Editorial Commentary

Exosomal miR-34a: the code for adipocyte-macrophage communication

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Comment on: Pan Y, Hui X, Hoo RLC, *et al.* Adipocyte-secreted exosomal microRNA-34a inhibits M2 macrophage polarization to promote obesity-induced adipose inflammation. J Clin Invest 2019;129:834-49.

Received: 08 May 2019; Accepted: 28 May 2019; published: 06 June 2019.

doi: 10.21037/ncri.2019.05.04

View this article at: http://dx.doi.org/10.21037/ncri.2019.05.04

The study "*Adipocyte-secreted exosomal microRNA-34a inhibits M2 macrophage polarization to promote obesity-induced adipose inflammation*", presented by Pan *et al.* and published in *J Clin Invest*, has been read by us with great interest (1). In this study, the authors uncovered adipocyte-secreted exosomes as a potentially novel mediator of obesity-induced adipose inflammation, acting by transporting miR-34a into the adjacent macrophages, where it drives the polarization program toward proinflammatory M1 phenotype by targeting the transcription factor KLF4. Indeed, this study provided a new question for obesity-induced systemic inflammation and metabolic dysregulation, but in terms of the molecular mechanism of miR-34a on M1/M2 polarization, there still are something to clarify and need for more investigation.

Traditionally, the IRF/STAT signaling regulates either M1 or M2 polarization in macrophages (2). TLR ligands and IFN-γ stimulate STAT1 to activate IRF/STAT-mediated M1 responses, while IL-4/IL-10 stimulate STAT6/KLF4 to induce IRF/STAT-mediated M2 responses (3,4). Given that miRNAs may target various transcription factors and adaptor proteins involved in IRF/STAT pathways, it is possible that these miRNAs could regulate either M1 or M2 polarization in macrophages. MiR-34a is one of the most highly studied miRNAs in mammalian cells due to its role in the pathophysiology of conditions such as solid tumors, cardiac injury and inflammation (5-7). However, there are contrasting views on the role of miR-34a in mediating macrophage polarization.

In a recent study performed by Jiang *et al.* (8), miR-34a blocked pro-inflammatory responses in LPS-stimulated macrophages. They observed that MiR-34a levels were downregulated in LPS-treated RAW 264.7 macrophages, but transfection of miR-34a mimics diminished pro-inflammatory responses, evidenced by lower levels of M1 cytokines TNF-α and IL-6 (8). These data suggest that miR-34a acts as an endogenous brake to block LPS-mediated generation of M1 macrophages. Mechanistically, miR-34a targeted Notch1, which is needed for LPS-mediated production of pro-inflammatory cytokines in macrophages (8), and thereby inhibited M1 polarization in macrophages.

In contract to the finding by Cheng *et al.* (9), Weng *et al.* (5) reported that miR-34a promoted M1 polarization and inhibited M2 polarization. miR-34a expression was tremendously increased in LPS-induced pulmonary macrophages and LPS-induced U937 cells (9). miR-34a silence inhibited iNOS secretion from pulmonary macrophages. Furthermore, in pre-miR-34a-treated macrophages, expression levels of M1 markers (CD86) were higher while M2 markers (CD163, CD206) were decreased remarkably compared to levels in scramble-miR Oligonucleotides-treated macrophages (and vice versa) (5). Mechanistically, miR-34a promotes iNOS secretion from LPS-induced pulmonary macrophages through activating STAT3 pathway and thereby, promoted M1 polarization in

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macrophages (9). In this study, Pan et al also demonstrated that adipose-specific ablation of miR-34a significantly decreased the mRNA expression of M1 macrophage-related genes (Tnfa, Il6, Il1b, iNos, and Mcp1) but significant upregulation of M2 macrophage-related genes (Fizz1, Ym1, Arg1, and Il10) in male and female mice on HFD (1). Mechanistically, Pan *et al.* adopted mirSVR/PhastCons analysis and a variety of methods to verify that Klf4 is crucial for maintaining adipose M2 macrophage phenotype in miR-34a-KO mice.

At this moment, the reasons behind the conflicting effects of miR-34a on macrophage polarization remain unclear. So, the differences between studies described above should be discussed in the discussion section of this study. Besides, to explore the mechanism by which adipocyte-secreted exosomal miR-34a induced M1 polarization, the effect of miR-34a on M1 polarization should be further determined. First, combined with or without IL-4 or LPS stimulation, miR-34a was overexpressed or knocked out at the level of primary macrophages or cell lines, and M1/M2 macrophage-related genes expression were detected. Then, it's also important to assess the level of miR-34a in macrophage after the dynamic process of M1-to-M2 re-polarization or M2-to-M1 re-polarization.

Accumulating evidence has shown that macrophage programming and phenotypic switch is regulated by different signal molecules, cytokines, and inflammatory factors.

Moreover, miR-34a can target multiple molecules to regulate M1/M2 polarization phenotype of macrophages (8,9). Therefore, if possible, RNA-seq should be used to find out the miR-34a target genes in order to clarify the inhibition effect of adipocyte-secreted exosomal microRNA-34a on M2 macrophage polarization.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Dr. Yuan Xie (Shanghai Tongji Hospital, Shanghai, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ncri.2019.05.04). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Pan Y, Hui X, Hoo RLC, et al. Adipocyte-secreted exosomal microRNA-34a inhibits M2 macrophage polarization to promote obesity-induced adipose inflammation. J Clin Invest 2019;129:834-49.
2. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. J Clin Invest 2012;122:787-95.
3. Kapoor N, Niu J, Saad Y, et al. Transcription factors STAT6 and KLF4 implement macrophage polarization via the dual catalytic powers of MCPIP. J Immunol 2015;194:6011-23.
4. Wang N, Liang H, Zen K. Molecular mechanisms that influence the macrophage m1-m2 polarization balance. Front Immunol 2014;5:614.
5. Weng YS, Tseng HY, Chen YA, et al. MCT-1/miR-34a/IL-6/IL-6R signaling axis promotes EMT progression, cancer stemness and M2 macrophage polarization in triple-negative breast cancer. Mol Cancer 2019;18:42.
6. Boon RA, Iekushi K, Lechner S, et al. MicroRNA-34a regulates cardiac ageing and function. Nature 2013;495:107-10.
7. McCubbrey AL, Nelson JD, Stolberg VR, et al. MicroRNA-34a Negatively Regulates Efferocytosis by Tissue Macrophages in Part via SIRT1. J Immunol 2016;196:1366-75.
8. Jiang P, Liu R, Zheng Y, et al. MiR-34a inhibits lipopolysaccharide-induced inflammatory response

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through targeting Notch1 in murine macrophages. Exp Cell Res 2012;318:1175-84.
9. Cheng DL, Fang HX, Liang Y, et al. MicroRNA-34a promotes iNOS secretion from pulmonary macrophages in septic suckling rats through activating STAT3 pathway. Biomed Pharmacother 2018;105:1276-82.

doi: 10.21037/ncri.2019.05.04
Cite this article as: Han X, Zhang Y. Exosomal miR-34a: the code for adipocyte-macrophage communication. Non-coding RNA Investig 2019;3:22.

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