

The Research and Development of the Relationship between the Origin and Classification of Macrophages and Their Diseases

Yuanfeng Liao¹, Daxing Liu^{1*}

¹Department of Cardiovascular Surgery, Affiliated Hospital of Zunyi Medical University, Zunyi Medical University, Zunyi, China

Received: March 06, 2019; Accepted: April 15, 2019; Published: April 22, 2019

*Corresponding author: Daxing Liu, Department of Cardiovascular Surgery, Affiliated Hospital of Zunyi Medical University, Zunyi Medical University, Zunyi, China, E-mail: 13639222003@163.com

Abstract

Macrophages participate in the development of various diseases in the body due to their excellent plasticity and functional diversity. Macrophages play an essential role in various diseases, and the influence of matrix in various microenvironments in the receptor. The typing of macrophages M1 and M2 is not sufficient, and macrophages can only truly determine the type of action they play in the local microenvironment. Macrophage colony-stimulating factor 1 the receptor (colony-stimulating factor 1 receptor, CSF1R) and interleukin-34 (Interleukin, IL-34) regulate the evolution of macrophages. Macrophages not only play an important role in inflammation, but also in tissue damage and repair. Alzheimer's disease, liver damage, angiogenesis and myocardial protection also play an important role.

Key words: Macrophages; monocytes; macrophage colony-stimulating factor; mononuclear phagocytic system; interleukin-34

Introduction

In vitro, macrophages can be easily divided into two types of polarization according to their phenotype and secreted cytokines, namely, the classically activated M1 type and the alternatively activated M2 type macrophages. The polarization typing of macrophages is widespread in most tissues such as skin, fat, intestine, liver, and tumor, and has a guiding significance for the prognosis of some tumors. Various matrix factors in the tissue can have a significant impact on the polarization of macrophages, which in turn can have an important impact on the recovery and treatment of various diseases. This is a review for macrophage origin, polarization typing as well as its impact on diseases and could be concluded as below:

The Origin of Macrophages

Macrophages were originally identified in the late 19th century by Metchnikoff through their phagocytic properties and are ancient cells in the development of animal phylogenesis. In adult mammals, they are found in all tissues and they perform excellent anatomical and functional diversity. Although several macrophage

classification attempts have been made, the most successful definition is the mononuclear phagocytic system (MPS), which contains these phagocytic cells and their Bone Marrow (BM) progenitor cells. In the MPS mode, adult macrophages are defined as the terminal cells of the mononuclear phagocytic lineage, which are derived from circulating monocytes produced by BM, travel through the blood to all parts of the body, and eventually become metastatic to the tissue macrophage cells [1].

Classification and Regulation of Macrophages

Currently the most classic is the definition of macrophages by cytokines in vitro culture media: pro-inflammatory (M1) and anti-inflammatory (M2) [2]. In normal tissues, the proportion of M1-like/M2-like macrophages is highly regulated and increases during inflammation [3]. Gene expression profiling revealed that M1 macrophages can release high levels of pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), which is also known as monocyte chemo attractant protein-1 (MCP-1), IL-6, inducible nitric oxide synthase (iNOS), IL-1, IL-12, type I IFN, CXCL1-3, CXCL5 and CXCL8-10 [4]. M2 macrophages have been shown to express high levels of dendritic cell-associated C-type lectin-1 (dectin-1), mannose receptor (CD206), scavenger receptor A, scavenger receptor B-1, CD163, CCR2, CXCR1 and CXCR2 and produced a large number of IL-10, YM1, macrophage and granulocyte inducer type 1 (MgI1) and arginase-1, highlighting their remodeling in tissues. Correlation with the repair process [5, 6]. Macrophage polarization may be affected by microRNAs, DNA methylation and histone modifications, which are responsible for altered, cell signaling and gene expression during M1 or M2 polarization [7]. The main difference between these two cells is that in M2 macrophages, arginine metabolism is converted to ornithine and polyamines, whereas in M1 cells, it is converted to NO and citrulline [8]. The ornithine produced by M2 can be synthesized by polyamines and collagen. Fibrosis and other tissue remodeling functions promote cell proliferation and repair, while NO produced by M1 is an important effector molecule with microbicidal activity and cell proliferation inhibition ability

[9, 10]. Interestingly, polyamine production is reported to be a driving factor for M2 polarization and M2 is the normal “default” procedure used by tissue macrophages [11, 12].

Gene Regulation of Macrophages

Under the stimulation of lipopolysaccharide, peroxisome proliferator-activated receptor δ is regulated by miR-9 in primary human monocytes, which plays an important role in the development of macrophages toward the M1 subtype [13]. In particular, miR-155 (small non-coding RNAs (called microRNAs, miRs)) and miR-223 are involved in the regulation of macrophage activation by targeting SOCS1, C / EBP (a marker for M2 macrophages) and Pknox1 [14]. Over expression or silencing of miR-155 has been shown to drive macrophages to the M1 or M2 phenotype, respectively, confirming that miR-155 plays an important role in regulating Akt-dependent M1/M2 polarization of macrophages. It was also shown that miR-155 down-regulates IL-13R α 1 expression and inhibits polarization to the M2 phenotype [15, 16]. A study by Lin et, al. demonstrated that activation of type I interferon and the downstream interferon-I receptor-JAK1-STAT1 signaling cascade inhibit miR-145 expression in macrophages by direct inhibition of targeted genetic IL -10 gene silenced histone deacetylase 11 [17]. As a result, increasing IL-10 production leads to inhibition of the inflammatory response, which may tilt the phenotype of macrophages [18, 19].

Group Regulation and Protein Modification of Macrophages

DNA methylation has a significant effect on the polarization behavior of macrophages [20]. Kruppel-like transcription factors have been identified as controllable macrophage polarization, including Kruppel-like transcription factors 6 and 10 [21]. Kruppel-like transcription factors synergize with STAT6 to induce M2 gene signature and are required for the activation by integrating NF- κ B A co activator to inhibit M1 type targets. The expression of various genes encoding enzymes is responsible for catalyzing and modifying post-translational modifications of various histones, such as methyltransferases, demethylases, acetyltransferases and deacetylases, which differentiates state of expression of M1/M2 [22]. Specific methyltransferase SET and pro-inflammatory cytokine (TNF- α and IL-6) promoters containing MYND domain 2 have histone 3 lysine 4- and H3K36 dimethylation, which leads to M1 decreased polarization and signaling of NF- κ B and ERK [23]. Analysis of specific histone modifications indicated that they positively and negatively had regulated M1 / M2 gene expression as predictors of M1 / M2 polarization [7]. In fact, it is a limited attempt to use M1/M2 polarization to define the complexity and plasticity of mononuclear phagocytic cells. In vivo, macrophages can adopt multiple functional phenotypes depending on subtle and continuous changes in the tissue microenvironment. Therefore, the M1 / M2 polarization of macrophage function can be used as a simplified conceptual framework for describing continuums of different functional states, where the M1 and M2 activation states are not a subset of the original definition, but represent extreme values [4, 24].

Origins of Macrophages

However, simply defining macrophages as M1/M2 is inadequate because macrophages have several origins during ontogeny. In mice, macrophages develop from the primitive ectoderm of the yolk sac on day 8 of the embryo, but not form mononuclear progenitor cells. This primordial system is followed by a definitive hematopoiesis in the fetal liver, initially by hematopoietic progenitor cells from the yolk sac and subsequently from the embryonic aorta the blood-derived endothelium of the glomerular region of the kidney. Thereafter, during embryogenesis, the fetal liver is the source of definitive hematopoiesis that produces circulating monocytes. Consistent with postnatal bone formation, fetal liver hematopoiesis declines and is replaced by bone marrow hematopoiesis [25]. Pedigree tracking experiments have shown that microglia is mainly derived from yolk sac progenitor cells, while Langerhans cells are derived from the yolk sac and fetal liver [26]. Related studies have shown that tissue macrophages are composed of different mixed populations such as embryonic-derived macrophages and bone marrow-derived blood mononuclear cells [27]. In most tissues, tissue macrophages do not require continuous input from circulating monocytes and can be self-renewing to some extent [28, 29]. For an example, Langerhans cells in the skin present dual characteristics of dendritic cells and macrophages and are maintained primarily by self-renewal [30]. In many tissues of the body, different tissue macrophage populations are mainly derived from the yolk sac during embryogenesis, fetal liver and hematopoietic stem cells, and contribute some macrophages to tissues at a later time, but not all [31, 32]. These data indicate that at least three macrophages in mice are produced at different developmental stages and persist in mature individuals.

Major lineage regulators of macrophages

Decreasing CSF-1 levels result in a decrease in monocyte proliferation, thereby maintaining systemic or local cell counts to normal levels [33]. Under steady-state conditions CSF-1 promotes monocyte development and macrophage proliferation and is controlled in a negative feedback loop [34, 35]. Tissue macrophages can proliferate at low levels, but after macrophages are depleted, the proliferation rate is greatly increased [28]. There is an evidence that previously split macrophages have the same entry into the cell cycle as cells that do not enter the cell cycle possibility. This indicates that all macrophages have the same proliferative capacity [26]. The class III transmembrane tyrosine kinase receptor is expressed on most (if not all) mononuclear phagocytic cells, and reporter mice expressing the Green Fluorescent Protein (GFP) from the CSF1R locus indicate their relative abundance (5-20% cells) and tissue distribution [36]. Furthermore, an initial comparison of homozygous for spontaneous null mutations in CSF1R null mice and their cognate ligands demonstrated that all phenotypes in CSF1R null mice were also expressed in homologous ligand mice, which indicates CSF1 has only a single receptor [37]. However, the phenotype of CSF1R null mice was more severe than that of CSF1

null mice, including complete loss of microglia and Langerhans cells in CSF1R null mice indicating the presence of another ligand [38]. In fact, Interleukin (IL-34) has a uniqueness but overlapping expression pattern with CSF1, so IL-34 is identified as an additional ligand for CSF1R [39]. Targeted ablation of IL-34 results in loss of microglia and Langerhans cells, but has little effect on macrophages in bone marrow, liver or spleen [40]. Macrophage colony-stimulating factor 1 receptor and IL-34 play important roles in the transformation of macrophages. Recent studies have shown that CD5L is (CD5 molecular type: a secretory glycoprotein, which controls inflammation) the key mechanism in the reaction, involved in infection, atherosclerosis and cancer, etc. In macrophages, CD5L drives macrophages to polarize towards M2 in a manner similar to IL10 [41].

The Effect of Macrophages on Related Diseases

Macrophages not only play an important role in inflammation, but also play an important role in tissue damage and repair, Alzheimer's disease, liver damage, blood vessel formation and myocardial protection.

After tissue injured, monocytes and macrophages undergo significant phenotypic and functional changes. At the onset of tissue repair, the maintenance and resolution phases play a key role [42]. In a skin model, studies have shown that macrophage-dependent iron transporter-mediated iron release is required for hair growth and effective wound healing under steady-state conditions. Which iron transporter deletion will cause iron in macrophages retention is responsible for impaired angiogenesis and stromal cell proliferation, resulting in delayed skin repair. The study found that iron retention in macrophages had no effect on leukocyte recruitment and activation and macrophage polarization. In this study, iron accumulation does not exacerbate the expression of proinflammatory phenotypes in wound healing-associated macrophages [43]. Macrophage dysfunction can lead to abnormal repair, uncontrolled inflammatory mediators and growth factors, as well as the production of anti-inflammatory macrophage defects, resulting in persistent damage, which may eventually lead to the development of pathological fibrosis [41]. Studies have suggested that mononuclear cells and yolk sac-derived tissue macrophages recruited from bone marrow play different roles in different repair stages of some organs. For instance, although genetic results mapping studies have demonstrated that most macrophages in adult hearts are derived from yolk sac and fetal progenitor cells, CCR2 + monocyte-derived macrophages drive early inflammatory responses in heart tissue after injury primary cells [32]. In contrast, embryonic-derived cardiac macrophages are key cells that promote recovery [44].

Jay and colleagues conducted an exciting study showing that the expression of receptor-inducing macrophages on bone marrow cells 2 is required for the development of Alzheimer's disease. Inflammation of Ly6c + macrophages highly expresses trigger receptors on bone marrow cells 2, when the trigger receptor activity on bone marrow cells 2 is genetically deleted,

the Ly6c + group is virtually eliminated, resulting in reducing inflammation and improving amyloid and tau symptoms. Therefore, expression of a trigger receptor on bone marrow cells 2 has been identified as an important guiding signal in the development of inflammatory macrophages, suggesting that it may represent a therapeutic target in neurodegenerative diseases such as Alzheimer's disease [45]. Studies have shown that oxidative stress is associated with neurodegenerative diseases such as Alzheimer's disease. In addition, post-mortem examination of patients with these diseases showed that areas of the brain affected by neuro degeneration showed an increase in the active oxygen index. Macrophages play an important role in inflammation and constitute a major source of reactive oxygen species in the human body. Although reactive oxygen species were previously thought to be produced primarily by tissue macrophages in the brain ie, microglia. Recent reports have indicated the important role of peripheral cells, especially macrophages, suggesting that they are important for the regulation and progression of inflammation [46].

A particularly important source of reactive oxygen species is activated macrophages, whose increased production may adversely affect the antioxidant-antioxidant balance [47]. In the experiment, acetyl cholinesterase inhibitors used as a standard for the treatment of Alzheimer's disease showed possible antioxidant activity in macrophages and inhibited the formation of reactive oxygen species, thereby achieving a certain therapeutic effect [48].

Acute liver failure is one of the rare and life-threatening major diseases that most frequently present in patients without pre-existing liver disease [49]. In the experiment, HepG2 and HL-7702 cells were pretreated with M0, M1 or M2 medium. Hepatocyte apoptosis is then induced by human TNF- α /D-GalN. Exposure of HepG2 cells to M0 medium or M1 medium had no significant effect on apoptosis. However, the frequency of hepatocyte apoptosis was significantly reduced in HepG2 cells pretreated with M2 medium. Similarly, hepatocyte apoptosis was significantly reduced in HL-7702 cells pretreated with M2 medium. Thus, M2-like macrophages confer strong apoptosis resistance to human hepatocytes [50].

Wound angiogenesis is an integral part of tissue repair. In wounds by stimulating neovascular sprouting in real time and in vivo, studies of mouse and zebra fish wounds indicate that macrophages are attracted to wound vessels shortly after injury and are closely related to the entire repair process. In addition, macrophage ablation leads to impaired neovascularization. Macrophages not only play a role in the stage of wound repair, but also play a non-negligible role in vascular degeneration. Their activation or loss of activation may impair proper vascular clearance [51].

Since macrophages play a key role in the pathophysiological process triggered by myocardial infarction (MI), monocytes/macrophages represent potential therapeutic targets for

promoting myocardial repair and functional regeneration [52]. Sestrins is a family of stress-inducing proteins that regulate metabolic homeostasis [53]. In this family of proteins, Sestrin2 is important for protecting myocardium from ischemic injury, and it acts as an LKB1-AMPK scaffold to initiate AMPK signaling after ischemia [54]. The study found that Sestrin2 regulated the role of cardiac macrophage inflammatory response after MI. Cardiac macrophages up-regulated the expression of Sestrin2 in a mouse MI model. Sestrin2 was over-expressed in polarized M1 and M2 macrophages using a lentiviral transduction system, whereas Sestrin2 functions primarily on M1 but not on M2 macrophages. Overexpression of Sestrin2 inhibits the proinflammatory response of M1 macrophages. Furthermore, in the case of a mouse MI model with selective depletion of endogenous macrophages and macrophages over expressing exogenous Sestrin2, anti-inflammatory and repair promoting effects of Sestrin2-expressing macrophages were demonstrated [55].

Prospects for Macrophages

Much of the current researches have focused on signaling pathways that regulate the production of inflammatory mediators and subpopulations, but we are more eager to find more solutions to new problems in the context of normal homeostasis and acute or chronic disease. At present, we need to determine the relevant research areas, which is crucial for the next research work of macrophages. First, it is still unclear how the status of macrophages in tissues is regulated. For example, in situ M2 macrophage proliferation was discovered shortly. We do not understand how to restore homeostasis after infection, how to take actions to damaged tissue, and the mechanisms involved in activating macrophages in situ. In fact, the magnitude and diversity of signals and the magnitude of the response required to convert macrophages into pro-inflammatory states remain unclear. How is the fate of recruited monocytes regulated? What happens to excess macrophages in the tissue after depositing a large number of newly recruited monocytes?

Macrophages are ubiquitous cells in all major tissues. We know that tissue macrophages in many organs have been colonized and self-renewing during embryonic development, independent of blood mononuclear cells. Under inflammatory conditions, those tissue macrophages are replaced by mononuclear cell-derived macrophages that are linked and sometimes recruited. The function of macrophages in homeostasis and disease depends not only on their developmental origin, but also on the tissue environment. Macrophages have attracted worldwide attention because of their great plasticity and functional diversity. In a disease model, it may be that macrophage M1 first exerts anti-inflammatory effects, clears and phagocytose necrotic and apoptotic cells, and then macrophage M2 reconstitutes to promote vascular and tissue production. For macrophages Classification, there is still much controversy in the academic world, but it is clear that the microenvironment and various chemokines in the organization have an indelible contribution to the differentiation of macrophages. Exploring the mechanisms of macrophages in

various diseases can sometimes play a crucial role in the disease.

References

1. Gautier EL, Shay T, Miller J, Greter M, Jakubzick C, Ivanov S, et, al. Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. *Nat Immunol.* 2012;13(11): 1118-1128. doi: 10.1038/ni.2419
2. Melton DW, McManus LM, Gelfond JA, Shireman PK. Temporal phenotypic features distinguish polarized macrophages in vitro. *Autoimmunity.* 2015;48(3): 161-176. doi: 10.3109/08916934.2015.1027816
3. Fujisaka S, Usui I, Bukhari A, Ikutani M, Oya T, Kanatani Y, et, al. Regulatory mechanisms for adipose tissue M1 and M2 macrophages in diet-induced obese mice. *Diabetes.* 2009;58(11):2574-2582. doi: 10.2337/db08-1475
4. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest.* 2012;122(3):787-795. doi: 10.1172/JCI59643
5. Martinez FO, Helming L, Gordon S. Alternative Activation of Macrophages: An Immunologic Functional Perspective. *Annu Rev Immunol.* 2009;27:451-483. doi: 10.1146/annurev.immunol.021908
6. Galvan-Pena S, O'Neill LA. Metabolic reprogramming in macrophage polarization. *Front Immunol.* 2014;5:420. doi: 10.3389/fimmu.2014.00420
7. Zhou D, Yang K, Chen L, Zhang W, Xu Z, Zuo J, et, al. Promising landscape for regulating macrophage polarization: epigenetic viewpoint. *Oncotarget.* 2017;8(34): 57693-57706. doi: 10.18632/oncotarget.17027
8. Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM. M-1/M-2 Macrophages and the Th1/Th2 Paradigm. *J Immunol.* 2000;164(12): 6166-6173.
9. Pesce JT, Ramalingam TR, Mentink-Kane MM, Wilson MS, El Kasmi KC, Smith AM, et, al. Arginase-1-expressing macrophages suppress Th2 cytokine-driven inflammation and fibrosis. *PLoS Pathog.* 2009;5(4): e1000371. doi: 10.1371/journal.ppat.1000371
10. John MacMicking, Xie QW, Nathan C. Nitric oxide and macrophage function. *Annu Rev Immunol.* 1997;15:323-350.
11. Van den Bossche J, Lamers WH, Koehler ES, Geuns JM, Alhonen L, Uimari A, et, al. Pivotal Advance: Arginase-1-independent polyamine production stimulates the expression of IL-4-induced alternatively activated macrophage markers while inhibiting LPS-induced expression of inflammatory genes. *J Leukoc Biol.* 2012;91(5): 685-699. doi: 10.1189/jlb.0911453
12. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol.* 2011;11(11): 723-737. doi: 10.1038/nri3073
13. Thulin P, Wei T, Werngren O, Cheung L, Fisher RM, Grander D, et, al. MicroRNA-9 regulates the expression of peroxisome proliferator-activated receptor delta in human monocytes during the inflammatory response. *Int J Mol Med.* 2013;31(5):1003-1010. doi: 10.3892/ijmm.2013.1311
14. Graff JW, Dickson AM, Clay G, McCaffrey AP, Wilson ME. Identifying functional microRNAs in macrophages with polarized phenotypes. *J Biol Chem.* 2012;287(26):21816-21825. doi: 10.1074/jbc.M111.327031
15. Martinez-Nunez RT, Louafi F, Sanchez-Elsner T. The interleukin 13 (IL-13) pathway in human macrophages is modulated by microRNA-155

- via direct targeting of interleukin 13 receptor alpha1 (IL13Ralpha1). *J Biol Chem.* 2011;286(3):1786-1794. doi: 10.1074/jbc.M110.169367
16. Zhang C-Y, Zhu D, Zhang J, Zen K, Li N, Cai X et al. Re-polarization of tumor-associated macrophages to pro-inflammatory M1 macrophages by microRNA-155. *J Mol Cell Biol.* 2012;4(5): 341-343. doi: 10.1093/jmcb/mjs044
17. Lin L, Hou J, Ma F, Wang P, Liu X, Li N, et, al. Type I IFN inhibits innate IL-10 production in macrophages through histone deacetylase 11 by down regulating microRNA-145. *J Immunol.* 2013;191(7):3896-3904. doi: 10.4049/jimmunol.1203450
18. Qi L, Yu H, Zhang Y, Zhao D, Lv P, Zhong Y, et, al. IL-10 secreted by M2 macrophage promoted tumorigenesis through interaction with JAK2 in glioma. *Oncotarget.* 2016;7(44): 71673-71685. doi: 10.18632/oncotarget.12317
19. Ambade A, Satishchandran A, Saha B, Gyongyosi B, Lowe P, Kodys K, et, al. Hepatocellular carcinoma is accelerated by NASH involving M2 macrophage polarization mediated by hif-1alpha-induced IL-10. *Oncoimmunology.* 2016;5(10): e1221557.
20. Barnawi J, Jersmann H, Haberberger R, Hodge S, Meech R. Reduced DNA methylation of sphingosine-1 phosphate receptor 5 in alveolar macrophages in COPD: A potential link to failed efferocytosis. *Respirology.* 2017;22(2):315-321. doi: 10.1111/resp.12949
21. Date D, Das R, Narla G, Simon DI, Jain MK, Mahabeleshwar GH. Kruppel-like transcription factor 6 regulates inflammatory macrophage polarization. *J Biol Chem.* 2014;289(15):10318-10329. doi: 10.1074/jbc.M113.526749
22. Harbower DM, Asim M, Luis PB, Singh K, Barry DP, Yang C, et, al. Ornithine decarboxylase regulates M1 macrophage activation and mucosal inflammation via histone modifications. *Proc Natl Acad Sci U S A.* 2017;114(5): E751-E760. doi: 10.1073/pnas.1614958114
23. Xu G, Liu G, Xiong S, Liu H, Chen X, Zheng B. The histone methyltransferase Smdy2 is a negative regulator of macrophage activation by suppressing interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) production. *J Biol Chem.* 2015;290(9):5414-5423. doi: 10.1074/jbc.M114.610345
24. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol.* 2008;8(12):958-969. doi: 10.1038/nri2448
25. Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K. Development of monocytes, macrophages, and dendritic cells. *Science.* 2010;327(5966): 656-661. doi: 10.1126/science.1178331
26. Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, et, al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science.* 2010;330(6005):841-845. doi: 10.1126/science.1194637
27. Gordon S, Pluddemann A. Tissue macrophages: heterogeneity and functions. *BMC biology.* 2017;15(1):53. doi: 10.1186/s12915-017-0392-4
28. Hashimoto D, Chow A, Noizat C, Teo P, Beasley MB, Leboeuf M, et, al. Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. *Immunity.* 2013;38(4):792-804. doi: 10.1016/j.immuni.2013.04.004
29. Jakubzick C, Gautier EL, Gibbins SL, Sojka DK, Schlitzer A, Johnson TE, et, al. Minimal differentiation of classical monocytes as they survey steady-state tissues and transport antigen to lymph nodes. *Immunity.* 2013;39(3): 599-610. doi: 10.1016/j.immuni.2013.08.007
30. Hoeffel G, Wang Y, Greter M, See P, Teo P, Malleret B, et, al. Adult Langerhans cells derive predominantly from embryonic fetal liver monocytes with a minor contribution of yolk sac-derived macrophages. *J Exp Med.* 2012;209(6): 1167-1181. doi: 10.1084/jem.20120340
31. Epelman S, Lavine KJ, Beaudin AE, Sojka DK, Carrero JA, Calderon B, et, al. Embryonic and adult-derived resident cardiac macrophages are maintained through distinct mechanisms at steady state and during inflammation. *Immunity.* 2014;40(1):91-104. doi: 10.1016/j.immuni.2013.11.019
32. Perdiguero EG, Klapproth K, Schulz C, Busch K, de Bruijn M, Rodewald HR, et, al. The Origin of Tissue-Resident Macrophages: When an Erythromyeloid Progenitor Is an Erythro-myeloid Progenitor. *Immunity.* 2015;43(6):1023-1024. doi: 10.1016/j.immuni.2015.11.022
33. Bartocci A, Mastrogiannis DS, Migliorati G, Stockert RJ, Wolkoff AW, Stanley ER. Macrophages specifically regulate the concentration of their own growth factor in the circulation. *Proc Natl Acad Sci U S A.* 1987;84(17):6179-6183.
34. Davies LC, Rosas M, Jenkins SJ, Liao CT, Scurr MJ, Brombacher F, et, al. Distinct bone marrow-derived and tissue-resident macrophage lineages proliferate at key stages during inflammation. *Nat Commun.* 2013;4:1886. doi: 10.1038/ncomms2877
35. Hume DA. Differentiation and heterogeneity in the mononuclear phagocyte system. *Mucosal immunol.* 2008;1(6):432-441. doi: 10.1038/mi.2008.36
36. Wynn TA, Barron L. Macrophages: master regulators of inflammation and fibrosis. *Semin Liver Dis.* 2010;30(3):245-257. doi: 10.1055/s-0030-1255354
37. Chitu V, Stanley ER. Colony-stimulating factor-1 in immunity and inflammation. *Curr Opin Immunol.* 2006;18(1):39-48.
38. Erbllich B, Zhu L, Etgen AM, Dobrenis K, Pollard JW. Absence of colony stimulation factor-1 receptor results in loss of microglia, disrupted brain development and olfactory deficits. *PLoS one.* 2011;6(10): e26317. doi: 10.1371/journal.pone.0026317
39. Wei S, Nandi S, Chitu V, Yeung YG, Yu W, et, al. Functional overlap but differential expression of CSF-1 and IL-34 in their CSF-1 receptor-mediated regulation of myeloid cells. *J Leukoc Biol.* 2010;88(3):495-505. doi: 10.1189/jlb.1209822
40. Wang Y, Szretter KJ, Vermi W, Gilfillan S, Rossini C, Cella M, et al. IL-34 is a tissue-restricted ligand of CSF1R required for the development of Langerhans cells and microglia. *Nat Immunol.* 2012;13(8):753-760. doi: 10.1038/ni.2360
41. Sanjurjo L, Aran G, Tellez E, Amezcua N, Armengol C, Lopez D, et, al. CD5L Promotes M2 Macrophage Polarization through Autophagy-Mediated Upregulation of ID3. *Front Immunol.* 2018; 9:480. doi: 10.3389/fimmu.2018.00480
42. Wynn TA, Vannella KM. Macrophages in Tissue Repair, Regeneration, and Fibrosis. *Immunity.* 2016;44(3):450-462. doi: 10.1016/j.immuni.2016.02.015
43. Recalcati S, Gammella E, Buratti P, Doni A, Anselmo A, Locati M, et, al. Macrophage ferroportin is essential for stromal cell proliferation in wound healing. *Haematologica.* 2019;104(1):47-58. doi: 10.3324/haematol.2018

44. Lavine KJ, Epelman S, Uchida K, Weber KJ, Nichols CG, Schilling JD, et al. Distinct macrophage lineages contribute to disparate patterns of cardiac recovery and remodeling in the neonatal and adult heart. *Proc Natl Acad Sci U S A*. 2014;111(45):16029-16034. doi: 10.1073/pnas.1406508111
45. Jay TR, Miller CM, Cheng PJ, Graham LC, Bemiller S, Broihier ML, et al. TREM2 deficiency eliminates TREM2+ inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. *J Exp Med*. 2015;212(3):287-295. doi: 10.1084/jem.20142322
46. Kim E, Cho S. Microglia and Monocyte-Derived Macrophages in Stroke. *NeuroTherapeutics*. 2016;13(4):702-718. doi: 10.1007/s13311-016-0463-1
47. Liao P-C, Chien S-C, Ho C-L, Wang EIC, Lee S-C, Kuo Y-H, et al. Osthole Regulates Inflammatory Mediator Expression through Modulating NF- κ B, Mitogen-Activated Protein Kinases, Protein Kinase C, and Reactive Oxygen Species. *J Agric Food Chem*. 2010;58(19):10445-10451. doi: 10.1021/jf102812t
48. Goschorska M, Gutowska I, Baranowska-Bosiacka I, Piotrowska K, Metryka E, Safranow K, et al. Influence of Acetylcholinesterase Inhibitors Used in Alzheimer's Disease Treatment on the Activity of Antioxidant Enzymes and the Concentration of Glutathione in THP-1 Macrophages under Fluoride-Induced Oxidative Stress. *Int J Environ Res Public Health*. 2018;16(1):doi: 10.3390/ijerph16010010
49. Bernal W, Lee WM, Wendon J, Larsen FS, Williams R. Acute liver failure: A curable disease by 2024? *J Hepatol*. 2015;62 (1 Suppl): S112-120. doi: 10.1016/j.jhep.2014.12.016
50. Bai L, Fu L, Li L, Ren F, Zheng Q, Liu S, et al. Cellular Mechanisms of Hepatoprotection Mediated by M2-Like Macrophages. *Med Sci Monit*. 2018;24:2675-2682. doi: 10.12659/MSM.907222
51. Gurevich DB, Severn CE, Twomey C, Greenhough A, Cash J, Teye AM, et al. Live imaging of wound angiogenesis reveals macrophage orchestrated vessel sprouting and regression. *EMBO J*. 2018;37(13):doi: 10.15252/embj.201797786
52. Leblond AL, Klinkert K, Martin K, Turner EC, Kumar AH, Browne T et al. Systemic and Cardiac Depletion of M2 Macrophage through CSF-1R Signaling Inhibition Alters Cardiac Function Post Myocardial Infarction. *PloS one*. 2015;10:e0137515.
53. Lee JH, Budanov AV, Karin M. Sestrins orchestrate cellular metabolism to attenuate aging. *Cell Metab*. 2013;18(6):792-801. doi: 10.1016/j.cmet.2013.08.018
54. Morrison A, Chen L, Wang J, Zhang M, Yang H, Ma Y, et al. Sestrin2 promotes LKB1-mediated AMPK activation in the ischemic heart. *FASEB J*. 2015;29(2):408-417. doi: 10.1096/fj.14-258814
55. Yang K, Xu C, Zhang Y, He S, Li D. Sestrin2 Suppresses Classically Activated Macrophages-Mediated Inflammatory Response in Myocardial Infarction through Inhibition of mTORC1 Signaling. *Front Immunol*. 2017;8:728. doi: 10.3389/fimmu.2017.00728