates Immune Evasion in Triple-Negative Breast Cancer by Suppressing Dendritic Cell Activation via *TLR4*

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Abstract

Background: This study investigates the role of exosomal integrin beta-2 (*ITGB2*) from triple-negative breast cancer (TNBC) cells in modulating immune responses, with a focus on its interaction with Toll-like receptor 4 (*TLR4*) in dendritic cells (DCs). This study aimed to understand how *ITGB2* contributes to the immunosuppressive tumor microenvironment in TNBC.

Methods: *ITGB2* expression in TNBC tissues and cell lines was analyzed using qPCR and Western blot at the Affiliated Cancer Hospital of Xinjiang Medical University between 2013 and 2015. Knockdown and overexpression models of *ITGB2* were established in MDA-MB-231 cells to explore their effects on *TLR4* expression in DCs. Exosomes were isolated from these cells, and DCs were co-cultured with exosomes to measure *TLR4* expression and cytokine secretion using flow cytometry and ELISA.

Results: *ITGB2* was overexpressed in TNBC tissues, correlating with poor prognosis. Exosomal *ITGB2* from TNBC cells suppressed *TLR4* expression in DCs, leading to impaired DC maturation and reduced cytokine secretion, thus promoting an immunosuppressive microenvironment.

Conclusion: Targeting the *ITGB2-TLR4* axis could enhance anti-tumor immunity in TNBC. *ITGB2* holds potential as a biomarker and therapeutic target, suggesting that inhibition of exosomal *ITGB2* or restoration of DC function may improve therapeutic outcomes in TNBC.

Keywords: Triple-negative breast cancer; Dendritic cell; Exosome

Introduction

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer, comprising 10%-20% of all cases. It is characterized by the absence of estrogen receptors, progesterone receptors, and HER2 amplification. TNBC is associated with a poor prognosis due to its high recurrence and metastatic potential, and it lacks targeted therapies, leaving chemotherapy as the primary treatment, which often yields suboptimal results (1,2). One of the key challenges in TNBC is its immunosuppressive tumor microenvironment, which promotes tumor progression and resistance to therapy. Exosomes, small extracellular vesicles secreted by cells, play a crucial role in modulating the tumor microenvironment. They carry bioactive molecules such as proteins, lipids,

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and nucleic acids, which influence recipient cells. In TNBC, exosomes contribute to immune evasion and metastasis (3).

Integrin beta-2 (*ITGB2*), also known as CD18, is a key leukocyte integrin involved in cell adhesion and signaling (4). *ITGB2* forms heterodimers with alpha subunits, creating integrins like LFA-1 and Mac-1, critical for immune cell trafficking and synapse formation (5). *ITGB2* is upregulated in cancers like melanoma and leukemia, promoting cell adhesion, invasion, and metastasis (6-9). In melanoma, *ITGB2* interacts with ICAM-1 to aid invasion, while in leukemia, it supports progression and chemoresistance by homing cells to bone marrow niches. *ITGB2* is essential for T-cell activation and immune surveillance (10), but tumors exploit *ITGB2* pathways to evade detection, creating an immunosuppressive environment (11). This duality makes *ITGB2* a promising therapeutic target, as disrupting its interactions could inhibit tumor spread and enhance immunity.

Dendritic cells (DCs) are key antigen-presenting cells responsible for initiating and regulating immune responses (12,13). Toll-like receptor 4 (*TLR4*), a pattern recognition receptor expressed on DCs, triggers DC maturation and the release of pro-inflammatory cytokines, such as IL-12 and TNF-α (14,15). In tumors, DCs are often suppressed by tumor-derived factors, thereby promoting immune evasion.

This study explores the role of exosomal *ITGB2* from TNBC in modulating DC-mediated immune responses. We hypothesize that exosomal *ITGB2* downregulates *TLR4* expression, inhibiting DC maturation and promoting an immunosuppressive microenvironment. Understanding this interaction could offer insights into TNBC immune evasion and provide targets for immunotherapy.

Materials and Methods

Human tissue specimen

TNBC patients (n=148) diagnosed according to the WHO criteria (16) and recruited at the Affiliated Cancer Hospital of Xinjiang Medical University between 2013 and 2015, were included in this study.

Inclusion criteria: Patients diagnosed with TNBC according to the WHO criteria (17), with no prior history of other cancers, and not received any treatment before sample collection. Exclusion criteria: Patients with other types of breast cancer, those undergone any preoperative treatment, or patients with a history of other malignancies. Cancer tissue 148 cases and adjacent normal tissue 30 cases of TNBC patients were flash-frozen in liquid nitrogen and stored at -80 °C until processing for further RNA and protein extraction, and prognostic information was collected to analyze the impact of *ITGB2* expression on prognosis.

Extraction and identification of dendritic cells

Mononuclear cells were isolated from human peripheral blood and adherent cells were retained as detailed in the procedure described as before (18). Adherent cells were cultured and treated with rh-GM-CSF (Thermo Fisher Scientic, Waltham, MA, United States) and rh-IL-4 (Thermo Fisher Scientic, Waltham, MA, United States) for 7 d, and then dendritic cells were identified using antibodies against CD80 (BD Biosciences, San Jose, CA, United States) and CD83 (BD Biosciences, San Jose, CA, United States) detected by flow cytometry (FCM). Isotype control antibodies (BD Biosciences, San Jose, CA, United States) were used to ensure the specificity and accuracy of the FCM staining. Treat DC cells with 50 ng/mL lipopolysaccharide (LPS) (Beyotime Biotechnology, Shanghai, China) for 24 hours to stimulate their maturation.

Cell culture

Human breast epithelial cell line MCF-10A and TNBC cell line MD-AMB-231 were purchased from Shanghai Cell Bank (Chinese Academy of Sciences, Shanghai, China) and cultured with Dulbecco's modified eagle medium containing 10% fetal bovine serum (Thermo Fisher Scientic, Waltham, MA, United States) and 1% Penicillin-Streptomycin (Thermo Fisher Scientic, Waltham,

MA, United States) in the 37 °C, 5% CO2 incubator.

Generation of stable cell lines

To generate *ITGB2* overexpression or knockdown cell models, the pcDNA3.1-*ITGB2* or NC plasmid, sh-*ITGB2*-1, sh-*ITGB2*-2 or sh-NC were introduced along with lentivirus packaging vectors (pVSVG and pPAX2) into MDA-MB-231 cells by Lipofectamine 2000 (Thermo Fisher Scientic, Waltham, MA, United States) respectively. NC denotes scramble vector. To obtain stable cells, 2μg/ml puromycin was used to treat the cells for about 7 d. Vector, OE-*ITGB2*, sh-NC, sh-*ITGB2*-1, and sh-*ITGB2*-2 stable MDA-MB-231 cell lines were generated. sh-NC: GAACAAGATGAAGAGCACCAA; sh-*ITGB2*-1: CGTAAGAGGACGACCAGTAGA; sh-*ITGB2*-2: CCACACTGTGACCGATGTAAC.

Extraction and observation of exosomes

Exosomes were extracted from the culture supernatant of stable MDA-MB-231 cell lines by differential centrifugation. Dead cells were removed by 3,000×g centrifugation (15 min), followed by 6,000×g (40 min) and 10,000×g (40 min) centrifugation to remove cell debris. The exosome pellet was collected after 100,000×g centrifugation (60 min), re-suspended, and analyzed for particle size and distribution using Nano Measurer software (Fudan University, Shanghai, China).

Cell co-culture with exosomes

DC cells were co-cultured with exosomes extracted from MDA-MB-231 cells. Briefly, DC cells in the control group were cultured without any intervention. For the DC + Vector, DC + OE-*ITGB2*, DC + sh-NC, DC + sh-*ITGB2*-1, and DC + sh-*ITGB2*-2 groups, DC cells were co-cultured with 50 μg/mL exosomes for 24 h, respectively isolated from the corresponding MDA-MB-231 cells with different *ITGB2* expression levels.

Western blot

Protein expression in tissues, cells, and exosomes was analyzed by Western blot. Total proteins were extracted, and concentrations were determined using the bicinchoninic acid method. After SDS-PAGE separation and PVDF membrane transfer, membranes were incubated overnight at 4°C with primary antibodies against *ITGB2* (#72607), *TLR4* (#14358), and β-actin (#3700), which all were purchased from Cell Signaling Technology. After incubation with HRP-conjugated secondary antibodies for 2 h at room temperature, protein bands were visualized using the ChemiScope mini. β-actin was used for normalization.

Enzyme-linked immunosorbent assay (ELISA)

The co-cultured dendritic cells were collected and lysed. Then, the contents of IL-12, IL-4, TNF-α, TGF-β, and IFN-β in the lysate were determined with the corresponding ELISA Kits (abcam, Cambridge, UK). Briefly, the lysate was mixed with carbonate buffer, which was then added to the detection plate and incubated at 4 °C overnight. After rinsing, 1% bovine serum albumin was added and incubated at 37 °C for 60 min. Then, 0.1 mL anti-serum was added for incubation at 37 °C for 40 min. After washing, 3,3',5,5'-tetramethylbenzidine color development was performed. Finally, the optical density value at 450 nm was detected, and concentrations of IL-12, IL-4, TNF-α, TGF-β, and IFN-β were determined.

Real-time quantitative polymerase chain reaction (PCR)

Total RNAs prepared by TRIzol reagent (Invitrogen, Carlsbad, CA, United States) were quantified with a NanoDrop 2000 instrument (Thermo Fisher Scientic, Waltham, MA, United States) spectrophotometer, followed by synthesis into cDNA with a PrimeScript RT reagent kit (Takara, Tokyo, Japan) and the subsequent determination of the relative gene expression with the use of a SYBR Green PCR Kit (TaKaRa, Tokyo, Japan). After normalization against β-actin, the relative fold changes were counted with the 2–ΔΔCt formula (Table 1).

Table 1: Primer sequences for real-time quantitative PCR

Gene	Forward primer sequences (5'-3')	Reverse primer sequences (5'-3')
ITGB2	TTCGGGTCCTTCGTGGACA	ACTGGTTGGAGTTGTTGGTCA
TLR4	AGACCTGTCCCTGAACCCTAT	CGATGGACTTCTAAACCAGCCA
β-actin	CATGTACGTTGCTATCCAGGC	CTCCTTAATGTCACGCACGAT

Statistical methods

Data were obtained from experiments run independently in triplicate at least with the results analyzed using GraphPad Prism 7 (GraphPad Prism software, San Diego, CA, United States), and statistical significance was indicated by $P<0.05$. Meanwhile, the mean±SD was used for statistical description of the data. Intergroup and multigroup differences were identified by two-tailed Student's t-test and one-way analysis of variance (ANOVA) with Tukey's tests, respectively.

Ethics Approval

This study was approved by the Ethics Committee of the Affiliated Cancer Hospital of Xinjiang Medical University in accordance with the Declaration of Helsinki (Approval Number: 2018BC013), and all individuals were informed of the study's purpose and voluntarily signed informed consent.

Results

High Expression of ITGB2 in TNBC and Its Association with Poor Prognosis

We initially explored the expression of *ITGB2* in cancerous and adjacent non-cancerous tissues from patients with TNBC using qPCR. The results indicated that *ITGB2* gene expression was significantly higher in TNBC tissues compared to adjacent non-cancerous tissues, with statistical significance ($P=0.0038$) (Fig.1A). Western blot analysis further confirmed that the protein expression level of *ITGB2* was significantly elevated in TNBC tissues compared to adjacent tissues ($P<0.0001$) (Fig. 1B and C). Subsequently, we validated the expression of *ITGB2* in the human breast epithelial cell line MCF-10A and the TNBC cell line MD-AMB-231. Both qPCR and Western blot results demonstrated higher *ITGB2* expression in TNBC cells compared to human breast epithelial cells (Fig. 1D-F). We then investigated the relationship between *ITGB2* expression in TNBC tissues and patient prognosis. TNBC patients were divided into high and low *ITGB2* expression groups based on the median expression level of *ITGB2*, with each group consisting of 74 patients (Table 2). The Kaplan-Meier method with the log-rank test was used to compare the survival data between the two groups, and the results showed that the survival of patients in the *ITGB2* high expression group was significantly lower than that of the *ITGB2* low expression group, and the difference was statistically significant ($P=0.033$) (Fig.1G), indicating that the high expression of *ITGB2* was associated with the TNBC with poor prognosis. *ITGB2* may serve as a novel oncogene in TNBC.

Identification of ITGB2 Knockdown and Overexpression in TNBC Cell-Derived Exosomes

We utilized shRNA targeting *ITGB2* and overexpression plasmids to transfect MD-AMB-231 cells, thereby constructing *ITGB2* knockdown and overexpression TNBC cell models. qPCR analysis showed that *ITGB2* expression was significantly upregulated in the OE-*ITGB2* group compared to the NC and Vector groups. Conversely, *ITGB2* expression was significantly downregulated in the sh-*ITGB2*-1 and sh-*ITGB2*-2 groups compared to the NC and sh-NC groups (Fig.2A). Specifically, at the mRNA level, the expression of *ITGB2* in the sh-*ITGB2* group was reduced by 66%-75% compared to sh-NC group, while in the OE-*ITGB2* group, *ITGB2* expression was increased by 230%-300% compared to Vector group. At the protein level, *ITGB2* expression in the sh-*ITGB2* group was reduced by 66%-75% compared to sh-NC group, and in the OE-*ITGB2* group, *ITGB2* expression was increased by 250%-330% compared to Vector group,

which confirmed the successful construction of *ITGB2* knockdown and overexpression models in TNBC cells. We then extracted exosomes from these cells and examined *ITGB2* expression in the exosomes. Western blot results indicated no difference in the expression of exosome markers across groups; however, exosomal *ITGB2* expression was significantly upregulated in the OE-*ITGB2* group and significantly downregulated in the sh-*ITGB2*-1 and sh-*ITGB2*-2 groups (Fig. 2B and C).

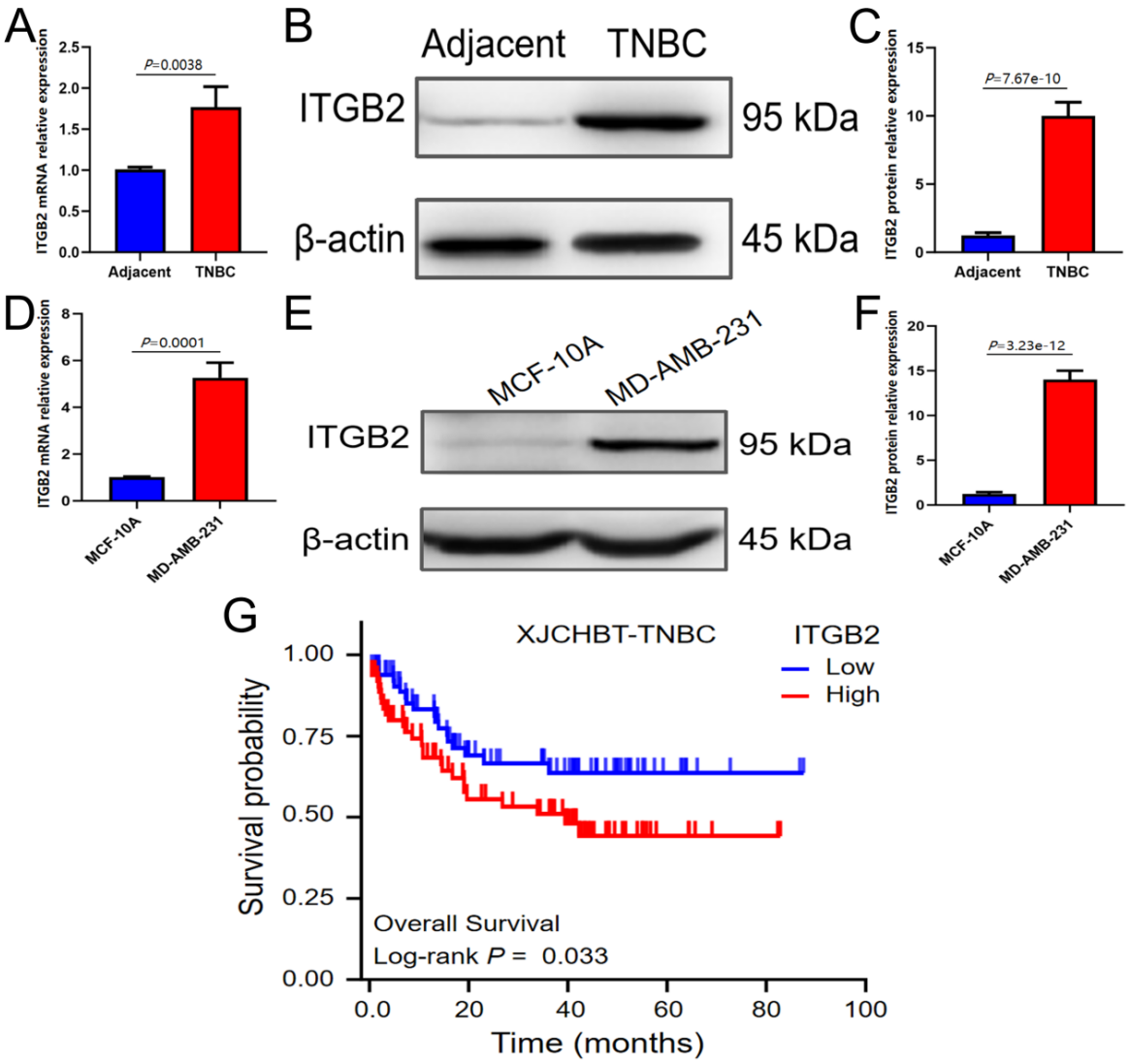

Fig. 1: *ITGB2* Expression in TNBC and Its Correlation with Prognosis. (A) Relative expression of *ITGB2* mRNA in TNBC tissues compared to adjacent non-cancerous tissues, as determined by qPCR (P=0.0038). (B-C) Western blot analysis showing *ITGB2* protein expression levels in TNBC tissues compared to adjacent tissues (P<0.0001). (D-F) Expression of *ITGB2* in human breast epithelial cell line MCF-10A and TNBC cell line MD-AMB-231 analyzed by qPCR and Western blot, indicating higher expression in TNBC cells. (G) Kaplan-Meier survival analysis of TNBC patients stratified by *ITGB2* expression levels, demonstrating a significantly lower OS in the high *ITGB2* expression group (P=0.033)

Table 2: Relationship between *ITGB2* expression and clinicopathological characteristics in TNBC patients.

Characteristics	Number	ITGB2 expression(x±s)	F-value	*P*-value
Age			2.162	0.121
≤35	13	3.89±1.74		
35<Age≤55	100	3.52±2.23		
55<	35	2.71±2.58		
Menopausal Status			1.023	0.313
Premenopausal	86	3.54±2.18		
Postmenopausal	62	3.13±2.60		
Tumor Stage			4.395	**0.014**
I	37	2.37±2.11		
II	83	3.63±2.25		
III	28	3.90±2.28		
Lymph Node Metastasis			4.839	**0.029**
No	119	3.37±1.58		
Yes	29	4.40±1.76		
Tumor Size (cm)			3.274	**0.041**
T≤2	59	2.59±1.15		
2<T≤5	80	3.48±2.14		
5<T	9	3.75±1.89		
Histological Grade			5.156	**0.025**
Grade 2	55	2.57±1.35		
Grade 3	93	3.49±2.11		
ki-67(%)			28.207	**< 0.001**
≤50	36	2.77±1.60		
>50	112	4.85±1.92		
Vascular Invasion			6.373	**0.013**
No	125	3.27±2.27		
Yes	23	4.51±2.32		

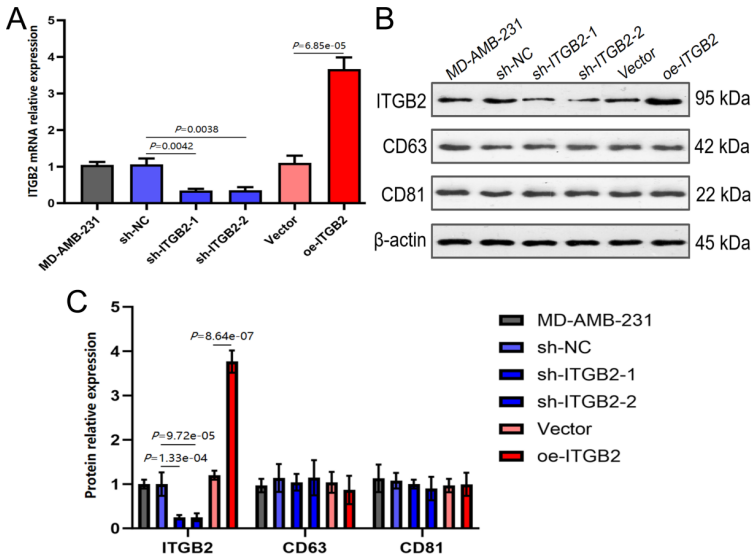

Fig. 2: ITGB2 Expression in TNBC Cell-Derived Exosomes with Knockdown and Overexpression. (A) qPCR analysis of ITGB2 expression in MD-AMB-231 cells transfected with shRNA and overexpression plasmids, showing significant upregulation in the OE-ITGB2 group and downregulation in sh-ITGB2-1 and sh-ITGB2-2 groups compared to controls. (B-C) Western blot analysis of ITGB2 expression in exosomes derived from MD-AMB-231 cells, demonstrating increased expression in the OE-ITGB2 group and decreased expression in the sh-ITGB2 groups, with consistent exosome marker levels across groups

Alteration of TLR4 Expression in DC Cells by Exosomal ITGB2 Derived from TNBC Cells

In previous studies, we observed a significantly lower proportion of mature DCs within tumors compared to adjacent non-cancerous tissues in TNBC. Therefore, we investigated the relationship between *ITGB2* expression in TNBC cells and DCs. DCs were induced and expanded in vitro from peripheral blood mononuclear cells of TNBC patients using GM-CSF and IL-4, and characterized by FCM as shown in Fig. 3A and B. The proportion of CD80 and CD83 positive cells increased from 0.06% and 0.04% before induction to 66.90% and 82.96% after induction, respectively, indicating successful in vitro DC culture. Mature DCs were divided into six groups: a blank control group with no treatment, and five groups co-cultured with exosomes derived from MD-AMB-231, sh-NC, sh-*ITGB2*-1, Vector, and OE-*ITGB2* cells. Since *TLR4* is critical for DC maturation and activation in tumor immunity, we assessed the effect of TNBC exosomes with different *ITGB2* expression levels on *TLR4* expression in DCs. As shown in Fig. 3C and D, exosomes from MD-AMB-231 cells reduced *TLR4* expression in DCs, while exosomes from *ITGB2*-knockdown MD-AMB-231 cells (sh-*ITGB2*) restored *TLR4* expression in DCs. Conversely, exosomes from *ITGB2*-overexpressing MD-AMB-231 cells (OE-*ITGB2*) significantly decreased *TLR4* expression in DCs. LPS is an agonist of *TLR4*, which induces DC maturation by binding to *TLR4*. We then examined the effect of exosomal *ITGB2* derived from TNBC cells on DC maturation in the presence of LPS. FCM results (Fig. 3E, F) showed that exosomes from MD-AMB-231 cells reduced the expression of CD80 and CD83 in DCs, while exosomes from sh-*ITGB2* cells restored the expression of CD80 and CD83 in DCs. Conversely, exosomes from OE-*ITGB2* cells significantly decreased the expression of *TLR4* in DCs. Exosomal *ITGB2* derived from TNBC cells can modulate *TLR4* expression in DCs, thereby inhibiting DC maturation.

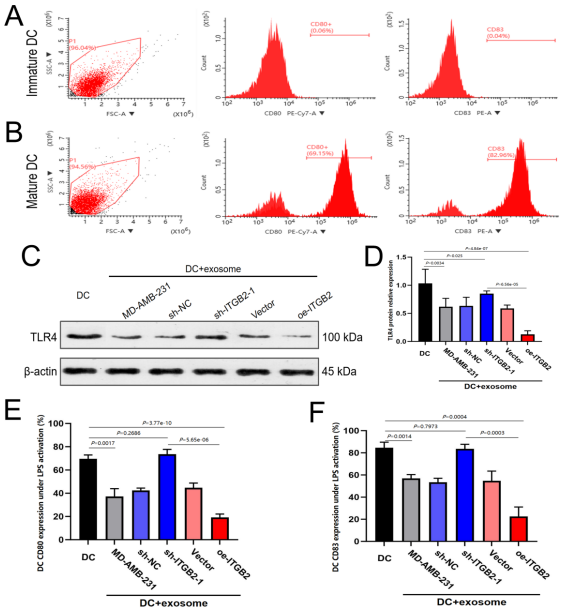

Fig. 3: Modulation of TLR4 Expression in DCs by Exosomal ITGB2 from TNBC Cells. (A-B) Flow cytometry analysis of dendritic cells (DCs) induced from TNBC patient PBMCs, showing increased proportions of CD80 and CD83 positive cells post-induction, indicating successful DC culture. (C-D) Effects of exosomes from MD-AMB-231 cells with varied ITGB2 expression levels on TLR4 expression in DCs. Exosomes from MD-AMB-231 cells decreased TLR4 expression, while exosomes from ITGB2-knockdown cells restored it, and exosomes from ITGB2-overexpressing cells further reduced TLR4 expression. (E-F) The effect of exosomal ITGB2 on DC maturation (CD80, CD83) in the presence of LPS was evaluated by FCM

Regulation of Cytokine Secretion in DCs by Exosomal ITGB2 Derived from TNBC Cells

Mature dendritic cells (DCs) initiate immune responses by secreting various cytokines. Since exosomal *ITGB2* from TNBC cells modulates *TLR4* expression in DCs, we examined the cytokine secretion profile of DCs. As shown in Fig. 4A-E, the levels of cytokines IL-12, IL-4, TNF-α, TGF-β, and IFN-β were downregulated in DCs treated with exosomes from MD-AMB-231 cells. In the OE-*ITGB2* exosome-treated group, these cytokines were significantly downregulated, whereas their levels were restored in the sh-*ITGB2* exosome-treated group. *ITGB2* from TNBC-derived exosomes inhibits dendritic cell maturation and immune response by modulating *TLR4*. A schematic representation of the mechanism is shown in Fig. 4F.

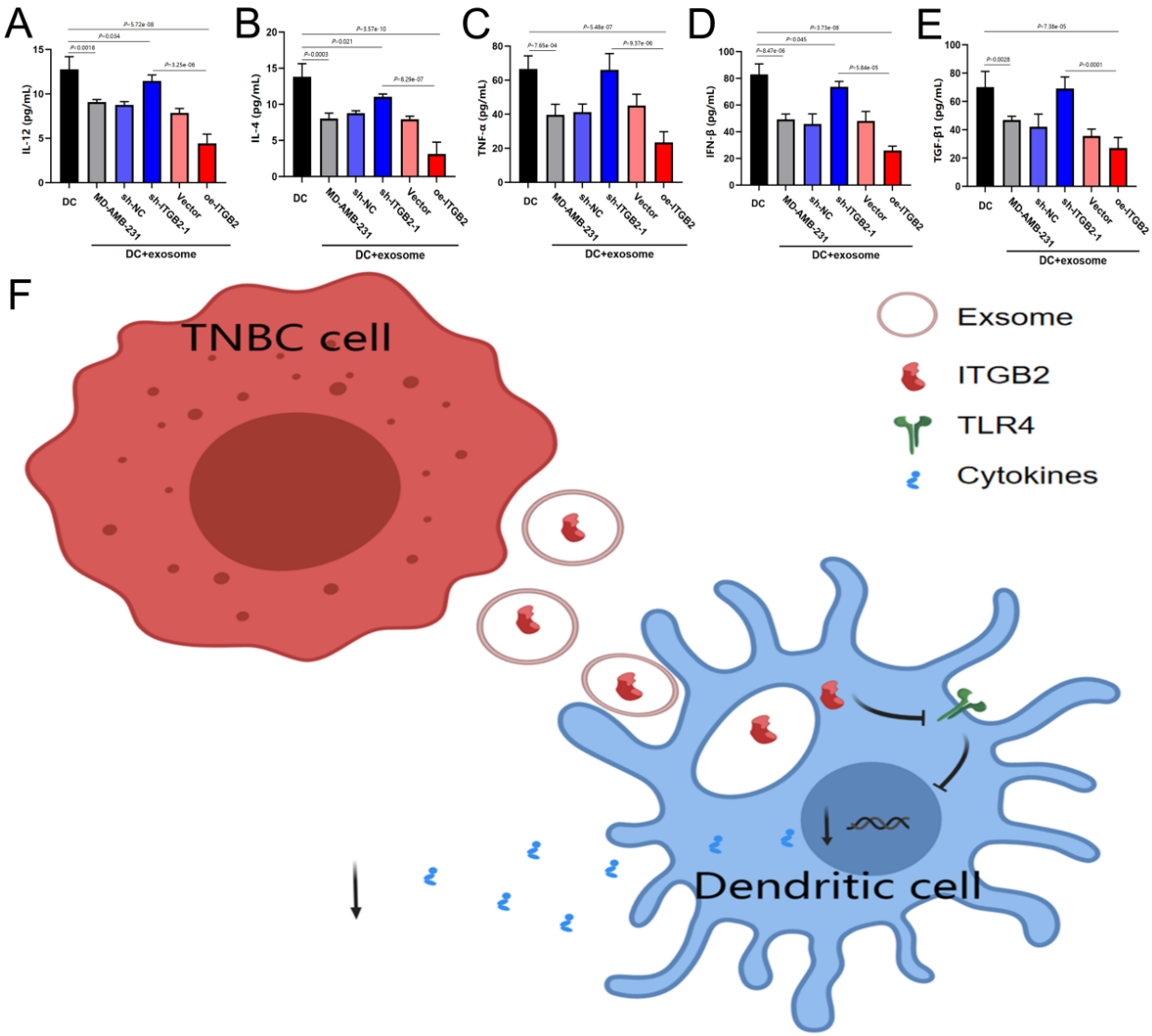

Fig. 4: Modulation of Cytokine Secretion in DCs by Exosomal *ITGB2* from TNBC Cells. (A-E) Levels of cytokines IL-12, IL-4, TNF-α, TGF-β, and IFN-β in DCs treated with exosomes from MD-AMB-231 cells, showing downregulation in MD-AMB-231 and OE-*ITGB2* exosome-treated groups and restoration in sh-*ITGB2* exosome-treated group. (F) Schematic representation of the mechanism by which TNBC-derived exosomal *ITGB2* regulates *TLR4* and inhibits dendritic cell maturation and immune response

Discussion

This study provides valuable insights into the immunosuppressive mechanisms of TNBC by investigating the role of exosomal *ITGB2* in regulating DC function. Our findings reveal that exosomal *ITGB2* derived from TNBC cells inhibits *TLR4* expression in DCs, suppressing their maturation and immune activation. This novel pathway explains how TNBC increases invasiveness and worsens prognosis by evading immune surveillance, highlighting the critical role of *ITGB2* in promoting immune suppression.

Furthermore, we demonstrate that *ITGB2*-enriched exosomes from TNBC cells suppress *TLR4* expression on DCs, which in turn inhibits the release of pro-inflammatory cytokines such as IL-12 and TNF-α. This observation is consistent with previous studies indicating that tumor-derived exosomes can downregulate *TLR4* signaling and impair DC function. Unlike studies focusing on soluble factors like TGF-β (19-21), our work emphasizes the role of exosomal integrins, specifically *ITGB2*, in immune suppression and suggests that targeting exosomal integrins could be a promising strategy to enhance anti-tumor immunity.

The underlying mechanisms by which *ITGB2* modulates *TLR4* expression in DCs appear to involve integrin-mediated signaling pathways, including PI3K/Akt, NF-κB, and MAPK, which are known to influence immune cell activation and cytokine production (22-26). *ITGB2* may alter *TLR4* expression by regulating receptor internalization or trafficking, potentially through changes in the cytoskeleton. Additionally, exosomes could carry integrins or microRNAs that directly target *TLR4*, modulating its expression in DCs (27,28). This cross-talk between integrins and TLRs highlights the complex interplay through which *ITGB2* modulates immune responses, driving immune evasion and tumor progression.

Given its role in immune modulation and tumor progression, *ITGB2* holds promise as a prognostic biomarker for TNBC, with high expression levels linked to poorer overall survival. *ITGB2* could complement existing biomarkers (e.g., PD-L1, Ki-67) by identifying high-risk TNBC patients who may benefit from more aggressive treatments or immunotherapy (29,30). Unlike PD-L1, which exhibits variable expression, *ITGB2* provides more consistent insights into immune regulation, particularly through exosome-mediated immune suppression. *ITGB2*'s dual role in immune regulation and tumor aggressiveness makes it a comprehensive marker that could guide immunotherapy decisions. However, further validation in larger cohorts is needed to confirm its clinical utility for patient stratification and treatment.

Finally, *ITGB2* presents a promising therapeutic target in TNBC, with strategies such as small molecule inhibitors and RNA interference being actively explored. While small molecule inhibitors targeting integrin signaling have shown preclinical promise, challenges related to bioavailability, toxicity, and resistance persist (31). RNAi therapies have been effective in preclinical models, reducing tumor growth and immune evasion by knocking down *ITGB2*, but issues with efficient delivery and off-target effects remain (32,33). Despite the absence of approved *ITGB2*-targeted therapies, ongoing clinical trials are investigating integrin inhibitors and RNAi-based therapies, often in combination with chemotherapy or immunotherapy. Overcoming the challenges of targeting *ITGB2* requires optimizing delivery methods and addressing tumor heterogeneity and resistance mechanisms.

While our study provides new insights into exosomal *ITGB2* in TNBC, most experiments were conducted in vitro, requiring in vivo studies in animal models to confirm clinical relevance. Future studies should explore interactions between exosomal *ITGB2* and other immune cells, like macrophages and T cells, to understand fully immune modulation. Understanding how *ITGB2* is encapsulated into exosomes and targeted to DCs could lead to new strategies for manipulat-

ing exosomal cargo and improving therapeutic outcomes.

Conclusion

Our study highlights the critical role of TNBC-derived exosomal *ITGB2* in regulating DC function and promoting immune evasion. By targeting the *ITGB2-TLR4* axis, it may be possible to develop new therapeutic strategies that enhance anti-tumor immunity and improve the prognosis of TNBC patients. As we continue to uncover the complex interactions within the tumor microenvironment, it is crucial to leverage these insights to advance the field of cancer immunotherapy and develop more effective treatments for aggressive cancers like TNBC.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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