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RESEARCH ARTICLE

From data to hypothesis: Exploring monocyte immunometabolism by principal component analysis of multiparametric flow cytometry

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Objective: Principal component analysis is a powerful dimensionality reduction tool that can uncover hidden patterns in complex biological data. In cellular immunology research, principal component analysis may help identify meaningful relationships between various biomarkers. This study aims to investigate the applicability of principal component analysis for exploring immunometabolic cellular pathways and behaviors in the context of human peripheral blood monocytes.

Methods: This methodological case study analyzed data from 19 healthy young individuals, including body mass index, fasting lipid profiles, and multiparametric flow cytometry of monocyte subsets. Monocytes were classified as classical, intermediate, or nonclassical based on CD14/CD16 expression, and surface markers, cell size, granularity, and intracellular lipid content were assessed. Principal component analysis was performed to explore clusters of correlated parameters and their possible biological significance.

Results: In classical and intermediate monocytes, principal component analysis revealed consistent patterns linking decreased CD14 expression with increased cell size, granularity, and lipid accumulation, reflecting known monocyte maturation processes from CD16– to CD16+. An inverse relationship between body mass index and LDL receptor expression was consistently observed, suggesting metabolic influences on monocyte phenotype. Strong positive loadings for CD11b and CD36 further indicated a link between immune activation and lipid uptake pathways.

Conclusions: This methodological case study demonstrates that principal component analysis can reveal biologically plausible clusters in multiparametric flow cytometry data, offering new perspectives on immunometabolic interactions. While the small sample size limits generalizability, the findings highlight the potential of principal component analysis for hypothesis generation and pathway discovery in immune cell research.

Keywords: body mass index, LDLR, monocyte, multiparametric flow cytometry, principal component analysis

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Introduction

Monocytes are a central link between metabolism and inflammation, playing critical roles in health and disease. Their ability to take up and process lipids makes them key contributors to metabolic conditions such as atherosclerosis [1-4]. Understanding how factors like body mass index (BMI) and plasma lipids shape monocyte phenotype is essential but often limited by the complexity of the data generated.

Principal component analysis (PCA) is a useful tool for exploring relationships within large, multiparametric datasets. Applied thoughtfully, PCA can help identify clusters of variables that may reflect underlying biological processes. As a disclaimer, we emphasize that this is a methodological case study using PCA to explore potential immunometabolic patterns in monocytes. Rather than presenting definitive interpretations, this study aims to illustrate how dimensionality reduction can generate hypotheses and offer insight into complex cell–environment interactions.

Methods

This study was approved by the Ethics Committee of the George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș (Approval No. 3217/10.06.2024). All procedures and investigations were conducted at the University's Center for Advanced Medical and Pharmaceutical Research (CCAMF) in Târgu Mureș, Romania.

The study was conducted using data collected from 19 healthy young individuals, including a lipid profile and *ex vivo* analysis of fasting blood samples. The technical details of cell processing are not particularly relevant here, as this is intended as a case study demonstrating how data generated from such an experiment can be interpreted.

During the experiment, BMI was calculated for each participant. Data from the fasting samples included a standard lipid profile and mean fluorescence intensity (MFI) values obtained by flow cytometry. In the flow cytometry analysis, monocytes were classified into three subsets based on CD14/CD16 expression: classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and

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nonclassical ($CD14^{+}CD16^{++}$). The following parameters were analyzed for these monocyte populations: forward scatter (FSC – cell size), side scatter (SSC – cellular granularity/complexity); expression of surface markers CD14, CD16, CD11b, CD36, and LDLR; and fluorescence of the neutral lipid dye BODIPY, which indicates intracellular lipid accumulation.

Statistical analysis included PCA of the flow cytometry markers and relevant plasma lipids. Several PCA models were tested, and the best-fitting model was selected based on the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity. A KMO value below 0.500 and/or a Bartlett's p-value greater than 0.05 were considered evidence that the model was unsuitable for PCA. For PCA, components with Eigenvalues greater than 1 were extracted, and Varimax rotation with Kaiser normalization was applied. The maximum number of iterations for convergence was set at 25. Coefficients were sorted by size, and those below 0.400 were considered weak and were suppressed. All PCA analyses were performed using IBM SPSS Statistics version 20.0.0.

The results of the PCA were interpreted as follows: each component was regarded as a cluster of biological parameters with potential biological meaning, serving as a possible reflection of cellular mechanisms and illustrating how cells interact with plasma lipids. Based on the known biology of monocytes, we aimed to provide a rationale for how the parameters were grouped in the PCA.

Results

The chosen model for classical monocytes is shown in Figure 1 and includes BMI, total cholesterol concentration, and all monocyte markers except for CD16, which is not a defining marker of classical monocytes. An identical model was used for the intermediate monocytes (Figure 2). Due to statistical limitations, the nonclassical monocyte subset was not analyzed, as the data for this subset did not meet the assumptions required for PCA (KMO < 0.500 and/or Bartlett's $p > 0.05$ for all tested models).

Discussions

Immunometabolic framing of the experiment

The fasting state, on which this study was based, is widely regarded as the standard in clinical practice for laboratory investigations. Interindividual variability is minimized in the fasting state, which is why most research involving metabolic and immunological parameters relies on fasting samples.

BMI has been shown to be associated not only with plasma lipid levels but also with levels of proinflammatory cytokines and with the number and phenotype of peripheral immune cells, including monocytes [5-13].

Total Variance Explained[a]

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	3.132	34.800	34.800	3.132	34.800	34.800	2.430	26.998	26.998
2	1.975	21.944	56.744	1.975	21.944	56.744	2.064	22.930	49.928
3	1.227	13.634	70.379	1.227	13.634	70.379	1.652	18.353	68.281
4	1.144	12.706	83.085	1.144	12.706	83.085	1.332	14.804	83.085
5	.545	6.054	89.139						
6	.440	4.892	94.031						
7	.223	2.478	96.509						
8	.188	2.091	98.600						
9	.126	1.400	100.000						

Extraction Method: Principal Component Analysis.

a. Only cases for which Population = 1 are used in the analysis phase.

KMO and Bartlett's Test[a]

Kaiser-Meyer-Olkin Measure of Sampling Adequacy.		.657
Bartlett's Test of Sphericity	Approx. Chi-Square	63.874
	df	36
	Sig.	.003

a. Only cases for which Population = 1 are used in the analysis phase.

Rotated Component Matrix[a,b]

	Component			
	1	2	3	4
FSC	.908			
SSC	.883			
CD14	-.827			
BMI		.917		
LDLR		-.862		
CD36			.868	
CD11b			.794	
BODIPY				-.813
TC		.432		.684

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

a. Rotation converged in 5 iterations.

b. Only cases for which Population = 1 are used in the analysis phase.

Fig. 1. Principal component analysis of classical monocytes (exported from SPSS 20.0.0)

Total Variance Explained[a]

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	3.140	34.893	34.893	3.140	34.893	34.893	2.969	32.988	32.988
2	2.503	27.806	62.698	2.503	27.806	62.698	2.221	24.682	57.670
3	1.271	14.117	76.815	1.271	14.117	76.815	1.723	19.145	76.815
4	.792	8.797	85.612						
5	.466	5.173	90.785						
6	.361	4.016	94.800						
7	.236	2.625	97.425						
8	.145	1.616	99.041						
9	.086	.959	100.000						

Extraction Method: Principal Component Analysis.

a. Only cases for which Population = 2 are used in the analysis phase.

KMO and Bartlett's Test[a]

Kaiser-Meyer-Olkin Measure of Sampling Adequacy.		.525
Bartlett's Test of Sphericity	Approx. Chi-Square	78.424
	df	36
	Sig.	.000

a. Only cases for which Population = 2 are used in the analysis phase.

Rotated Component Matrix[a,b]

	Component		
	1	2	3
SSC	.904		
FSC	.872		
CD14	-.790		
TC	-.567		
BMI		.809	
BODIPY	.428	.803	
LDLR		-.787	
CD36			.905
CD11b			.802

Extraction Method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization.

a. Rotation converged in 5 iterations.

b. Only cases for which Population = 2 are used in the analysis phase.

Fig. 2. Principal component analysis of intermediate monocytes (exported from SPSS 20.0.0)

Regarding plasma lipids, it is well established that lipoproteins can influence immune cell activation, particularly monocytes [1,14-20]. These cells are capable of taking up LDL through the "physiological" LDL receptor (LDLR) and can also internalize oxidized lipids such as oxLDL via scavenger receptors like CD36 [21-23]. Moreover, monocytes play a central role in the development of atherosclerotic plaques — a process in which they ingest lipids and differentiate into macrophages known as "foamy cells" [1,15,17,24].

It should also be noted that monocyte subsets differ in how they process and respond to lipids. While all subsets can uptake lipids, they vary in their capacity for metabolization and in how their phenotype changes in response to lipid internalization. Briefly, classical monocytes are known as efficient phagocytes, capable of ingesting large quantities of material [2,4]. Intermediate monocytes represent the most inflammatory subset [2,4] and have been linked to coronary artery disease — including plaque burden, plaque instability, and adverse cardiovascular events [25-28]. Nonclassical monocytes function as patrolling sentinels and are thought to have reparative potential [2,4].

Taken together, these serve as a brief justification for the inclusion of BMI, plasma lipids, and monocyte parameters in the PCA.

PCA of classical monocytes

Principal component analysis (PCA) of classical monocytes identified four principal components (PCs) that together explain 83% of the total variance in the data.

PC1 (27%) consists of positive loadings for forward scatter (FSC) and side scatter (SSC) and a negative loading for CD14. This suggests that larger and more granular monocytes tend to have lower CD14 expression. Put another way, as CD14 expression decreases, cell size and granularity increase. The decrease in CD14 may reflect monocyte "maturation", a known process whereby monocytes, which are released from the bone marrow entirely in the classical form, undergo phenotypic shifts toward CD16+ monocytes as they circulate [2]. This transition is characterized by decreasing CD14 expression, particularly evident during the shift from intermediate (CD14++CD16+) to nonclassical (CD14+CD16++) subsets [2]. Thus, PC1 may reflect that the longer monocytes remain in circulation, the more they progress towards CD16+ phenotypes, changing their surface marker expression and increasing in size and granularity — possibly due to lipid accumulation.

PC2 (23%) shows positive loadings for BMI and total cholesterol and a negative loading for LDLR. The relationship between these variables is intuitive: higher BMI is associated with higher total cholesterol and lower LDLR

expression. A well-established link exists between BMI and elevated cholesterol and other plasma lipid levels [5-8,10,12]. Additionally, a cholesterol-rich environment promotes increased LDL uptake by classical monocytes, resulting in receptor internalization and thus decreased surface LDLR expression [21,29]. Also, lipid uptake can prompt monocytes to differentiate into macrophages, a process during which LDLR expression is typically downregulated while CD36 is upregulated [30]. Moreover, reduced LDLR expression and diminished LDL uptake have been linked to increased BMI [29]. Therefore, PC2 may highlight how metabolic disturbances (reflected by elevated BMI) can drive higher cholesterol levels, which in turn modulate the classical monocyte phenotype. This likely represents a physiological mechanism governed by ligand–receptor interactions and receptor internalization dynamics, but it may also hint at dysfunctional lipid uptake pathways that can emerge in monocytes under obese conditions.

PC3 (18%) shows positive loadings for CD11b and CD36. Given that both markers are immunometabolic, this combination suggests interconnected pathways that link immune activation (CD11b — an integrin involved in adhesion, migration, and phagocytosis) with lipid scavenging and uptake (CD36) [23,31]. This is consistent with literature showing that lipid-rich environments activate monocytes and that lipid uptake itself can promote monocyte activation [1,14-18]. Unlike LDLR, which is downregulated through ligand-mediated internalization [21,29], CD36 expression can increase in response to lipid-rich conditions, further supporting the concept that atherogenic lipoproteins such as oxLDL enhance monocyte activation [23,30,32].

PC4 (15%) shows a positive loading for total cholesterol and a negative loading for BODIPY. This suggests two possible scenarios with diametrically opposed interpretations. In the first scenario, lower plasma cholesterol is associated with higher neutral lipid content within classical monocytes. This could reflect increased lipid clearance by monocytes, which results in reduced circulating cholesterol levels — a "physiological" lipid-handling process. Conversely, in the second scenario, higher plasma cholesterol is associated with lower intracellular lipid accumulation. As described for PC2, elevated cholesterol would typically promote lipid uptake and LDLR internalization, reflecting normal lipid processing. However, PC4 may suggest that despite high circulating cholesterol, monocytes fail to internalize and store lipids efficiently. This could be due to alternative physiological pathways or a predisposition of classical monocytes toward maladaptive lipid handling in dyslipidemic states. Monocytes that do not properly process and store lipids may exhibit defective lipid metabolism, a phenomenon relevant to the pathogenesis of atherosclerosis [29]. Overall, PC4 points to two possible mechanisms: one physiological and another potentially pathological.

PCA of intermediate monocytes

PCA of intermediate monocytes revealed a strong PC1, accounting for nearly half of the total variance explained (33% of 77%). PC1 showed positive loadings for FSC, SSC, and BODIPY, and negative loadings for CD14 and total cholesterol. The positive FSC and SSC and negative CD14 loadings resemble those seen in the classical monocyte PC1, suggesting that intermediate PC1 represents a continuation of the same biological pattern. However, intermediate PC1 also includes a positive loading for BODIPY and a negative loading for total cholesterol, effectively the mirror image of classical monocytes' PC4 (where BODIPY loaded negatively and total cholesterol positively). This sign inversion is common in PCA and does not alter the biological interpretation. Thus, intermediate PC1 appears to combine elements of the interpretations from classical PC1 and PC4. In summary, as intermediate monocytes progress toward the nonclassical subset (reflected by the negative CD14 loading — a shift from CD14++ to CD14+), they internalize lipids (positive BODIPY), resulting in increased cell size and granularity (positive FSC and SSC). Consequently, plasma cholesterol decreases (negative total cholesterol). Overall, intermediate PC1 seems to illustrate a continuation of the monocyte maturation trajectory, additionally highlighting a physiological process of cholesterol clearance.

Intermediate PC2 resembles classical PC2, with both showing positive BMI loadings and negative LDLR loadings. Also, both components explain similar portions of variance (23% for classical, 25% for intermediate). Unlike classical PC2, which included a positive cholesterol loading, intermediate PC2 instead shows a positive BODIPY loading. Nevertheless, both PCs appear to reflect physiological processes. Specifically, this pattern suggests that as BMI increases, so does lipid uptake by intermediate monocytes — consistent with obesity-associated dyslipidemia. As a result, LDLR expression decreases due to receptor internalization, a phenomenon also described in classical PC2.

Intermediate PC3 is identical to classical PC3, with strong positive loadings for CD11b and CD36 and a similar proportion of variance explained (18% for classical, 19% for intermediate). The biological relationship between CD11b and CD36, previously discussed, is considered to apply here as well.

PCA – a tool for exploring cellular pathways

PCA is a statistical tool best used for data dimensionality reduction. It analyzes patterns of variation in data and generates groups of parameters that share variance (positive or negative). However, we hypothesized that these groups represent more than just statistical artifacts — that the shared variance may have intrinsic biological meaning within the framework of monocyte biology. By examining each group, we aimed to find plausible explanations

for why certain parameters cluster together and how their positive or negative correlations might be explained by underlying cellular processes.

As expected, the PCA presented in this study revealed several clusters of monocyte parameters whose groupings appear to align with known or plausible biological mechanisms in health and/or disease. Briefly, the first major observation was that as CD14 expression decreases — marking the transition of classical monocytes toward intermediate and then nonclassical subsets — monocytes increase in size and granularity. This change appears to be associated with intracellular lipid accumulation, which in turn seems to contribute to plasma cholesterol clearance, at least within the intermediate subset.

The second key observation was the inverse relationship between BMI and monocyte LDLR expression. Data from both classical and intermediate monocytes suggest that this may be part of a broader pattern in which higher BMI is linked with elevated total cholesterol, leading to greater lipid internalization and increased intracellular lipid content, as shown by BODIPY fluorescence.

Third and finally, a consistent relationship emerged between CD11b — involved in adhesion, migration, and phagocytosis — and CD36, a scavenger receptor responsible for the uptake of oxidized LDL and fatty acids. Their strong positive loadings across both classical and intermediate subsets support the idea of a functional link between monocyte immune activation and lipid uptake via CD36, effectively bridging two major roles of monocytes in an shared immunometabolic context.

Taken together, these findings support the value of PCA as a tool for uncovering clusters of cellular markers that may mirror genuine cellular pathways in health and disease. This is particularly relevant given that, despite extensive research, there is still no available therapy that targets specific key regulators or immune and metabolic pathways at the monocyte level, for preventing or treating immunometabolic diseases such as atherosclerosis. A breakthrough with genuine translational potential remains long overdue in this field, underscoring the importance of tools like PCA in advancing the understanding of complex cellular interactions and ultimately helping translate knowledge into real-world therapies.

Strengths and limitations

This study brings an element of novelty, as it is the first, to our knowledge, to report a consistent inverse relationship between body mass index (BMI) and LDLR expression on monocytes. While this has been discussed in detail elsewhere, it is worth noting here that LDLR expression showed strong negative correlations with BMI across all monocyte subsets (data not shown). In addition, parameters such as FSC, as an indicator of cell size, SSC, as an indicator of cellular granularity, and intracellular lipid content (represented here by BODIPY staining) are not commonly highlighted in studies on monocytes. We consider this noteworthy, as morphological changes are among the earliest detectable signs of cell activation. By incorporating these parameters into our analysis, this work extends the current understanding of monocyte biology in an immunometabolic context.

Nevertheless, this study has several limitations, the most significant being the relatively small number of participants, which limits the statistical power and generalizability of the findings. Additionally, the panel of fluorescent markers was limited, constraining the depth at which the biological significance of the identified clusters could be interpreted. Despite these limitations, we emphasize that this work should be regarded as a methodological case study — an exploration of how principal component analysis can be applied to complex data sets generated by multiparametric flow cytometry. The aim was to test whether this approach could reveal potential new cellular pathways and interactions between cells and their environment, rather than to establish definitive conclusions.

Conclusion

This methodological case study highlights the usefulness of principal component analysis for exploring complex flow cytometry data in the context of monocyte immunometabolism. Despite the small sample size, principal component analysis revealed biologically plausible clusters of parameters that appear to reflect known and potentially novel processes like monocyte maturation, lipid handling, and immunometabolic activation. Notably, we found a consistent inverse relationship between BMI and LDLR expression on monocytes, which to our knowledge has not been described before. While these results need validation in larger studies, they demonstrate how PCA can help generate new hypotheses about cellular pathways and interactions, supporting future research into immune-metabolic diseases such as atherosclerosis.

Authors' contribution

IBM (Conceptualization; Investigation; Methodology; Formal analysis; Project administration; Resources; Writing – review & editing)
DG (Investigation; Data curation; Formal analysis)
ST (Investigation; Data curation; Formal analysis)
AF (Methodology; Formal analysis; Writing – original draft)
LD (Investigation; Data curation; Formal analysis)

Conflict of interest

None to declare.

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