MEFV/miR-326 axis involvement in human macrophage polarization

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Background and objectives: Familial Mediterranean fever (FMF) is an inherited autoinflammatory disease, characterized by acute self-resolving attacks of fever and serositis, which mainly prevails in populations around the Mediterranean sea. It is caused by mutations in the MEFV gene, which encodes the pyrin protein. The alteration of MEFV mRNA expression in monocytes is related to both genotype and phenotype of the disease, suggesting that the pathophysiology of FMF can be regulated on a quantitative defect of MEFV mRNA. Since microRNAs (miRNAs) are implicated in a number of diseases including FMF, the present study aimed at identifying miRNA regulators of MEFV expression involved in monocyte inflammatory response.
Materials and Methods: miRWalk2.0 database was used to identify putative miRNA target sequences within the 3'-UTR mRNA of MEFV. Human primary CD14+ monocytes were sorted from peripheral blood of healthy donors using magnetic microbeads and differentiated into M1 or M2 macrophages following IFNγ/LPS or IL4/IL13 stimulation, respectively. Using RT-qPCR, M1/M2 polarization was validated by measuring the expression of prototypic M1 and M2 markers: the chemokine CXCL10 and the macrophage mannose receptor 1 (MRC1 also known as CD206), respectively, as well as the MEFV mRNA. We used loss-of-function method to evaluate the effect of candidate miRNA on CD14+ monocytes, i.e. its role on macrophages classical versus alternative polarization. IL-10 expression was quantified using ELISA.
Results: In silico analyses revealed that miR-326 targets putatively the 3'UTR mRNA of MEFV. miRNAs and mRNAs quantification in polarized macrophages showed that miR-326 is mainly expressed by the M2-type macrophages, and MEFV by the M1-type macrophages. Loss-of-function studies showed that neutralization of miR-326 in M2 macrophages induced the expression of MEFV and CXCL10 while reducing MRC1 expression level. Furthermore, enforced expression of miR-326 in M1 macrophages significantly repressed MEFV expression and induced the production of IL-10.
Conclusion: A miR-326/MEFV axis seems to be implicated in macrophage polarization and might explain the observed monocyte versatility in FMF.

Keywords :
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References : , , ,

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