

RESEARCH ARTICLE



Identification and Functional Characterization of Maturation-Dependent Changes in Dendritic Cell Exosome-Shuttle Targetome

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Abstract: Among the different types of antigen-presenting cells, dendritic cells (DCs) are the most professional, exhibiting a hallmark transition from an immature to a mature state. DCs release high levels of miRNA-containing exosomes that orchestrate the tolerogenic or immunogenic functions of these cells. This study identifies the exosome-shuttle miRNAs, which are expressed differentially between the mature and immature states of DCs, and ascribes functional enrichments to the molecular targets of these miRNAs. A GEO data series comparing the expression of miRNA between exosomes derived from mature and immature states of DC was analyzed, and all the miRNAs that are dysregulated significantly between the mature and immature states of DC were identified. Interactions and targets of the up-regulated and down-regulated miRNAs were annotated separately, and the functional enrichments and interaction networks of the targets were mapped and visualized. Nineteen miRNAs were found down-regulated in the exosomes of mature DCs, and twenty-four miRNAs were found up-regulated over exosomes of immature DCs with 1186 and 1949 targets involved in thirty-two and 131 pathways, respectively. Further, the functional enrichment of the targets revealed miRNA-targeted changes in expression of biomolecules involved in cytoskeletal remodeling and energy metabolism as key maturation-dependent processes. The results present prominent miRNA signatures for identifying the state of maturation of DC and uncover miRNA targets, which may prove useful as therapeutic options in the treatment of immune dysfunctions.

Keywords: dendritic cell, maturation, exosome, shuttle, miRNA, target

1. Introduction

Despite a growing number of cells being recognized as antigen-presenting cells (APCs), only three types of cells viz. dendritic cells (DCs), macrophages, and B lymphocytes are distinguished by their ability to present exogenous antigens on MHC-II molecules to CD4+ helper T lymphocytes, along with co-stimulatory molecules. Such APCs that can provide all three signals viz. antigen presentation via MHC molecules, expression of co-stimulatory molecules, and cytokine secretion, needed together to activate naïve T lymphocytes, are classified as professional APCs. Among the professional APCs, DCs are the most specialized and effective type, playing a critical role in immune homeostasis and the adaptive immune response [1, 2].

The process of maturation is a hallmark of DC biology. DCs exist in two discrete developmental stages, determined by exposure to pathogens, with dissimilar functional characteristics. Under physiological conditions, DCs exist in an immature, steady state to effect immune tolerance and maintain immune homeostasis. These immature DCs (iDCs), acting as sentinels of the immune system to detect pathogens, are specialized for the uptake of antigens by macropinocytosis or phagocytosis and processing internalized antigen. In response to infection or injury, the accompanying inflammatory

stimuli trigger downstream signaling pathways that induce molecular reprogramming of the iDCs. Specifically, the stimulation of toll-like receptor (TLR) causes DCs to transition from an immature state to a mature state, which is characterized by evidently up-regulated membrane molecules, MHC-II, and co-stimulatory molecules, needed for efficient T cell priming. In distinct contrast to iDCs, mature DCs (mDCs) exhibit low capacity for antigen uptake and processing [3–5].

Besides other modes of communication within themselves via direct cell-to-cell contact, soluble mediators, exchange of plasma membrane patches, and nanotubules, DCs prominently rely on exosomes to orchestrate their tolerogenic or immunogenic functions [6, 7]. Exosomes are small (usually <100 nm in size) membrane-bound vesicles, generated in the endocytic compartment that are released to the extracellular milieu by living cells. Exosomes appear to serve intercellular communication through the horizontal transfer of proteins, antigens, prions, morphogens, mRNA, and non-coding regulatory RNAs, notably, microRNAs (miRNAs). These miRNAs, termed exosome-shuttle miRNAs, are believed to constitute both a means of intercellular communication for post-transcriptional regulation as well as a mechanism for disposing off unwanted miRNAs. DCs release relatively high levels of exosomes and also interact with free exosomes present in the extracellular space [7, 8]. Therefore, DCs have come to be recognized as good models for the analysis of exosome-shuttle miRNAs and their horizontal propagation between cells [9, 10].

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This study aimed to identify the miRNAs that are differentially expressed in the exosomes between mature and immature states of DCs, all protein targets, i.e., the targetome of such miRNAs, and to assign enrichments to the targets of these miRNAs in terms of functions and networks.

2. Methods

2.1. Data sources and groups

Gene Expression Omnibus (GEO) is a database repository of high-throughput gene expression data, hybridization arrays, chips, and microarrays with in-built tools for analysis of the data. The GEO data series GSE33179 [11] was analyzed with GEO2R [12]. For analysis by GEO2R, the mature dendritic cell exosome (mDCEs) group, comprising of datasets GSM821401, GSM821402, GSM821403, and GSM821410, was defined first followed by the immature dendritic cell exosome (iDCEs) group, comprising of datasets GSM821405, GSM821406, GSM821407, and GSM821411, as per GEO2R convention [12]. All analysis settings were initially kept at their default configuration.

2.2. Identification of differentially expressed miRNAs

Boxplot analysis of the selected datasets was performed to view the distribution of values within datasets and check cross-comparability. Subsequently, forced normalization and log-transformation were invoked for improving the cross-comparability of the mDCEs and iDCEs groups, and the GEO2R analysis was repeated without multiple-testing corrections.

2.3. Analysis of targets, interactions, and functions

All miRNA sequences showing significant ($p \leq 0.01$) changes in expression between the mDCEs and iDCEs groups in the GEO2R output were selected for downstream targetome analysis. The

miRNA sequences with missing nomenclature were queried in miRBase [13, 14]. The mapping of interactions and targets was performed separately for the up-regulated and for the down-regulated miRNAs using miRNet [15]; the targets were queried against the miRTarBase v8.0 [16]. Further, the interaction networks of the targets were mapped and functional enrichments ascribed using StringDB v11.5 [17]. Finally, the interaction networks generated with StringDB were visualized in Cytoscape v3.8.2 [18].

3. Results

Boxplot analysis of the data series revealed that the values in the datasets GSM821410 and GSM821411 were not cross-comparable with other dataset values. This was corrected when forced normalization and log-transformation were applied (Figure 1). In all, the expression levels of forty-three miRNAs were found to be significantly ($p \leq 0.01$) altered. Of these forty-three miRNAs, nineteen miRNAs were down-regulated and twenty-four miRNAs were up-regulated (Figure 2, Supplementary File 1) in mDCEs over iDCEs.

The miRNAs down-regulated in mDCEs showing greatest fold-changes were mmu-miR-1249-3p, mmu-miR-805, and mmu-miR-467f. The miRNAs up-regulated in mDCEs showing greatest fold-changes were mmu-miR-672, mmu-miR-335-3p, and mmu-miR-124.

As shown in Figure 3 (Supplementary File 1), the highest number of targets was ascribed to mmu-mir-9-5p, followed by mmu-mir-124-3p and mmu-mir-34b-5p among the up-regulated miRNAs. 930013L23Rik, ankrd28, arrdc3, bcl6, bloc1s3, cd93, cenpl, cercam, cnnm3, ctdsp2, ctsa, cxcl12, dnase2a, dupl11, epb4.2, fam118a, foxp1, fycol, klhl21, mapre1, myo10, phc3, pofut1, prex2, rab11p, rgs17, rmtl1, sco1, sema4b, sgk3, shisa7, slc14a2, slc35e2, smco1, snx27, tbc1d2, trmt10a, vcl, wipf2, ywhag, zfp317, zfp446, and zfp704 were the most promiscuous targets of the up-regulated miRNAs. Among the down-regulated miRNAs, the highest number of targets was ascribed to mmu-mir-466f-3p, followed by mmu-mir-467f. For the down-regulated miRNAs, adams9, ap1g1, fam160b2, neu3, pappa, pgm211, and zfand2a were the most promiscuous targets.

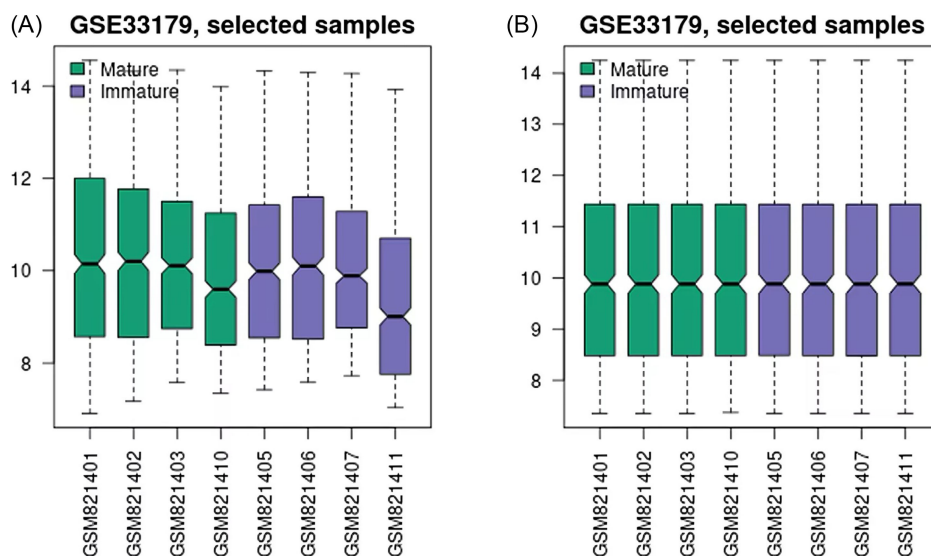


Figure 1. Boxplot analysis of the datasets. (A) Boxplot analysis of the datasets GSM821401, GSM821402, GSM821403, and GSM821410 (green) and GSM821405, GSM821406, GSM821407, and GSM821411 (blue) showed that the datasets GSM821410 and GSM821411 were not cross-comparable with other dataset values. (B) This was corrected when forced normalization and log-transformation were applied.

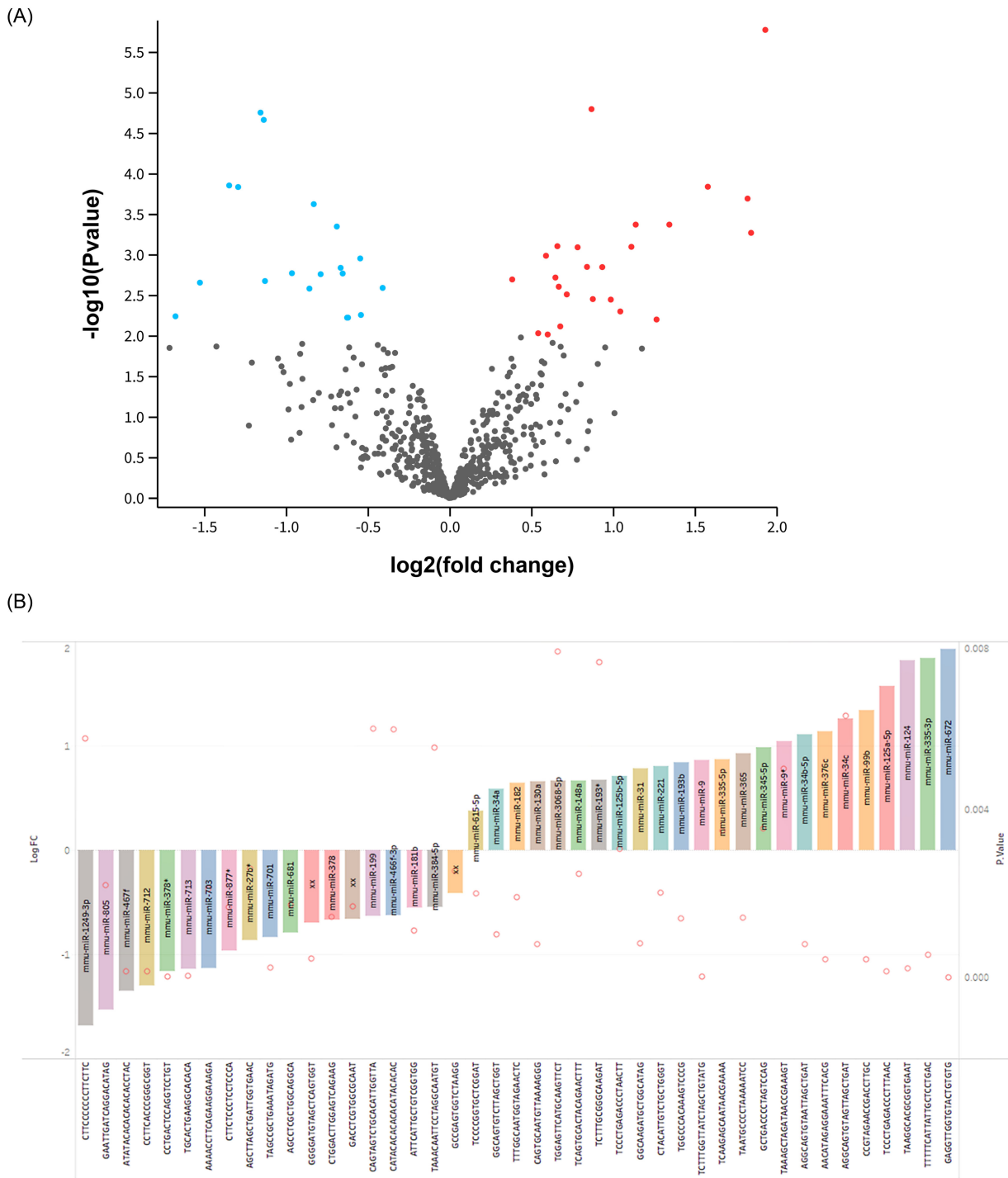


Figure 2. Shuttle miRNAs differentially expressed in exosomes of mature DC origin over exosomes of immature DC origin. (A) Volcano plot from the GEO2R showing 43 differentially expressed miRNAs, of which 24 miRNAs were up-regulated (red dots) and 19 miRNAs were down-regulated (blue dots). (B) The sequences, nomenclature, and log fold-changes (bars) of the 43 differentially expressed miRNAs have been shown; 03 of the down-regulated miRNAs (X, Y, Z) could not be assigned nomenclature.

StringDB was able to map the interactions for 1546 of the 1949 unique targets of the miRNAs up-regulated in mDCEs. The network is shown in Figure 4 and the particulars of the interaction network are given in Table 1. Similarly, StringDB mapped the interactions for only 625 of the 1186 unique targets of the miRNAs down-regulated in mDCEs (Figure 4, Table 1, Supplementary File 1).

The pathways enriched in the interaction networks of the targets of the up-regulated and down-regulated shuttle miRNAs are shown

in Figure 5 (Supplementary File 1). Mapk14 and casp3 were found to be the central nodes of the two networks, respectively.

4. Discussion

The pioneering study on murine DC exosome-shuttle miRNAs by Montecalvo et al. [6] forms an important part of our understanding of the transfer of functional miRNAs between DCs via exosomes.

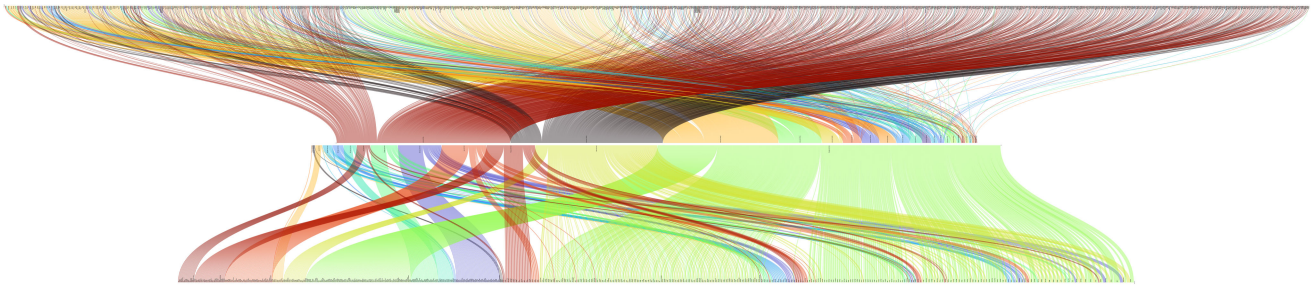


Figure 3. Targets of the shuttle miRNAs differentially expressed in exosomes of mature DC origin over exosomes of immature DC origin. The targets of the up-regulated miRNAs (upper half) and down-regulated miRNAs (lower half) determined by miRTarBase have been shown; the weights of the edges represent the strength of the evidence for the interaction.

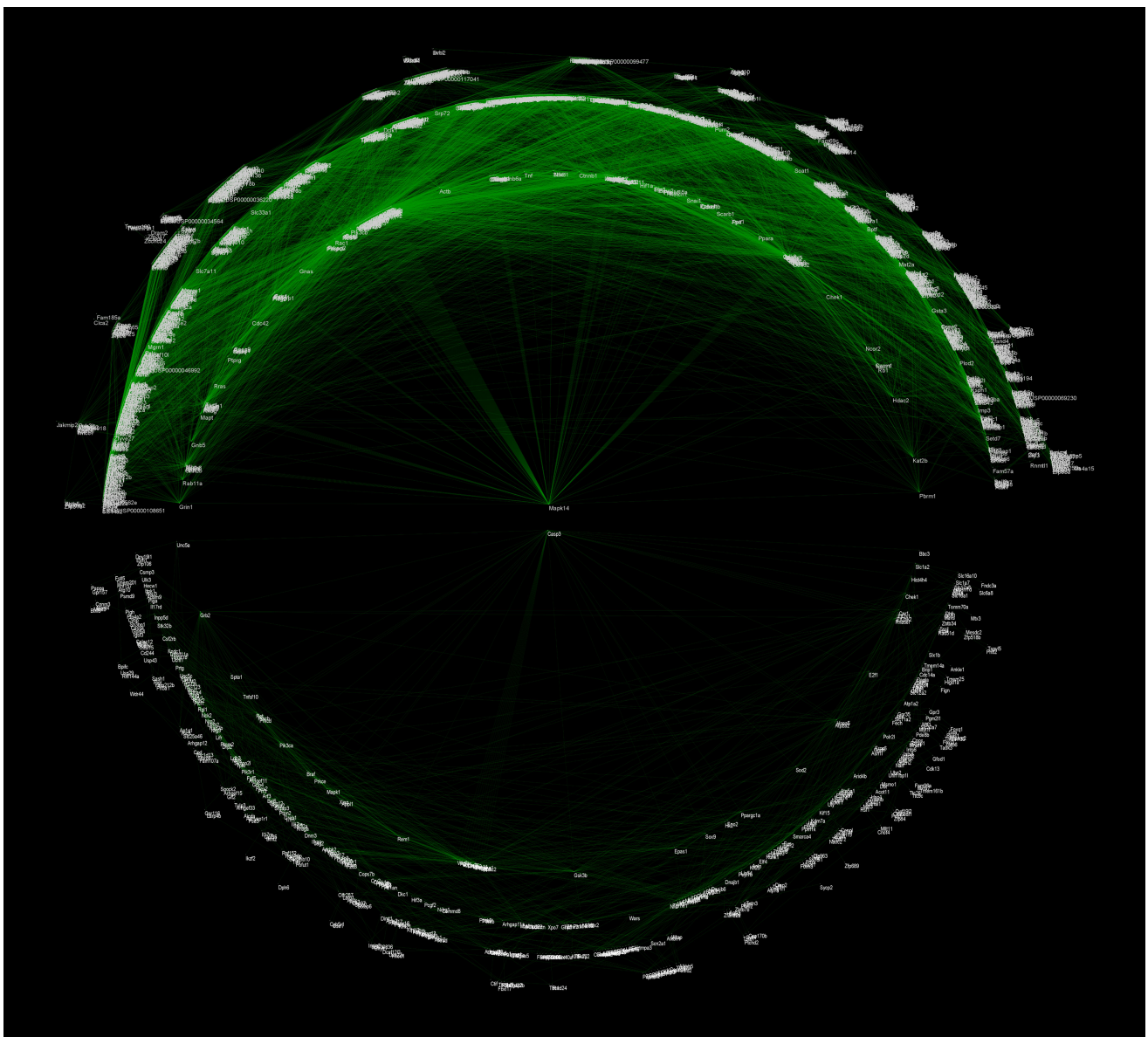


Figure 4. Interaction network of the targets of the shuttle miRNAs differentially expressed in exosomes of mature DC origin over exosomes of immature DC origin. The mutual interactions of targets of the up-regulated miRNAs have been shown in the upper half, and those of the down-regulated miRNAs have been shown in the lower half. The interactions were predicted by STRING and visualized in Cytoscape.

Table 1. Network statistics of the interactions of targets of up-regulated and down-regulated shuttle miRNAs

	Network of targets of up-regulated miRNAs	Network of targets of down-regulated miRNAs
Number of nodes	1536	619
Number of edges	11822	1353
Average node degree	15.4	4.37
Avg. local clustering coefficient	0.278	0.324
Expected number of edges	9171	1135
Enrichment P-Value	<1.0e-16	1.94E-10

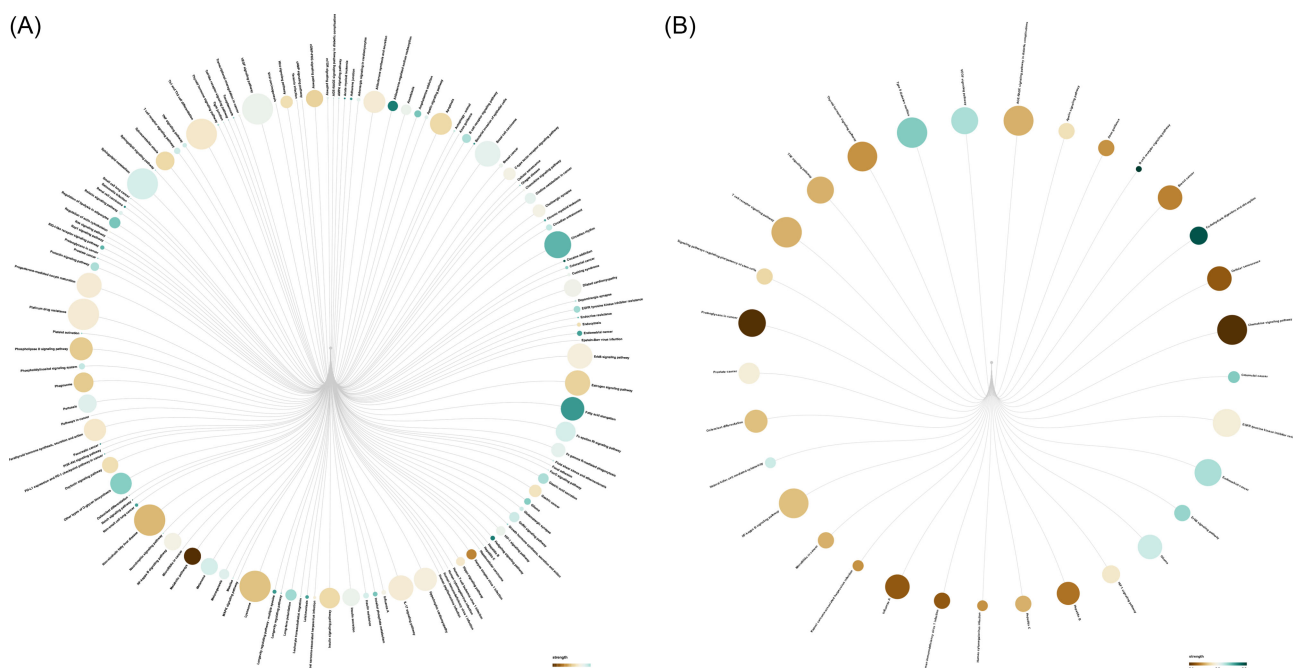


Figure 5. Functional pathways enriched in the interactions of the targets of the differentially expressed shuttle miRNAs. Peacock plot of KEGG pathways involved in (A) the interactions of targets of the up-regulated miRNAs and (B) the down-regulated miRNAs was determined by STRING. The color represents the strength of the enrichment, and the size of the nodes represents the false-discovery rate from the network involved in a pathway.

However, this study focused primarily on the mechanistics of transfer of the shuttle miRNAs. In the present communication, the data of Montecalvo et al. [6] were re-analyzed with particular emphasis on the differential and functional profiling of mature versus iDC exosome-shuttle miRNAs. Specifically, the miRNAs that were dysregulated (up-regulated or down-regulated) in mDC exosomes compared to iDC exosomes were identified along with their targets, which were further enriched functionally.

mmu-miR-672, mmu-miR-335-3p, and mmu-miR-124 showed greatest fold-changes among the 24 miRNAs that were found up-regulated in mDCEs over iDCEs. Interestingly, phb2, one of the major targets of mmu-miR-672 [19], cooperates with CD86 to mediate CD86-signaling in B cells that regulates the level of IgG1 produced through the activation of distal signaling intermediates. Further, upon CD40 engagement, phb2 is required to activate NF-κB signaling pathway via phospholipase C and protein kinase C activation [20]. Remodeling of the actin cytoskeleton is required in mDCs to meet maturation-associated changes such as down-regulation of endocytosis, increased migratory behavior, and prime T cells [21]. Enah, a major target of mmu-miR-335-3p, encourages the formation of F-actin-rich outgrowths and acts synergistically with

BAIAP2-alpha and downstream of NTN1 to support filipodia formation [22]. Complementing their role as APCs, DCs are also crucial efferocytes, and activation of efferocytic function is usually maturation-agonistic [23]. Based on the above evidence, it is also hypothesized that the targeting of Enah by mmu-miR-335-3p may underlie the mechanisms by which the phago-endocytic functions of DCs as efferocytes and the maturation functions of DCs as APCs are linked.

Among others, mmu-miR124 targets CD55b, which is known to be essential for tolerogenic DC responses [24]. Among the up-regulated miRNAs, the maximum number of targets was assigned to mmu-mir-9-5p; miR-9-5p has been shown to activate NF-κB in microglial cells and to promote the production of proinflammatory cytokines by targeting MCP1 [25]. Notably, and true to the observations of Montecalvo et al. [6], mmu-miR-155 was not found to be significantly up-regulated.

Among the miRNAs down-regulated in mDCEs showing greatest fold-changes, mmu-miR-1249-3p is recognized as a pro-differentiation miRNA [26]; it is apparent that mDCs would not require such modulators. Similar to the findings of this study, Pang et al. [27] also reported lower levels of mmu-miR-805 in

exosomes from bone marrow-derived mDCs as compared to those from iDCs. The maximum number of targets was ascribed to mmu-mir-466f-3p. Intriguingly, although low levels of mmu-mir-466f-3p have been associated with the maintenance of a mesenchymal state [28], its low levels have also been recorded upon exposure to pathogens [29] and antigens [30]. Among the down-regulated miRNAs, mmu-mir-467f showed third highest fold-change besides having the second greatest number of targets assigned to it. Importantly, low levels of mmu-miR-467f may be a signature of proliferating T-helper cells [31].

The most promiscuous targets of the up-regulated miRNAs revealed an over-representation of RNA polymerase II transcription and rho GTPase signaling reactomes and of the Slit/Robo pathway. The activation of the Slit/Robo pathway has previously been implicated in inhibition of DC migration [32]. It can be reasoned that the Slit/Robo pathway is repressed by miRNAs in mDCs to allow migratory behavior. The glycogenolysis and galactose catabolism reactomes were over-represented among the most promiscuous targets of the down-regulated miRNAs; achieving continuing glycogenolysis through the down-regulation of repressor miRNAs may be critical for mDC functioning [33] and glucose being inhibitory to DC functions [34], and energy metabolism in DCs may shift to galactose given the down-regulation of repressor miRNAs. Conversely, it may be stated that the tolerogenic state of iDCs is maintained under the repression of glycogenolysis and galactose catabolism by miRNAs. Lately, cross-talks, with possibilities for therapeutic intercepting, between the Slit/Robo pathway, glucose metabolism, and DC recruitment have also been established lately in certain cancers [35].

The top pathways enriched in the networks of the up-regulated miRNAs included pathways in cancer, miRNAs in cancer, (human) papillomavirus infection, Salmonella infection, Epstein-Barr virus infection, proteoglycans in cancer, MAPK signaling pathway, focal adhesion, Rap1 signaling pathway, and cellular senescence; in all 131 such pathways were identified. Similarly, 32 pathways were found enriched in the interactions of the targets of the down-regulated miRNAs, of which the topmost pathways were B cell receptor signaling pathway, (human) cytomegalovirus infection, natural killer cell-mediated cytotoxicity, Kaposi sarcoma-associated herpesvirus infection, colorectal cancer, ErbB signaling pathway, axon guidance, apelin signaling pathway, signaling pathways regulating pluripotency of stem cells, and hepatitis C pathway. 28 pathways viz. AGE-RAGE signaling pathway in diabetic complications, apelin signaling pathway, axon guidance, B cell receptor signaling pathway, breast cancer, cellular senescence, chemokine signaling pathway, colorectal cancer, EGFR tyrosine kinase inhibitor resistance, endometrial cancer, ErbB signaling pathway, glioma, hepatitis B, hepatitis C, HIF-1 signaling pathway, (human) cytomegalovirus infection, (human) immunodeficiency virus 1 infection, influenza A, Kaposi sarcoma-associated herpesvirus infection, miRNAs in cancer, NF-kappa B signaling pathway, osteoclast differentiation, prostate cancer, proteoglycans in cancer, T cell receptor signaling pathway, thyroid hormone signaling pathway, TNF signaling pathway, and VEGF signaling pathway were common to the networks of the targets of both up-regulated and down-regulated shuttle miRNAs. Mapk14 was found to be the central node in the network of targets of the up-regulated miRNAs. Mapk14, an important component of two dominant pathways involved in DC maturation viz. TLR signaling and the leukocyte transendothelial migration have been shown to be down-regulated by at least two-folds at both the RNA and protein level [36]. Casp3 was found to be the central node in the network of targets of the down-regulated

miRNAs. Casp3, reported to be induced in maturing DCs, may be a signature of mDCs [37], and its overexpression has been found to promote DC maturation and T cell activation [38].

5. Conclusion

This study identified a number of shuttle miRNAs, and their targets, which are differentially expressed in the exosomes of DCs in a maturation-dependent manner. Besides forming signatures of DC maturation state, these differentially expressed exosome-shuttle miRNAs and their targets may serve as important therapeutic candidates for various immune dysfunctions.

Acknowledgement

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Ethical Statement

This study does not contain any studies with human or animal subjects performed by the author.

Conflicts of Interest

The author declares that he has no conflicts of interest to this work.

Data Availability Statement

The data that support the findings of this study are openly available in data series GSE33179 of Gene Expression Omnibus, comprising datasets GSM821401, GSM821402, GSM821403, GSM821410, GSM821405, GSM821406, GSM821407, and GSM821411 at <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE33179>.

Author Contribution

Bhaskar Ganguly: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization.

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