Heliyon 10 (2024) e36218

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Increased circulating LOX-1^{+} neutrophils activate T cells and demonstrate a pro-inflammatory role in allergic rhinitis

Xiao-Hui Deng [a,b], Long-Xin Huang [a,b], Qi- Sun [a,b], Chan-Gu Li [a,b], Ying-Chun Xie [a,b], Xiao-Qing Liu [a,b], Qing-Ling Fu [a,b,*]

[a] Otorhinolaryngology Hospital, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510080, PR China
[b] Department of Allergy, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510080, PR China

ARTICLE INFO

Keywords:
Allergic rhinitis
LOX-1^{+} neutrophils
Pro-inflammatory role
Low-density neutrophils

ABSTRACT

Background: Low-density neutrophils are heterogeneous immune cells with immunosuppressive (such as polymorphonuclear myeloid-derived suppressor cells [PMN-MDSC]) or pro-inflammatory (such as low-density granulocytes [LDG]) properties that have been well described in multiple cancers and immune diseases. However, its role in allergic rhinitis (AR) is still unclear.

Methods: In the present study, we defined low-density neutrophils as CD14^{-}CD11B^{+}CD15^{+}LOX-1^{+} (LOX-1^{+} neutrophils), and their levels in the peripheral blood (PB) were evaluated and compared between patients with AR and healthy donors using flow cytometric analysis. LOX-1 expression on polymorphonuclear neutrophils was identified. Carboxyfluorescein succinimidyl ester (CFSE)-stained CD3^{+} T cells were cultured alone or with LOX-1^{+} neutrophils, T cell proliferation was assessed using flow cytometry, and pro-inflammatory cytokines in the supernatants were detected using enzyme-linked immunosorbent assay (ELISA). Clinicopathological analyses were performed to gain a thorough understanding of LOX-1^{+} neutrophils.

Results: We determined that LOX-1^{+} neutrophils were significantly increased in the PB of patients with AR, and LOX-1 expression in neutrophils from patients with AR was elevated. Interestingly, LOX-1^{+} neutrophils derived from patients with AR, unlike PMN-MDSC, promoted T cell proliferation and pro-inflammatory cytokine production. Moreover, clinicopathological analysis revealed that there was no any relation between circulating LOX-1^{+} neutrophil levels and the levels of IgE, age and sex.

Conclusion: These findings indicate that elevated circulating LOX-1^{+} neutrophils play a pro-inflammatory role in AR.

1. Introduction

Allergic rhinitis (AR) is a global concern and a growing public health, medical, economic, and social problem worldwide with a prevalence of up to 50 % in some regions [1,2]. AR is caused by immunoglobulin E (IgE)-mediated reactions to inhaled allergens and is

* Corresponding author. Otorhinolaryngology Hospital, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510080, PR China.
E-mail addresses: dengxh8@mail2.sysu.edu.cn, dengxiaohui94@163.com (X.-H. Deng), 13480396592@163.com (L.-X. Huang), 693264779@qq.com (Q. Sun), lcgyjy123@163.com (C.-G. Li), chunyx1214@163.com (Y.-C. Xie), liu_xq0963@163.com (X.-Q. Liu), fuqingl@mail.sysu.edu.cn (Q.-L. Fu).

https://doi.org/10.1016/j.heliyon.2024.e36218
Received 17 January 2024; Received in revised form 9 August 2024; Accepted 12 August 2024
Available online 16 August 2024

characterized by nasal itching, sneezing, nasal rhinorrhea, and congestion. Although AR is not typically life threatening, its detrimental effects cannot be ignored. AR is often trivialized, and the quality of life of patients with AR can be significantly affected, including, but not limited to, impaired work productivity and classroom performance, disturbed sleep, and heavy psychological burden [3,4]. Therefore, effective therapies for AR are an important unmet clinical need.

Low-density neutrophils are a heterogeneous population with anti-inflammatory (such as polymorphonuclear myeloid-derived suppressor cells [PMN-MDSC]) or pro-inflammatory (such as low-density granulocytes [LDG]) properties [5,6]. Notably, LDG and PMN-MDSC share overlapping neutrophil surface markers used for identification, including $CD11b^{+}$, $CD15^{+}$, $CD33^{+}$, $CD14^{-}$, and human leukocyte antigen-DR isotype $(HLA\text{-}DR)^{-}$ [6–9]. Lectin-type oxidized LDL receptor-1 (LOX-1), a 50 KDa transmembrane glycoprotein, is co-expressed in pro-inflammatory and suppressive low-density neutrophils and has been identified as a specific marker of PMN-MDSC in cancer [10–12]. Immune cells involved in AR processing and regulation, including T helper cells (Th), T regulatory cells (Tregs), group 2 innate lymphoid cells (ILC2), and dendritic cells (DCs), have attracted extensive attention and have been well described [13–20]. However, the role of $CD14^{-}CD11B^{+}CD15^{+}LOX\text{-}1^{+}$ neutrophils ($LOX\text{-}1^{+}$ neutrophils) in AR remains unclear.

In the present study, we investigated $LOX\text{-}1^{+}$ neutrophils and their effects in patients with AR. To the best of our knowledge, our study is the first to determine that these neutrophils are significantly elevated in patients with AR, and have a pro-inflammatory role.

2. Materials and methods

2.1. Participants

In this study, 25 patients with AR (female, n = 10; male, n = 15; average age, 25.6 years) and nine healthy individuals (female, n = 7; male, n = 2; average age, 24 years) were enrolled between May 2021 and September 2023. The diagnosis of AR was in accordance with the criteria of Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines [21]. The patients presented with nasal itching, sneezing, nasal congestion, and rhinorrhea. The subjects were excluded if pregnant, patients with allergic dermatitis. The subjects have not taken glucocorticoids or received the other treatments (eg, antihistamines or immunotherapy) for 4 weeks before the beginning of the study. This study was approved by the Ethics Committee of The First Affiliated Hospital, Sun Yat-sen University (No.2019-331), and informed consent was obtained from all participants.

2.2. Flow cytometry analysis

Peripheral blood (PB) samples were analyzed within 6 h of sampling. Blood samples were treated with red blood lysis buffer (64010-00-100; BioGems). Anti-human antibodies of CD14-PE-CYN7 (61D3, 25-0149-42, Invitrogen), CD11B-FITC (ICRF44, 11-0118-42, Invitrogen), CD15-EF450 (HI98, 48-0159-42, Invitrogen), LOX-1-APC (15C4, 358606, Biolegend) and its corresponding isotype control-APC (MOPC-173, 400222, Biolegend), and Fixable Viability Dye eFluor™ 506 (eBioscience, 65-0866-14) were used. For the $LOX\text{-}1^{+}$ neutrophil phenotype, $CD14^{-}CD11B^{+}CD15^{+}LOX\text{-}1^{+}$ was obtained from live whole blood cells. Cell phenotypes were analyzed using flow cytometry using the CytoFLEX S system (BECKMAN), and data were analyzed using FlowJo V10.8.1 software.

For flow cytometry sorting, a BD FACSAria III system (BD Biosciences) was used. Peripheral blood samples were analyzed within 6 h of sampling and treated with red blood lysis buffer. The isolated cells were co-incubated with anti-human antibodies of CD14-PE-CYN7, CD15-EF450 and LOX-1-APC/its corresponding isotype control-APC at 4 °C for 30 min. Subsequently, $LOX\text{-}1^{+}$ neutrophils were sorted using $CD14^{-}CD15^{+}LOX\text{-}1^{+}$ sorting from these stained cells.

2.3. $CD3^{+}$ T cell isolation

Peripheral blood mononuclear cells (PBMC) were isolated from fresh PB using Lymphocyte Separation Medium (LSM; 50494X-10, Cytiva) according to the manufacturer's instructions. The isolated PBMC were washed with phosphate-buffered saline (PBS) to remove residual medium, and $CD3^{+}$ T cells were isolated from PBMC using human CD3 MicroBeads (Miltenyi, 130-050-101), according to the manufacturer's instructions.

2.4. T cell proliferation and activation assay

T cell proliferation and activation assay were performed following previous studies [10,22,23]. Briefly, T cell proliferation was determined using the CellTrace™ carboxyfluorescein succinimidyl ester (CFSE) Cell Proliferation Kit (Invitrogen, C34570). Purified $CD3^{+}$ T cells were stained with CellTrace™ CFSE (1:1000 dilution), according to the manufacturer's instructions, and then stimulated with anti-CD3 (5 μg/mL) coated on plates and soluble anti-CD28 (1 μg/mL). Cells were then cultured alone or with $LOX\text{-}1^{+}$ neutrophils at different rations (T: LOX^{+} NEUT 1:0, 2:1, 1:1 or 1:2) for 3 d. After 3 d of culture, cells were stained for anti-human antibodies CD4-APC-Cy7 (RPA-T4, 561839, BD Bioscience) and CD8-FITC (SK1, 344703, Biolegend) and then analyzed using the CytoFLEX S system. The supernatants were collected and stored at −80 °C. Anti-CD3 (UCHT1, 14-0038-82) and anti-CD28 (CD28.2, 16-0289-81) antibodies were purchased from eBiosciences.

2.5. Enzyme-linked immunosorbent assay (ELISA) to determine levels of cytokines

Levels of pro-inflammatory and Th2 cytokines, IL-1β, IL-4, IL-5, IL-6, IL-13 and TNF-α, in cell culture supernatants and plasma were

determined using the IL-1β Human Uncoated ELISA Kit (88-7261-22, ThermoFisher), IL-4 Human Uncoated ELISA Kit (88-7046-88, ThermoFisher), IL-5 Human Uncoated ELISA Kit (88-7056-88, ThermoFisher), IL-6 Human Uncoated ELISA Kit (88-7066-22, ThermoFisher), IL-13 Human Uncoated ELISA Kit (88-7439-88, ThermoFisher), and TNF-α Human Uncoated ELISA Kit (88-7346-22, ThermoFisher), respectively. All procedures were performed according to the manufacturer's instructions.

2.6. Schematic diagram

Schematic diagram was performed using https://app.biorender.com/.

2.7. Statistical analyses

Statistical analyses were performed using GraphPad software. Statistical significance was determined using an unpaired *t*-test, ordinary one-way ANOVA and linear regression. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Circulating LOX-1$^+$ neutrophils were significantly increased in patients with AR

To investigate the potential role of LOX-1$^+$ neutrophils in AR, we first evaluated the number of LOX-1$^+$ neutrophils in the PB of patients with AR using flow cytometric analysis. Circulating LOX-1$^+$ neutrophils were defined by CD14$^-$CD11B$^+$CD15$^+$LOX-1$^+$ in live whole blood cells as showed in Fig. 1A. We determined that the frequencies of LOX-1$^+$ cells in polymorphonuclear neutrophils (PMN) were significantly increased in patients with AR when compared with those from healthy donors (HD) (Fig. 1B). Moreover, the results showed that both the frequencies and absolute cell counts of LOX-1$^+$ neutrophils in the PB were significantly increased in patients with AR compared to HD (Fig. 1C and D). These results indicate that LOX-1$^+$ neutrophils in the PB were significantly increased in patients with AR.

3.2. LOX-1 expression of neutrophils from patients with AR was significantly elevated

LOX-1 is a specific marker of PMN-MDSC in cancer, and is expressed in both pro-inflammatory and suppressive low-density neutrophils. Flow cytometry was performed to determine the expression of LOX-1 in neutrophils. We determined that, compared to HD, the mean fluorescence intensity (MFI) of LOX-1 in neutrophils derived from patients with AR was significantly elevated (Fig. 2A

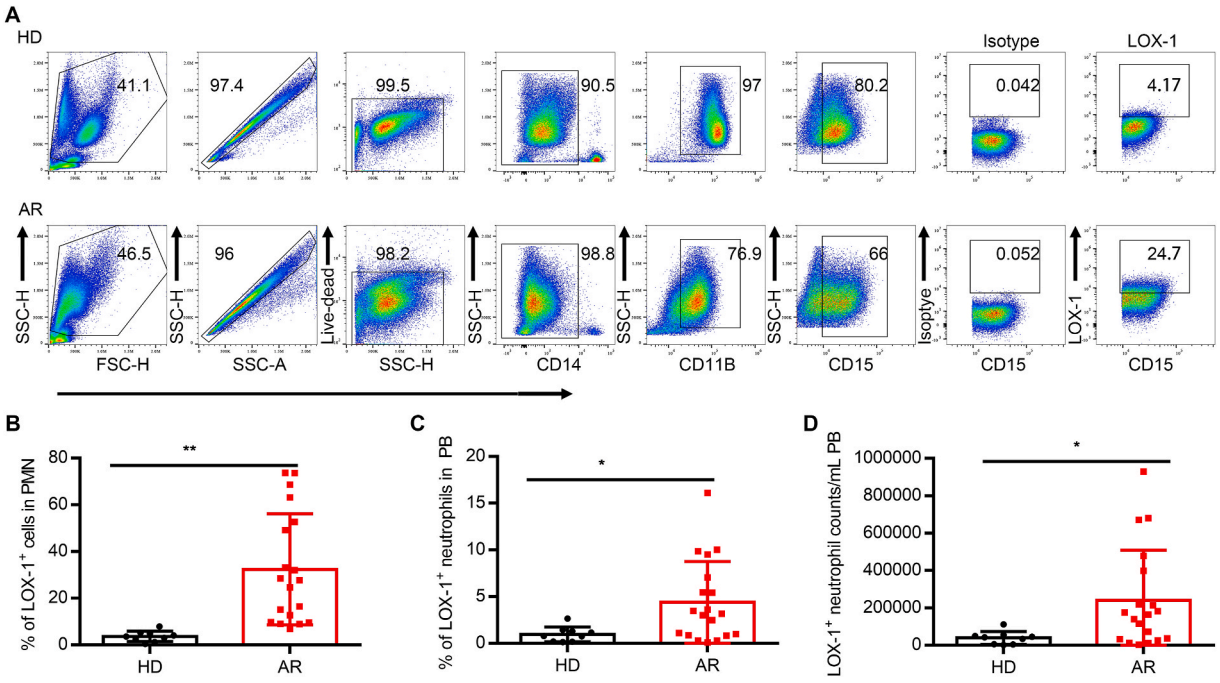


Fig. 1. Circulating LOX-1$^+$ neutrophils were increased in patients with AR.
(A) Gating strategy of LOX-1$^+$ neutrophils using flow cytometry analysis in healthy donors (HD) and patients with AR (AR). (B) Percentages of LOX-1$^+$ cells in PMN. (C) Percentages of LOX-1$^+$ neutrophils in PB. (D) Absolute cell counts of LOX-1$^+$ neutrophils in 1 mL PB. Nine healthy donors and 19 patients with AR were enrolled. In all plots, mean with standard deviation (SD) are shown. *$p < 0.05$, **$p < 0.01$ using the unpaired *t*-test.

and B).

3.3. LOX-1$^+$ neutrophils from patients with AR promoted T cell proliferation

Low-density neutrophils exert either pro-inflammatory or suppressive effects. To elucidate the effects of LOX-1$^+$ neutrophils in patients with AR, a T cell proliferation assay was performed. CFSE-labeled CD3$^+$ T cells were stimulated with anti-CD3 and anti-CD28 antibodies cultured alone or at the indicated ratios of LOX-1$^+$ neutrophils. Stimulation with anti-CD3 and anti-CD28 antibodies resulted in elevated proliferation of CD3$^+$, CD3$^+$CD4$^+$, and CD3$^+$CD8$^+$ T cells compared to the negative control group. Interestingly, when compared to CD3$^+$ T cells cultured alone, the addition of LOX-1$^+$ neutrophils from patients with AR significantly promoted the proliferation of T cell types (Fig. 3A–D). These results indicate that LOX-1$^+$ neutrophils may play a pro-inflammatory role in AR.

3.4. LOX-1$^+$ neutrophils induced a pro-inflammatory T cell cytokine profile

To further explore the effects of LOX-1$^+$ neutrophils on T cell cytokine production, cell culture supernatants were analyzed for different cytokines using ELISA. IL-13 is one of the most important cytokines in AR [24]. Firstly, we observed higher levels of IL-13 in the plasma in AR patients compared to those in healthy controls (Fig. 4A). We determined that the addition of LOX-1$^+$ neutrophils from patients with AR induced significantly higher production of pro-inflammatory cytokines, TNF-α and IL-6 (Fig. 4B). IL-1β production was elevated, as shown using statistical analysis, but this elevation was not statistically significant (Fig. 4B). For Th2 cytokines, IL-4 and IL-13 levels were significantly elevated in the T cells and LOX-1$^+$ neutrophils co-culture supernatants (Fig. 4C). IL-5 production was elevated as well, but this elevation was not statistically significant (Fig. 4C). Overall, the phenotypic and functional analyses of these cells indicated that LOX-1$^+$ neutrophils represent a pro-inflammatory subset of AR.

3.5. LOX-1$^+$ neutrophil levels were not affected by IgE levels, age, and sex

Clinicopathological analysis was performed to gain a thorough understanding of LOX-1$^+$ neutrophils. IgE is routinely examined in patients with AR, who we divided into two groups based on total IgE (tIgE) levels ($<$120 UI/mL and $\geq$120 UI/mL) and compared the LOX-1$^+$ neutrophil levels between these two groups. There were no significant differences between the two groups (Fig. 5A). Moreover, we compared LOX-1$^+$ neutrophil levels between allergen-specific IgE (sIgE)-negative (0) and-positive (1) patients with AR and elucidated that there was no significant difference (Fig. 5B). These results indicate that IgE may not affect LOX-1$^+$ neutrophil levels in patients with AR. Furthermore, the number of LOX-1$^+$ neutrophils was not related to age (Fig. 5C) and sex (Fig. 5D). Overall, these data revealed that IgE level, age, and sex did not affect the percentage of circulating LOX-1$^+$ neutrophils.

4. Discussion

AR is an increasingly prevalent global health, medical, and social problem. Recently, significant progress has been made to further understand the involvement of immune cells such as Th2, ILC2, Tregs, B cells, B regulatory cells (Breg), DCs, T follicular helper cells (Tfh), and follicular regulatory T cells (Tfr) in AR progression and regulation [25–28]. However, the role of LOX-1$^+$ neutrophils in AR

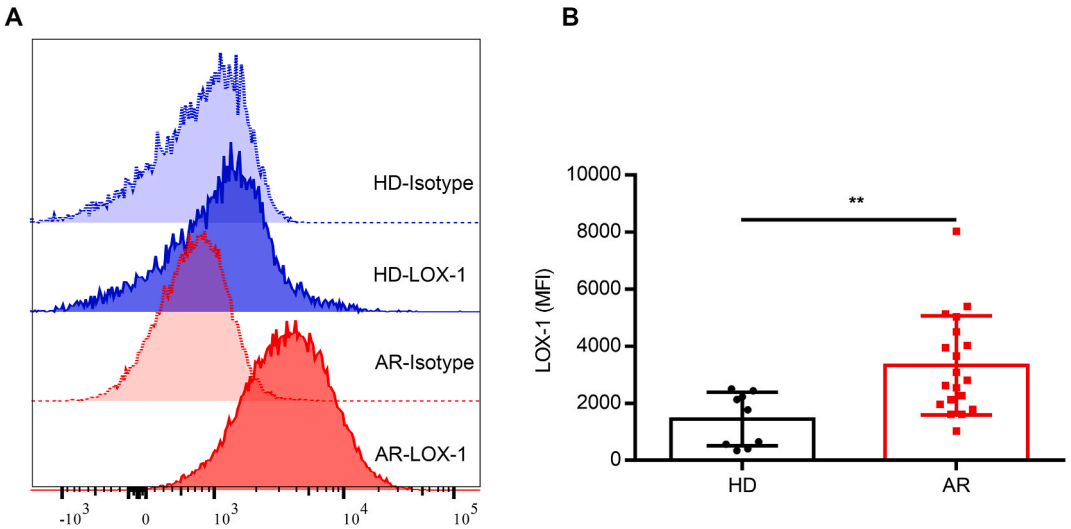
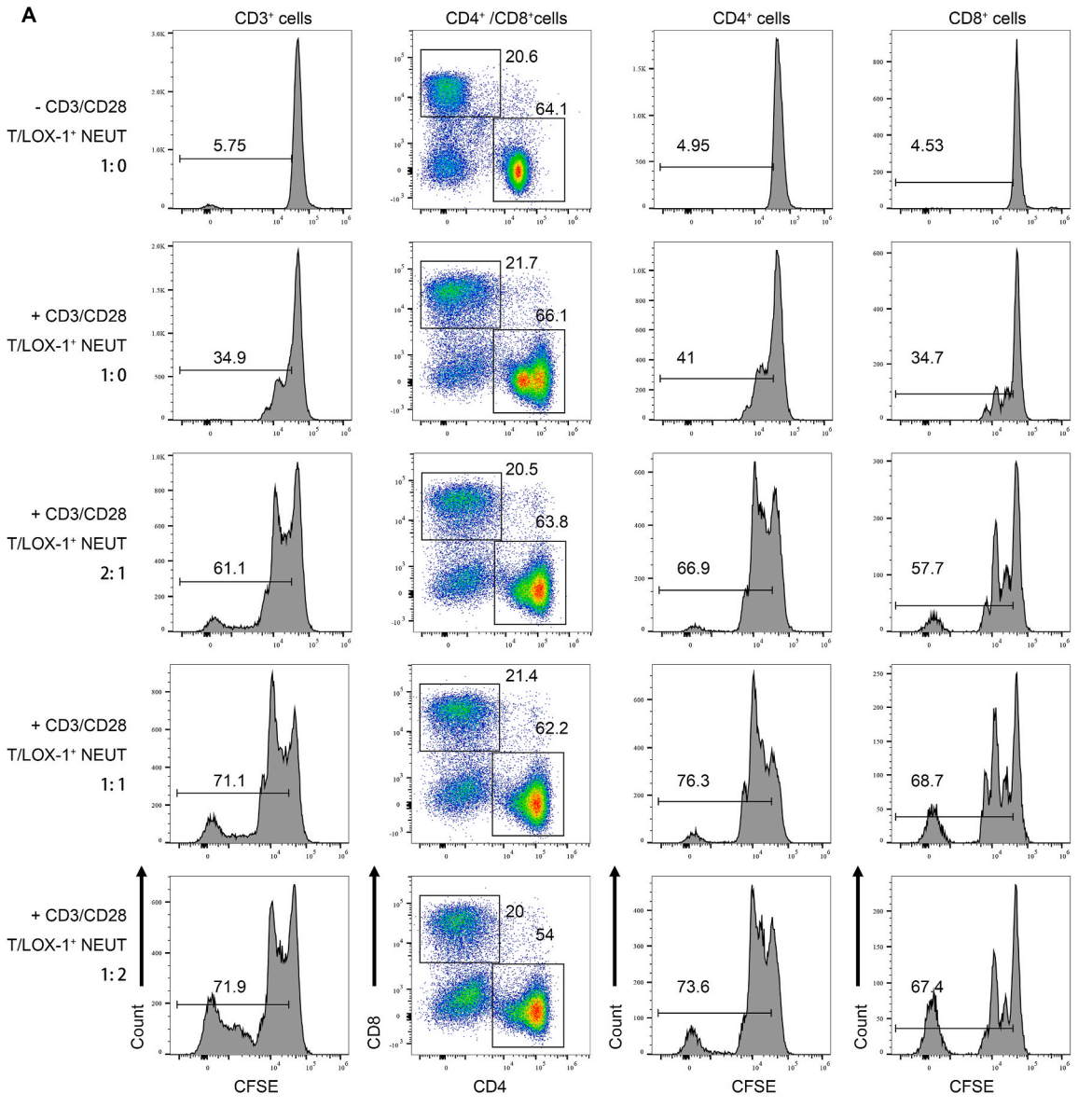


Fig. 2. LOX-1 expression was significantly elevated in neutrophils from patients with AR.
(A) Representative flow cytometric analysis of MFI of LOX-1 expression in CD15$^+$ neutrophils. (B) Statistical analysis of LOX-1 MFI in HD and AR groups. Nine healthy donors and 19 patients with AR were enrolled. In all plots, means with SD are shown. **p $<$ 0.01 using the unpaired *t*-test.



(caption on next page)

Fig. 3. LOX-1$^+$ neutrophils from patients with AR promoted T cell proliferation.
CD3$^+$ T cells isolated from PBMC were stained with CFSE, stimulated with anti-CD3 and anti-CD28, and cultured alone or with LOX-1$^+$ neutrophils for 3 d. (A) Representative flow cytometric analysis of T cell proliferation. (B) Statistical analysis of CD3$^+$ T cell proliferation. (C) Statistical analysis of CD3$^+$CD4$^+$ T cell proliferation. (D) Statistical analysis of CD3$^+$CD8$^+$ T cell proliferation. NEUT, neutrophils. n = 3–6. Means with SD are shown for all plots. **p < 0.01, ***p < 0.001, ****p < 0.0001 using the ordinary one-way ANOVA.

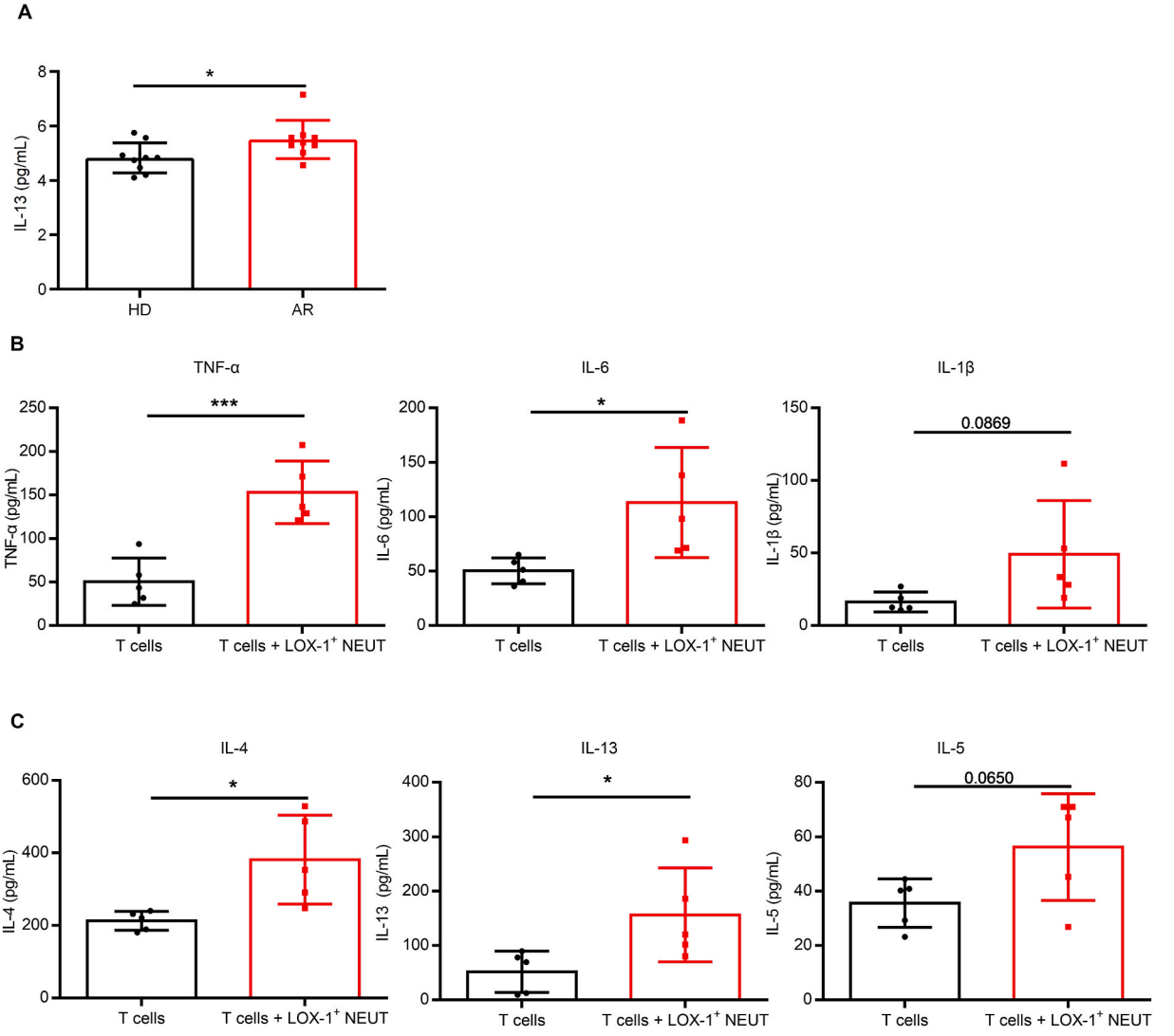


Fig. 4. LOX-1$^+$ neutrophils activated pro-inflammatory cytokine expression.
Cytokine levels in the plasma and the cell culture supernatants were determined by ELISA. (A) Statistical analysis of IL-13 levels in the plasma (n = 9). (B–C) A T/LOX-1$^+$ NEUT 1:1 ratio was used in this experiment. (B) Statistical analysis of pro-inflammatory cytokine (TNF-α, IL-6 and IL-1β) levels in the supernatants (n = 5). (C) Statistical analysis of Th2 cytokine (IL-4, IL-5 and IL-13) levels in the supernatants (n = 5). Means with SD are shown for all plots. *p < 0.05, **p < 0.01 using the unpaired *t*-test.

remains unclear. In this study, the levels and role of circulating LOX-1$^+$ neutrophils in patients with AR, as well as factors that influence them, were investigated.

LDG and PMN-MDSC are low-density neutrophils that share overlapping surface markers. AR is often associated with asthma. Previous preclinical and clinical studies have reported elevated circulating LDG levels in asthma both in preclinical and clinical research [29,30]; therefore, we hypothesized that there may be variations in low-density neutrophils in patients with AR. Circulating CD14$^-$CD11B$^+$CD15$^+$LOX-1$^+$ cells were defined as PMN-MDSC in cancers. In this study, we determined that LOX-1$^+$ neutrophils were significantly upregulated in the whole blood of patients with AR using percentages and absolute cell counts, which was in accordance with data from patients with asthma and horses. The expression of LOX-1, one of the primary receptors for oxidized low-density

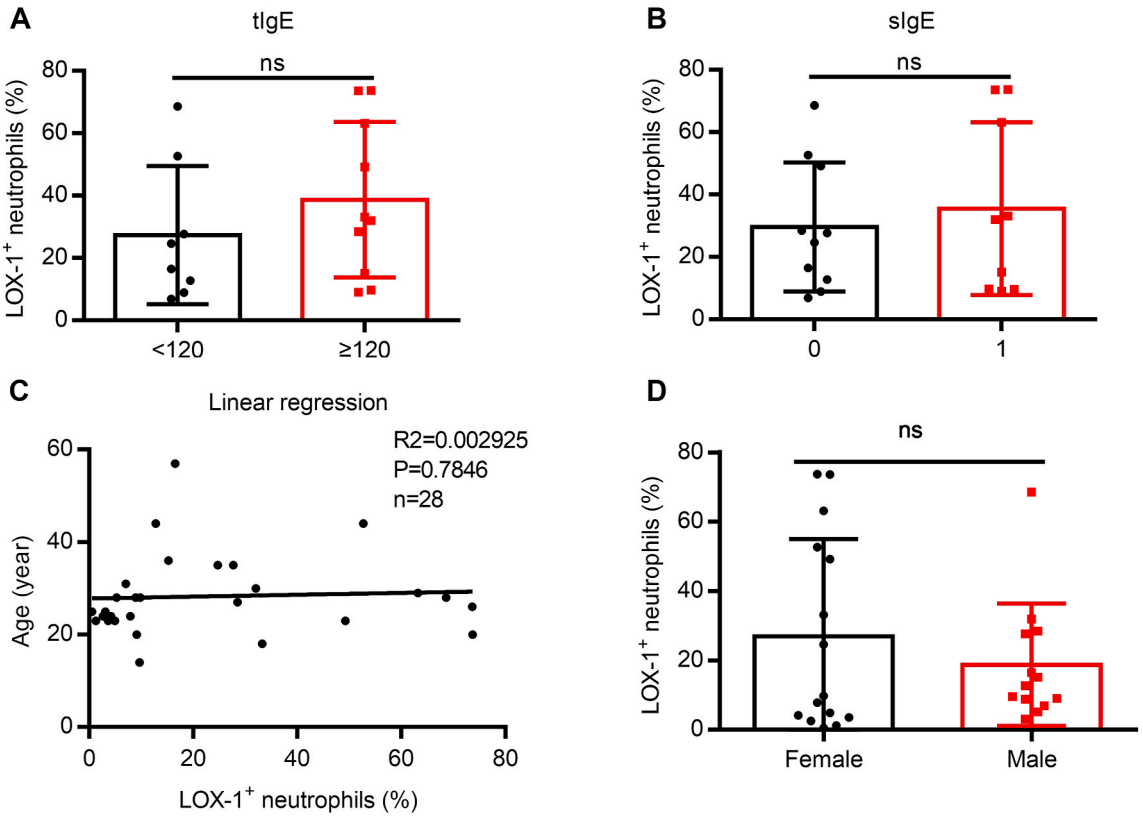


Fig. 5. LOX-1$^+$ neutrophil levels could not be affected by IgE levels, age and sex.
(A) Statistical analysis of LOX-1$^+$ neutrophils in low (<120 IU/mL) (n = 8) and high (≥120 IU/mL) (n = 10) tIgE (total IgE) group in patients with AR. (B) Statistical analysis of LOX-1$^+$ neutrophils in 0 (negative) (n = 10) and 1 (positive) (n = 9) sIgE (specific IgE) group in patients with AR. (C) Linear regression of LOX-1$^+$ neutrophils and age (n = 28). (D) Statistical analysis of LOX-1$^+$ neutrophils in female (n = 15) and male (n = 13) participants. In all plots, means with SD are shown; ns, no significant, using the unpaired *t*-test.

lipoproteins (oxLDL), on immature neutrophils is positively associated with coronavirus 2019 (COVID-19) severity and thromboembolic complications in critical patients with COVID-19 [31]. The expression of LOX-1 in polymorphonuclear neutrophils from patients with AR was significantly increased.

LOX-1$^+$ neutrophils suppress T cell immune responses in cancer and chronic inflammation, such as nasopharyngeal carcinoma, glioblastoma multiforme, hepatocellular carcinoma, and necrotizing enterocolitis [23,32–34]. Interestingly, these cells were reported for the first time to induce a pro-inflammatory T cell response in systemic lupus erythematosus [22]. We determined that LOX-1$^+$ neutrophils from patients with AR significantly promoted T cell proliferation, including CD3$^+$, CD3$^+$CD4$^+$, and CD3$^+$CD8$^+$ cell levels, in contrast to data on multiple cancers reported by previous studies. Interestingly, our results showed that cytokines, both pro-inflammatory cytokines (TNF-α and IL-6) and Th2 cytokines (IL-4 and IL-13), were elevated in T cells and LOX-1$^+$ neutrophils co-culture supernatants. These results revealed that LOX-1$^+$ neutrophils play a pro-inflammatory role in AR and reaffirmed that LOX-1 should not be used alone to assess whether neutrophils are pro-inflammatory or immunosuppressive.

AR is an IgE-mediated, type 2 inflammatory disease. Both tIgE and sIgE tests are routine tests for AR. Interestingly, LOX-1$^+$ neutrophil levels were not affected by either type of IgE in this study. This may be attributed to the insufficient detection (insufficient allergen detection). Furthermore, we elucidated that both age and sex did not influence LOX-1$^+$ neutrophil levels. Overall, LOX-1$^+$ neutrophil levels were not affected by IgE, age, or sex in our study; however, and the actual influencing factors remain to be explored.

We acknowledge that there are some limitations of this study. Although we showed that LOX-1$^+$ neutrophils can induce T cell proliferation and pro-inflammatory cytokine production, these were performed by in vitro experiments. Detailed effects of LOX-1$^+$ neutrophils in the pathogenesis of AR should be further determined in vivo using animal models and/or nasal mucosa from the patients. In addition, we did not include more experiments about the interaction between LOX-1$^+$ neutrophils and T cells by cell-cell contact or a paracrine effect, and more data to support that LOX-1$^+$ neutrophil levels were not affected by IgE, age, or sex. Finally, large sample size should be considered to fully elucidate the roles of LOX-1$^+$ neutrophils in AR and investigate of the roles of these cells in other inflammatory model system like atopic dermatitis in the future.

5. Conclusion

In conclusion, we determined that LOX-1$^+$ neutrophils were significantly upregulated in the whole blood of patients with AR. Unlike PMN-MDSC, these cells are involved in inducing T cell proliferation and production of pro-inflammatory cytokines. We excluded IgE, age, and sex as factors influencing LOX-1$^+$ neutrophil levels. Our findings provide new insights into the role of LOX-1$^+$ neutrophils in AR.

Ethical statement

This study was approved by The Ethics Committee of The First Affiliated Hospital, Sun Yat-sen University (No.2019-331).

Consent for publication

All authors agreed to publication of the work.

Disclosure of potential conflicting interests.

All authors declared no conflicts of interests.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 82271144 and 81970863), Guangdong Basic and Applied Basic Research Foundation (2021B1515120062), and Guangzhou Key R&D Program (2023B03J1233).

Availability of data and materials

Data supporting the findings of this study are available upon reasonable request from the corresponding authors. The data are not publicly available because of privacy and ethical restrictions.

CRediT authorship contribution statement

Xiao-Hui Deng: Writing – original draft, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Long-Xin Huang:** Project administration, Investigation. **Qi- Sun:** Data curation. **Chan-Gu Li:** Project administration, Investigation. **Ying-Chun Xie:** Project administration, Investigation. **Xiao-Qing Liu:** Project administration, Investigation. **Qing-Ling Fu:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are extremely grateful to the entire team of the Division of Allergy, First Affiliated Hospital, Sun Yat-sen University, including medical workers, graduate students, and volunteers.

Abbreviations

AR	allergic rhinitis
CFSE	carboxyfluorescein succinimidyl ester
ELISA	enzyme-linked immunosorbent assay
HD	healthy donors
IgE	immunoglobulin E
LDG	low-density granulocytes
LOX-1	lectin-type oxidized LDL receptor-1
LOX-1$^+$ neutrophils	CD14$^-$CD11B$^+$CD15$^+$LOX-1$^+$ neutrophils
MFI	mean fluorescence intensity
NEUT	neutrophils
ns	no significant
PB	peripheral blood
PBMC	peripheral blood mononuclear cells
PMN	polymorphonuclear neutrophils
PMN-MDSC	polymorphonuclear myeloid-derived suppressor cells

sIgE allergen-specific IgE
tIgE total IgE

References

[1] J. Bousquet, J.M. Anto, C. Bachert, I. Baiardini, S. Bosnic-Anticevich, G.W. Canonica, E. Melen, O. Palomares, G.K. Scadding, A. Togias, et al., Allergic rhinitis, Nat. Rev. Dis. Prim. 6 (1) (2020) 95.
[2] X.D. Wang, K. Du, W.Y. She, Y.H. Ouyang, Y.T. Sima, C.Y. Liu, L. Zhang, Recent advances in the diagnosis of allergic rhinitis, Expet Rev. Clin. Immunol. 14 (11) (2018) 957–964.
[3] P. Devillier, J. Bousquet, H. Salvator, E. Naline, S. Grassin-Delyle, O. de Beaumont, In allergic rhinitis, work, classroom and activity impairments are weakly related to other outcome measures, Clin. Exp. Allergy 46 (11) (2016) 1456–1464.
[4] S.K. Wise, C. Damask, L.T. Roland, C. Ebert, J.M. Levy, S.D. Lin, A. Luong, K. Rodriguez, A.R. Sedaghat, E. Toskala, et al., International consensus statement on allergy and rhinology: allergic rhinitis-2023, Int Forum Allergy Rh 13 (4) (2023) 293–859.
[5] M.D. Sanchez-Pino, W.S. Richardson, J. Zabaleta, R.T. Puttalingaiah, A.G. Chapple, J. Liu, Y. Kim, M. Ponder, R. DeArmitt, L.B. Baiamonte, et al., Increased inflammatory low-density neutrophils in severe obesity and effect of bariatric surgery: results from case-control and prospective cohort studies, EBioMedicine 77 (2022) 103910.
[6] J. Jablonska, Z. Granot, Neutrophil, quo vadis? J. Leukoc. Biol. 102 (3) (2017) 685–688.
[7] V. Bronte, S. Brandau, S.H. Chen, M.P. Colombo, A.B. Frey, T.F. Greten, S. Mandruzzato, P.J. Murray, A. Ochoa, S. Ostrand-Rosenberg, et al., Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards, Nat. Commun. 7 (2016) 12150.
[8] F. Veglia, M. Perego, D. Gabrilovich, Myeloid-derived suppressor cells coming of age, Nat. Immunol. 19 (2) (2018) 108–119.
[9] T.F. Greten, M.P. Manns, F. Korangy, Myeloid derived suppressor cells in human diseases, Int. Immunopharm. 11 (7) (2011) 802–807.
[10] T. Condamine, G.A. Dominguez, J.I. Youn, A.V. Kossenkov, S. Mony, K. Alicea-Torres, E. Tcyganov, A. Hashimoto, Y. Nefedova, C. Lin, et al., Lectin-type oxidized LDL receptor-1 distinguishes population of human polymorphonuclear myeloid-derived suppressor cells in cancer patients, Sci Immunol 1 (2) (2016) aaf8943.
[11] B. Zeya, A. Arjuman, N.C. Chandra, Lectin-like oxidized low-density lipoprotein (LDL) receptor (LOX-1): a chameleon receptor for oxidized LDL, Biochemistry-Us 55 (32) (2016) 4437–4444.
[12] Z. Wu, T. Sawamura, A.K. Kurdowska, H.L. Ji, S. Idell, J. Fu, LOX-1 deletion improves neutrophil responses, enhances bacterial clearance, and reduces lung injury in a murine polymicrobial sepsis model, Infect. Immun. 79 (7) (2011) 2865–2870.
[13] S.B. Fang, H.Y. Zhang, C. Wang, B.X. He, X.Q. Liu, X.C. Meng, Y.Q. Peng, Z.B. Xu, X.L. Fan, Z.J. Wu, et al., Small extracellular vesicles derived from human mesenchymal stromal cells prevent group 2 innate lymphoid cell-dominant allergic airway inflammation through delivery of miR-146a-5p, J. Extracell. Vesicles 9 (1) (2020) 1723260.
[14] Y.Q. Peng, Z.L. Qin, S.B. Fang, Z.B. Xu, H.Y. Zhang, D. Chen, Z. Liu, J.A. Bellanti, S.G. Zheng, Q.L. Fu, Effects of myeloid and plasmacytoid dendritic cells on ILC2s in patients with allergic rhinitis, J. Allergy Clin. Immunol. 145 (3) (2020), 855-+.
[15] Y.Q. Peng, X.H. Deng, Z.B. Xu, Z.C. Wu, Q.L. Fu, Mesenchymal stromal cells and their small extracellular vesicles in allergic diseases: from immunomodulation to therapy, Eur. J. Immunol. 53 (10) (2023) e2149510.
[16] M.H. Shamji, H. Sharif, J.A. Layhadi, R.F. Zhu, U. Kishore, H. Renz, Diverse immune mechanisms of allergen immunotherapy for allergic rhinitis with and without asthma, J. Allergy Clin. Immunol. 149 (3) (2022) 791–801.
[17] K. Orimo, M. Tamari, T. Takeda, T. Kubo, B. Ruckert, K. Motomura, H. Sugiyama, A. Yamada, K. Saito, K. Arae, et al., Direct platelet adhesion potentiates group 2 innate lymphoid cell functions, Allergy 77 (3) (2022) 843–855.
[18] T. Iinuma, Y. Okamoto, Pathogenicity of memory Th2 cell is linked to sensitization and stage of allergic rhinitis, Allergy 70 (2015) 4.
[19] T. Iinuma, Y. Okamoto, Y. Morimoto, T. Arai, T. Sakurai, S. Yonekura, D. Sakurai, K. Hirahara, T. Nakayama, Pathogenicity of memory Th2 cells is linked to stage of allergic rhinitis, Allergy 73 (2) (2018) 479–489.
[20] W.E. Jiao, L. Sun, S. Xu, Y.Q. Deng, Y.L. Qiao, Y. Xi, Z.Z. Tao, S.M. Chen, Notch2 suppresses the development of allergic rhinitis by promoting FOXP3 expression and Treg cell differentiation, Life Sci. 284 (2021) 119922.
[21] J.L. Brozek, J. Bousquet, I. Agache, A. Agarwal, C. Bachert, S. Bosnic-Anticevich, R. Brignardello-Petersen, G.W. Canonica, T. Casale, N.H. Chavannes, et al., Allergic rhinitis and its Impact on asthma (ARIA) guidelines-2016 revision, J. Allergy Clin. Immunol. 140 (4) (2017) 950–958.
[22] S. Rahman, D. Sagar, R.N. Hanna, Y.L. Lightfoot, P. Mistry, C.K. Smith, Z. Manna, S. Hasni, R.M. Siegel, M.A. Sanjuan, et al., Low-density granulocytes activate T cells and demonstrate a non-suppressive role in systemic lupus erythematosus, Ann. Rheum. Dis. 78 (7) (2019) 957–966.
[23] Y.F. Liu, M. Perego, Q. Xiao, Y.M. He, S.Y. Fu, J. He, W.K. Liu, X. Li, Y.L. Tang, X.Y. Li, et al., Lactoferrin-induced myeloid-derived suppressor cell therapy attenuates pathologic inflammatory conditions in newborn mice, J. Clin. Invest. 129 (10) (2019) 4261–4275.
[24] Zhong X-LF. Hua, Qiu-Ning Yu, Zi-Li Qin, Dong Chen, Rui Xu, De-Hua Chen, Zhi-Bin Lin, Weiping Wen, Qing-Ling Fu, Increased innate type 2 immune response in house dust mite-allergic patients with allergic rhinitis, Clin Immunol 183 (2017) 293–299.
[25] Y. Zhang, F. Lan, L. Zhang, Update on pathomechanisms and treatments in allergic rhinitis, Allergy 77 (11) (2022) 3309–3319.
[26] A.S. Kim, T.A. Doherty, M.R. Karta, S. Das, R. Baum, P. Rosenthal, A. Beppu, M. Miller, R. Kurten, D.H. Broide, Regulatory B cells and T follicular helper cells are reduced in allergic rhinitis, J. Allergy Clin. Immunol. 138 (4) (2016) 1192–1195.
[27] Y. Yao, N. Wang, C.L. Chen, L. Pan, Z.C. Wang, J. Yunis, Z.A. Chen, Y. Zhang, S.T. Hu, X.Y. Xu, et al., CD23 expression on switched memory B cells bridges T-B cell interaction in allergic rhinitis, Allergy 75 (10) (2020) 2599–2612.
[28] Y. Yao, C.L. Chen, D. Yu, Z. Liu, Roles of follicular helper and regulatory T cells in allergic diseases and allergen immunotherapy, Allergy 76 (2) (2021) 456–470.
[29] J. Fu, M.C. Tobin, L.L. Thomas, Neutrophil-like low-density granulocytes are elevated in patients with moderate to severe persistent asthma, Ann. Allergy Asthma Immunol. 113 (6) (2014), 635-U200.
[30] N. Herteman, A. Vargas, J.P. Lavoie, Characterization of circulating low-density neutrophils intrinsic properties in healthy and asthmatic horses, Sci. Rep. 7 (1) (2017) 7743.
[31] B. Combadiere, L. Adam, N. Guillou, P. Quentric, P. Rosenbaum, K. Dorgham, O. Bonduelle, C. Parizot, D. Sauce, J. Mayaux, et al., LOX-1-Expressing immature neutrophils identify critically-ill COVID-19 patients at risk of thrombotic complications, Front. Immunol. 12 (2021) 752612.
[32] X. Li, J.L. Li, N. Jiang, J. Chen, Z.M. Liang, Z.L. Zhao, Y.F. Xing, Accumulation of LOX-1(+) PMN-MDSCs in nasopharyngeal carcinoma survivors with chronic hepatitis B might permit immune tolerance to epstein-barr virus and relate to tumor recurrence, Aging-Us 13 (1) (2021) 437–449.
[33] E.Q. Chai, L. Zhang, C.Q. Li, LOX-1+PMN-MDSC enhances immune suppression which promotes glioblastoma multiforme progression, Cancer Manag. Res. 11 (2019) 7307–7315.
[34] J. Nan, Y.F. Xing, B. Hu, J.X. Tang, H.M. Dong, Y.M. He, D.Y. Ruan, Q.J. Ye, J.R. Cai, X.K. Ma, et al., Endoplasmic reticulum stress induced LOX-1(+)CD15(+) polymorphonuclear myeloid-derived suppressor cells in hepatocellular carcinoma, Immunology 154 (1) (2018) 144–155.