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Importance Of Physical Exercise On Macrophage Polarization: A Relation To Disease Concern

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Abstract

Macrophages are specialized cells, originated from blood monocyte, differentiate in tissues, and involved in the destruction of foreign pathogens. They also can release cytokines and activate other cells and initiate inflammation. Macrophage polarization from M1 type to M2 –type has been found to be related to various diseases including cancer, diabetes, coronary artery diseases (CAD), etc. Here we did a brief review to convince that regular light to intense type physical exercise can induce polarization of macrophage from its one form (M1) to the other form (M2), and can improve the various disease conditions. The cellular as well as the molecular events that are found with the physical exercise (PE) indicate that the PE could be a non-pharmacological management for various diseases having no side effects.

Keywords: Physical Exercise, Macrophages, Health and Disease, Immunity, Non-medicinal management.

Introduction

Macrophages and What it does Normally

Macrophages are motile defensive regiment in our bodies as they recognize the foreign pathogens and destroy them, The Toll-like recognition receptors of macrophages bind specifically to LPS, RNA, DNA or extracellular proteins (Flagellin) of different pathogens. Besides, macrophages can also present T-Cell antigens, initiate cytokine release to activate other cells, and inflammation. Since macrophages differentiate in different tissues, they are heterogenic which reflects the effects of the environment on any given tissue, and causes them to have different morphology. The recognition ability of the pathogens as well as the levels of the released cytokines, like IL-1, IL-6, TNFα, also differs. Macrophages, further, can produce Nitric oxide, a reactive oxygen species to kill the phagocytized bacteria. Macrophages are heterogenic which reflects

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the effects of different environment that causes them to have different morphology, varied recognition ability of the pathogens and different production ability of IL-1, IL-6, tumor necrosis factor alpha. Macrophages also produces nitric oxide, a reactive oxygen species, which can kill the phagocytized bacteria.

Types of Macrophages

Alveolar macrophages: They phagocytized dead cells, bacteria, and induce immunity against respiratory pathogens.

Kupffer cells: Presents in Liver, and control immunity to respiratory pathogens.

Microglia: Presents in central nervous system; eliminate dead neurons.

Splenic macrophages: Located in spleen, and eliminates dysfunctional or old erythrocytes.

Macrophage Polarization

It is a process in which macrophages response to the micro-environmental signals and adopt different functional programs, such as development of innate immune system, removal of dead cells, and tissue repair [1]. There are two different Macrophage phenotypes, one is M1 (classically activated macrophages), and the other one is M2 (alternatively activated macrophages) [2, 3]. M1 macrophages are known as pro-inflammatory type, involved in direct host-defense activity against foreign pathogens, while the M2 type macrophages are engaged for the repair of damaged tissues and also acts to reduce the inflammation. Later on it was revealed by *in vivo* as well as *ex-vivo* studies that macrophages phenotypes are much more diverse in connection with the gene expression and related functional activities [4-10].

The imbalance between M1 and M2 types of macrophages has been found in many immunological diseases [11, 12]. Inflammatory bowel disease (IBS) [13, 14], obesity in mice [15-17], tissue *fibrosis* [18], systemic sclerosis [11, 19-21], are few examples from many, where M1 vs M2 ratio differs. M1/M2 polarization are the results from arginine metabolism. Arginine can be metabolized by iNOS pathway which results M1-like macrophages, whereas M2-like macrophages are produced when arginine is metabolized to urea and ornithine [22].

Besides, activation by lipopolysaccharide (LPS) and Th1 cytokines (such as IFN-γ and TNF-α) can cause macrophages polarization M1-type, which can be detected by the surface expression of TLR-2, TLR-4, CD80, CD86, iNOS, and MHC-II. These M1-type cells, in turn, release various chemokines and cytokines (e.g., TNF-α, IL-1α, IL-1β, IL-6, IL-12, CXCL9, and CXCL10). The key transcription factors, STAT1, STAT5, IRF3, NF-κB, and IRF5, regulate the expression of M1 genes, and results in polarization of M1-type macrophages and their microbicidal and tumoricidal functions [23-27]. The various cytokine signaling molecules such as IL-4, IL-13, IL-10, IL-33, and TGF-β, enhances M2 polarization [25, 27]. Only IL-4 and IL-13 while directly acts on M2-type macrophage activation, IL-33 and IL-25 activates M2 polarization via Th2 cytokines [28].

M2 macrophages activation can be identified by their expression of surface markers, such as CD206, CD163, CD209, mannitol receptor (MR), Ym1/2, and FIZZ1 [28]. The induced expression of various chemokines and cytokines, like IL-10, TGF-β, CCLs, can polarize macrophages into its M2 state [27-30]. M2 macrophages are known to involve in infection prevention, angiogenesis tissue repairing and immunomodulation [25, 31]. Various transcription factors, such as JMJD3, IRF4, STAT6, PPARδ, and PPARγ activate macrophages [23]. Figure 1 shows the main differences of M1-type from M2-type of macrophages.

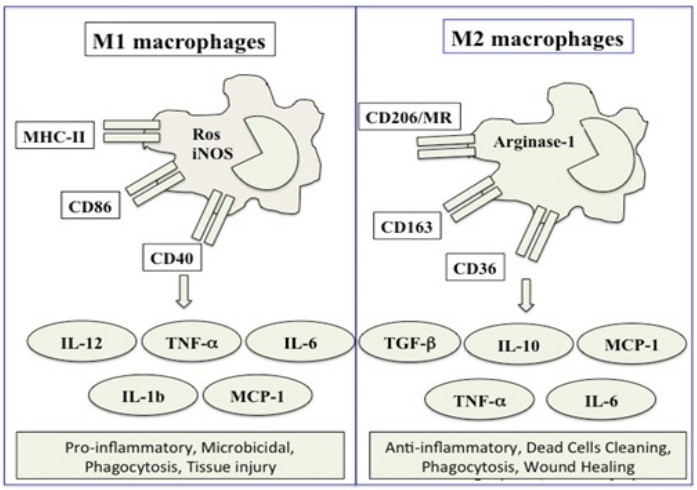

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Figure 1: Summary of the main macrophage polarization states of activated macrophages

Different stimuli and signaling pathways of M1-like or M2-like macrophages activation are summarized here.

LPS: Lipopolysaccharide; MR: Mannose receptor; TNF: Tumor necrosis factor;

IL: Interleukin; MCP: Monocyte chemoattractant protein; TGF: Transforming growth factor; iNOS: Inducible nitric oxide synthase.

Polarization of Macrophages Polarization in Health and Disease

Innate Immunity: Twenty percent of all mononuclear cells in mucosal tissues are macrophages, and they are responsible for any localized responses [32]. M1-type macrophages while facilitate Th1 responses, the M2-type of macrophages exhibit the development of Th2 responses [4, 33-35]. However, their role on natural killer (NK) cell activity and on T regulatory (Treg) immune-suppressive cells are still unknown.

A recent study revealed that both M1 and M2- type of macrophage cells can activate NK cell degranulation, but only M1-macrophages when infected with the human cytomegalovirus can trigger NK-cell-mediated IFN-γ production [36, 37]. Interestingly, Savage et al. (2008) have shown that only M2, and not M1, macrophages can cause differentiation of Treg cells with a strong suppressive phenotype [38, 39], and which involved the cell-cell contact and the expression of membrane-bound TGF-β1 [39]. Thus, macrophage polarization are involved in various aspects of adaptive as well as innate immunity [40].

Macrophage Diversity in Systems Biology

Systems biology include the heterogeneity of mononuclear phagocytes, the bio-mechanics and the molecular pathway of macrophage polarization. Transcriptome analysis should enable to obtain a clear picture of human macrophage polarization [34].

A prominent feature of macrophage polarization is the modulation of cellular metabolic gene(s), such as apolipoproteins which are involved in cholesterol transport [34]. However, it was noticed that M1-type macrophages polarization cause the changes in the transcriptome profile, whereas M2-type macrophages polarization are not associated with the gene expression. Epigenetic studies open up the question how macrophage polarization occurs and maintain their phenotype. It was shown that epigenetically regulation of transcription 6-(STAT6-) can modify the induction of the M2-macrophages genes, H3K27 demethylase, in mice [41, 42]. Zhang et al. (2011) recently, have shown that an alteration of expression of genes, IFN-γ, IFN-α, and IL-4, after macrophage polarization are involved with the cytokine-mediated H4 acetylation (H4ac) [43]. Thus, it appears that a broader view on macrophage polarization can explain their heterogeneity and plasticity.

Macrophage Polarization in Cancer Progression

All solid tumors are highly associated with macrophages into their microenvironment, and it is now evident that tumor-associated macrophages (TAMs) play several roles, sometimes “foe-to-friend” during tumor development [44]. Generally, it was known that macrophages kill tumor cells *in vitro* [45], however, later on it appears that TAMs can promote tumor progression, including their metastatic phase, rather than counteracting them [46, 47]. Both, experimental as well as clinical studies indicates that human tumors loaded with TAMs indicate a poor prognosis almost in >80% of the cases [48]. These observations suggest that the tumor environment causes a polarization of tumor-associated macrophages to adopt an M2-related profile which helps tumor progression.

Indeed, TAMs isolated from progressive tumors and in developing tissues are functionally similar, therefore the notion become obvious that macrophages can facilitate the tumor progression as well as their metastatic growth Table 1.

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Disease	Markers	References
Cancer		
Invasive macrophages:	WNT+; EGF+	[45, 7 1-73]
Activated macrophages:	IL-12+; MHC-IIHI; TNF-a+, CD80/86+	[74, 75]
Immunosuppressive macrophages:	Arginase+; MARCO+;	[76, 77]
	IL-10+; CCL-22+	
Angiogenic macrophages:	VEGFl +; VEGF+; CXCR4+;Tie2+; EST2+	[78-81]
Metastasis-associated macrophages:	VEGFl +; CXCR4+; CCR2+; Tie2+	[70, 82-84]
FoxP3+ (Regulatory macrophages):	PGE2; Arg-2; IL- la; CXCL4, CCI7 CCL9; CXCL12; CXCL13; PDGF,VEDF	[85]
HIV		
HIV-transn1itting macrophages:	DC-SIGN+; CD163; CD206; High Phagocytosis	[57]
HIV-resistant macrophages:	APOBEC3A +; Low phagocytosis	[57]
Other		
Perivascular macrophages:	Phagocytosis	[86, 87]

Table-I: Subpopulations of Macrophages in Different Pathologies

Macrophage Polarization in Viral Diseases

The function of macrophage polarization due to viral infections is not yet defined well. A good example is macrophage altered behavior in presence of HIV-1 pathogen. In advanced cases of the infection from HIV, the most dysfunction is the defective migration of monocytes to chemoattractants [49, 50], down-regulation of C5α chemotactic receptors and f-MLP, a bacterial tripeptide [51, 52]. However, HIV^+ monocytes and alveolar macrophages showed a reduced phagocytic activity [53, 54], decreased fusion of phagosome-lysosome, and poor intracellular killing of pathogens [55, 56]. It was reported that *in vitro* polarization of macrophages to M1 or M2-type, strongly inhibited the replication of HIV-1 and also affects the virus life cycle [57]. Besides all the above scenarios, macrophage polarization has been described for various other diseases like, diabetes, sclerosis, coronary artery disease (CAD), etc. [40, 58].

How physical exercise is Connected to Macrophage Polarization

It was reported that an intense exercise inhibits toll-like receptor 4 (TLR4) signalling pathway and thereby reduces the inflammation in obese rats [59]. Consistent with this, Xu et. al. (2011) also showed that exercise training has significant anti-inflammatory effects on obese mice [60]. In humans, exercise- induced anti-inflammations were also observed as noticed the lower levels of CD68, CD14, iNOS and TNF-α, all the macrophage-specific markers at post-exercise session [61]. All these indicate that regular aerobic physical activity, at least for 60 min a day, can promote an anti-inflammatory effects and macrophage polarization to its M2-state [62].

Intense Physical Exercise Induces the Expression of IL-10, and IL-4

A regular intense physical exercise can induce M2-type macrophages activation along with increased IL-10 expression. Further, an acute exercise can induce the expression of IL-4, a cytokine that triggers the alternative macrophage phenotype [63].

Physical Exercise Decreases the Blood Levels of LPS

LPS (Lipopolysaccharides) can regulate macrophage polarization [59, 64]. Both mild to intense aerobic physical exercises can decrease the blood levels of LPS, and there after reduces the M2 activation of macrophages. Physical activity, in human, positively impacts on both monocytes and macrophages, causing the polarization of macrophages in skeletal muscles,

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Discussion

Regular, even moderate-type aerobic exercise can induce a polarization M1 macrophages into M2-type in obese rats [62]. In addition, the rigorous exercise can reduced the expression of TNF-α, IL-1β, and MCP-1, some pro-inflammatory cytokines in rat adipocytes, and also induces insulin signaling there [62]. These suggest that exercise can induce macrophage polarization and thereby improves insulin signaling, at least in part. However, physical exercises although might decrease the pro-inflammatory status of macrophages in both rodents and human, it remains unclear whether exercises can affect the infiltrated macrophages or not.

IL-4 and IL-13 induced expression of PPAR δ was found to be associated with M2-macrophages in rat adipose tissues [63]. Accordingly, IL-4 and IL-13 cytokines produces immunosuppressive factors, such as IL-10, IL-1RA, and arginase [34]. Infact, IL-4 mRNA expression was higher in an acutely exercised animals [62].

Physical exercise enhances lipolysis. We can therefore hypothesize that the lipolysis and/or physical exercise, may have a role in the exercise-induced macrophage polarization towards the M2 activation [69]. In conclusion, we convince that regular moderate to intense physical aerobic exercises, like swimming, jogging, running, cycling, will induce macrophage polarization towards the M2 phenotype, and therefore may be a useful non-pharmacological management for various diseases with no side effects.

Ethical Statements

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References

1. Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. Nature. 2013 Apr;496(7446):445-55.

2. Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM. M-1/M-2 macrophages and the Th1/Th2 paradigm. The Journal of immunology. 2000 Jun 15;164(12):6166-73.

3. Sridharan R, Cavanagh B, Cameron AR, Kelly DJ, O'Brien FJ. Material stiffness influences the polarization state, function and migration mode of macrophages. Acta biomaterialia. 2019 Apr 15; 89:47-59.

4. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nature reviews immunology. 2008 Dec;8(12):958-69.

5. Kreider T, Anthony RM, Urban Jr JF, Gause WC. Alternatively, activated macrophages in helminth infections. Current opinion in immunology. 2007 Aug 1;19(4):448-53.

6. Rőszer T. Understanding the mysterious M2 macrophage through activation markers and effector mechanisms. Mediators of inflammation. 2015 Oct;2015.

7. Xue J, Schmidt SV, Sander J, Draffehn A, Krebs W, Quester I, De Nardo D, Gohel TD, Emde M, Schmidleithner L, Ganesan H. Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. Immunity. 2014 Feb 20;40(2):274-88.

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Advanced Biochemistry

Review Article Open Access

8. Gautier EL, Shay T, Miller J, Greter M, Jakubzick C, Ivanov S, Helft J, Chow A, Elpek KG, Gordonov S, Mazloom AR. Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. Nature immunology. 2012 Nov;13(11):1118-28.

9. Lavin Y, Winter D, Blecher-Gonen R, David E, Keren-Shaul H, Merad M, Jung S, Amit I. Tissue-resident macrophage enhancer landscapes are shaped by the local microenvironment. Cell. 2014 Dec 4;159(6):1312-26.

10. Ginhoux F, Schultze JL, Murray PJ, Ochando J, Biswas SK. New insights into the multidimensional concept of macrophage ontogeny, activation and function. Nature immunology. 2016 Jan;17(1):34-40.

11. Funes SC, Rios M, Escobar-Vera J, Kalergis AM. Implications of macrophage polarization in autoimmunity. Immunology. 2018 Jun;154(2):186-95.

12. Wermuth PJ, Jimenez SA. The significance of macrophage polarization subtypes for animal models of tissue fibrosis and human fibrotic diseases. Clinical and translational medicine. 2015 Dec;4(1):1-9.

13. Lissner D, Schumann M, Batra A, Kredel LI, Kühl AA, Erben U, May C, Schulzke JD, Siegmund B. Monocyte and M1 macrophage-induced barrier defect contributes to chronic intestinal inflammation in IBD. Inflammatory bowel diseases. 2015 Jun 1;21(6):1297-305.

14. Zhu W, Yu J, Nie Y, Shi X, Liu Y, Li F, Zhang XL. Disequilibrium of M1 and M2 macrophages correlates with the development of experimental inflammatory bowel diseases. Immunological investigations. 2014 Oct 1;43(7):638-52.

15. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. The Journal of clinical investigation. 2007 Jan 2;117(1):175-84.

16. Ohashi K, Parker JL, Ouchi N, Higuchi A, Vita JA, Gokce N, Pedersen AA, Kalthoff C, Tullin S, Sams A, Summer R. Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. Journal of Biological Chemistry. 2010 Feb 26;285(9):6153-60.

17. Cucak H, Grunnet LG, Rosendahl A. Accumulation of M1-like macrophages in type 2 diabetic islets is followed by a systemic shift in macrophage polarization. Journal of leukocyte biology. 2014 Jan;95(1):149-60.

18. Wermuth PJ, Jimenez SA. The significance of macrophage polarization subtypes for animal models of tissue fibrosis and human fibrotic diseases. Clinical and translational medicine. 2015 Dec;4(1):1-9.

19. Soldano S, Contini P, Brizzolara R, Montagna P, Sulli A, Paolino S, Cutolo M. A1. 13 Increased presence of CD206+ macrophage subset in peripheral blood of systemic sclerosis patients.

20. Yao Y, Xu XH, Jin L. Macrophage polarization in physiological and pathological pregnancy. Frontiers in immunology. 2019 Apr 15; 10:792.

21. Patel U, Rajasingh S, Samanta S, Cao T, Dawn B, Rajasingh J. Macrophage polarization in response to epigenetic modifiers during infection and inflammation. Drug discovery today. 2017 Jan 1;22(1):186-93.

22. Lampiasi N, Russo R, Zito F. The alternative faces of macrophage generate osteoclasts. BioMed research international. 2016 Oct;2016.

23. Murray PJ. Macrophage polarization. Annual review of physiology. 2017 Feb 10; 79:541-66.

Journal of
Advanced Biochemistry

Review Article Open Access

24. Weisser SB, McLarren KW, Kuroda E, Sly LM. Generation and characterization of murine alternatively activated macrophages. InBasic Cell Culture Protocols 2013 (pp. 225-239). Humana Press, Totowa, NJ.

25. Porta C, Riboldi E, Ippolito A, Sica A. Molecular and epigenetic basis of macrophage polarized activation. InSeminars in immunology 2015 Aug 1 (Vol. 27, No. 4, pp. 237-248). Academic Press.

26. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000prime reports. 2014;6.

27. Wang N, Liang H, Zen K. Molecular mechanisms that influence the macrophage M1–M2 polarization balance. Frontiers in immunology. 2014 Nov 28; 5:614.

28. O'Shea JJ, Paul WE. Mechanisms underlying lineage commitment and plasticity of helper CD4+ T cells. Science. 2010 Feb 26;327(5969):1098-102.

29. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. Immunity. 2010 May 28;32(5):593-604.

30. Mulder R, Banete A, Basta S. Spleen-derived macrophages are readily polarized into classically activated (M1) or alternatively activated (M2) states. Immunobiology. 2014 Oct 1;219(10):737-45.

31. Mantovani A, Biswas SK, Galdiero MR, Sica A, Locati M. Macrophage plasticity and polarization in tissue repair and remodelling. The Journal of pathology. 2013 Jan;229(2):176-85.

32. Carter CA, Ehrlich LS. Cell biology of HIV-1 infection of macrophages. Annu. Rev. Microbiol.. 2008 Oct 13; 62:425-43.

33. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Nature reviews immunology. 2005 Dec;5(12):953-64.

34. Martinez FO, Gordon S, Locati M, Mantovani A. Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression. The Journal of Immunology. 2006 Nov 15;177(10):7303-11.

35. Mantovani A, Sica A, Allavena P, Garlanda C, Locati M. Tumor-associated macrophages and the related myeloid-derived suppressor cells as a paradigm of the diversity of macrophage activation. Human immunology. 2009 May 1;70(5):325-30.

36. Altfeld M, Fadda L, Frleta D, Bhardwaj N. DCs and NK cells: critical effectors in the immune response to HIV-1. Nature Reviews Immunology. 2011 Mar;11(3):176-86.

37. Romo N, Magri G, Muntasell A, Heredia G, Baía D, Angulo A, Guma M, López-Botet M. Natural killer cell-mediated response to human cytomegalovirus-infected macrophages is modulated by their functional polarization. Journal of leukocyte biology. 2011 Oct;90(4):717-26.

38. Tiemessen MM, Jagger AL, Evans HG, van Herwijnen MJ, John S, Taams LS. CD4+ CD25+ Foxp3+ regulatory T cells induce alternative activation of human monocytes/macrophages. Proceedings of the national academy of sciences. 2007 Dec 4;104(49):19446-51.

39. Savage ND, de Boer T, Walburg KV, Joosten SA, van Meijgaarden K, Geluk A, Ottenhoff TH. Human anti-inflammatory macrophages induce Foxp3+ GITR+ CD25+ regulatory T cells, which suppress via membrane-bound TGFβ-1. The Journal of Immunology. 2008 Aug 1;181(3):2220-6.

40. Cassetta L, Cassol E, Poli G. Macrophage polarization in health and disease. TheScientificWorldJournal. 2011 Jan 1;11.

41. Pena OM, Pistolic J, Raj D, Fjell CD, Hancock RE. Endotoxin tolerance represents a distinctive state of alternative polarization (M2) in human mononuclear cells. The Journal of Immunology. 2011 Jun 15;186(12):7243-54.

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Advanced Biochemistry

Review Article Open Access

42. Ishii M, Wen H, Corsa CA, Liu T, Coelho AL, Allen RM, Carson WF, Cavassani KA, Li X, Lukacs NW, Hogaboam CM. Epigenetic regulation of the alternatively activated macrophage phenotype. Blood. 2009 Oct 8;114(15):3244-54.

43. Zhang Z, Song L, Maurer K, Bagashev A, Sullivan KE. Monocyte polarization: the relationship of genome-wide changes in H4 acetylation with polarization. Genes & Immunity. 2011 Sep;12(6):445-56.

44. Allavena P, Mantovani A. Immunology in the clinic review series; focus on cancer: tumour-associated macrophages: undisputed stars of the inflammatory tumour microenvironment. Clinical & Experimental Immunology. 2012 Feb;167(2):195-205.

45. Klimp AH, De Vries EG, Scherphof GL, Daemen T. A potential role of macrophage activation in the treatment of cancer. Critical reviews in oncology/hematology. 2002 Nov 1;44(2):143-61.

46. Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell. 2006 Jan 27;124(2):263-6.

47. Mantovani A, Schioppa T, Porta C, Allavena P, Sica A. Role of tumor-associated macrophages in tumor progression and invasion. Cancer and Metastasis Reviews. 2006 Sep;25(3):315-22.

48. Mantovani A, Schioppa T, Porta C, Allavena P, Sica A. Role of tumor-associated macrophages in tumor progression and invasion. Cancer and Metastasis Reviews. 2006 Sep;25(3):315-22.

49. Smith PD, Ohura K, Masur H, Lane HC, Fauci AS, Wahl SM. Monocyte function in the acquired immune deficiency syndrome. Defective chemotaxis. The Journal of clinical investigation. 1984 Dec 1;74(6):2121-8.

50. Poli G, Bottazzi B, Acero R, Bersani L, Rossi V, Introna M, Lazzarin A, Galli M, Mantovani A. Monocyte function in intravenous drug abusers with lymphadenopathy syndrome and in patients with acquired immunodeficiency syndrome: selective impairment of chemotaxis. Clinical and experimental immunology. 1985 Oct;62(1):136.

51. Mastroianni CM, Lichtner M, Mengoni F, Claudia D, Forcina G, Santopadre P, Vullo V. Improvement in neutrophil and monocyte function during highly active antiretroviral treatment of HIV-1-infected patients. Aids. 1999 May 28;13(8):883-90.

52. Wahl SM, Allen JB, Gartner S, Orenstein JM, Popovic M, Chenoweth DE, Arthur LO, Farrar WL, Wahl LM. HIV-1 and its envelope glycoprotein down-regulate chemotactic ligand receptors and chemotactic function of peripheral blood monocytes. The Journal of Immunology. 1989 May 15;142(10):3553-9.

53. Kedzierska K, Crowe SM. The role of monocytes and macrophages in the pathogenesis of HIV-1 infection. Current medicinal chemistry. 2002 Nov 1;9(21):1893-903.

54. Musher DM, Watson DA, Nickeson D, Gyorkey F, Lahart C, Rossen RD. The effect of HIV infection on phagocytosis and killing of Staphylococcus aureus by human pulmonary alveolar macrophages. The American journal of the medical sciences. 1990 Mar 1;299(3):158-63.

55. Kedzierska K, Crowe SM. The role of monocytes and macrophages in the pathogenesis of HIV-1 infection. Current medicinal chemistry. 2002 Nov 1;9(21):1893-903.

56. Pittis MG, Prada F, Mangano A, Perez L, Sternik G, Redondo J, Bologna R, Sen L. Monocyte phagolysosomal fusion in children born to human immunodeficiency virus-infected mothers. The Pediatric infectious disease journal. 1997 Jan 1;16(1):24-8.

Journal of
Advanced Biochemistry

Review Article Open Access

57. Cassol E, Cassetta L, Rizzi C, Alfano M, Poli G. M1 and M2a polarization of human monocyte-derived macrophages inhibits HIV-1 replication by distinct mechanisms. The Journal of Immunology. 2009 May 15;182(10):6237-46.

58. Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, Seifi B, Mohammadi A, Afshari JT, Sahebkar A. Macrophage plasticity, polarization, and function in health and disease. Journal of cellular physiology. 2018 Sep;233(9):6425-40.

59. Stein M, Keshav S, Harris N, Gordon S. Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. The Journal of experimental medicine. 1992 Jul 1;176(1):287-92.

60. Xu X, Ying Z, Cai M, Xu Z, Li Y, Jiang SY, Tzan K, Wang A, Parthasarathy S, He G, Rajagopalan S. Exercise ameliorates high-fat diet-induced metabolic and vascular dysfunction, and increases adipocyte progenitor cell population in brown adipose tissue. American journal of physiology-regulatory, integrative and comparative physiology. 2011 May;300(5): R1115-25.

61. Bruun JM, Helge JW, Richelsen B, Stallknecht B. Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects. American Journal of Physiology-Endocrinology and Metabolism. 2006 May;290(5): E961-7.

62. Oliveira AG, Araujo TG, Carvalho BM, Guadagnini D, Rocha GZ, Bagarolli RA, Carvalheira JB, Saad MJ. Acute exercise induces a phenotypic switch in adipose tissue macrophage polarization in diet-induced obese rats. Obesity. 2013 Dec;21(12):2545-56.

63. Kang K, Reilly SM, Karabacak V, Gangl MR, Fitzgerald K, Hatano B, Lee CH. Adipocyte-derived Th2 cytokines and myeloid PPARδ regulate macrophage polarization and insulin sensitivity. Cell metabolism. 2008 Jun 4;7(6):485-95.

64. Nau GJ, Richmond JF, Schlesinger A, Jennings EG, Lander ES, Young RA. Human macrophage activation programs induced by bacterial pathogens. Proceedings of the National Academy of Sciences. 2002 Feb 5;99(3):1503-8.

65. Shinkai S, Shore S, Shek PN, Shephard RJ. Acute exercise and immune function. International journal of sports medicine. 1992 Aug;13(06):452-61.

66. Walton RG, Kosmac K, Mula J, Fry CS, Peck BD, Groshong JS, Finlin BS, Zhu B, Kern PA, Peterson CA. Human skeletal muscle macrophages increase following cycle training and are associated with adaptations that may facilitate growth. Scientific reports. 2019 Jan 30;9(1):1-4.

67. Kawanishi N, Yano H, Yokogawa Y, Suzuki K. Exercise training inhibits inflammation in adipose tissue via both suppression of macrophage infiltration and acceleration of phenotypic switching from M1 to M2 macrophages in high-fat-diet-induced obese mice. Exercise immunology review. 2010 Jan 1;16.

68. Blanks AM, Wagamon TT, Lafratta L, Sisk MG, Senter MB, Pedersen LN, Bohmke N, Shah A, Mihalick VL, Franco RL. Impact of physical activity on monocyte subset CCR2 expression and macrophage polarization following moderate intensity exercise. Brain, Behavior, & Immunity-Health. 2020 Feb 1; 2:100033.

69. Kosteli A, Sugaru E, Haemmerle G, Martin JF, Lei J, Zechner R, Ferrante AW. Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. The Journal of clinical investigation. 2010 Oct 1;120(10):3466-79.

70. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell. 2010 Apr 2;141(1):39-51.

Journal of
Advanced Biochemistry

Review Article Open Access

71. Wyckoff J, Wang W, Lin EY, Wang Y, Pixley F, Stanley ER, Graf T, Pollard JW, Segall J, Condeelis J. A paracrine loop between tumor cells and macrophages is required for tumor cell migration in mammary tumors. Cancer research. 2004 Oct 1;64(19):7022-9.

72. Wyckoff JB, Wang Y, Lin EY, Li JF, Goswami S, Stanley ER, Segall JE, Pollard JW, Condeelis J. Direct visualization of macrophage-assisted tumor cell intravasation in mammary tumors. Cancer research. 2007 Mar 15;67(6):2649-56.

73. Ojalvo LS, Whittaker CA, Condeelis JS, Pollard JW. Gene expression analysis of macrophages that facilitate tumor invasion supports a role for Wnt-signaling in mediating their activity in primary mammary tumors. The journal of immunology. 2010 Jan 15;184(2):702-12.

74. Enzler T, Gillessen S, Manis JP, Ferguson D, Fleming J, Alt FW, Mihm M, Dranoff G. Deficiencies of GM-CSF and interferon γ link inflammation and cancer. The Journal of experimental medicine. 2003 May 5;197(9):1213-9.

75. Deng L, Zhou JF, Sellers RS, Li JF, Nguyen AV, Wang Y, Orlofsky A, Liu Q, Hume DA, Pollard JW, Augenlicht L. A novel mouse model of inflammatory bowel disease links mammalian target of rapamycin-dependent hyperproliferation of colonic epithelium to inflammation-associated tumorigenesis. The American journal of pathology. 2010 Feb 1;176(2):952-67.

76. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nature reviews immunology. 2009 Mar;9(3):162-74.

77. Pucci F, Venneri MA, Biziato D, Nonis A, Moi D, Sica A, Di Serio C, Naldini L, De Palma M. A distinguishing gene signature shared by tumor-infiltrating Tie2-expressing monocytes, blood "resident" monocytes, and embryonic macrophages suggests common functions and developmental relationships. Blood. 2009 Jul 23;114(4):901-14.

78. Kimura YN, Watari K, Fotovati A, Hosoi F, Yasumoto K, Izumi H, Kohno K, Umezawa K, Iguchi H, Shirouzu K, Takamori S. Inflammatory stimuli from macrophages and cancer cells synergistically promote tumor growth and angiogenesis. Cancer science. 2007 Dec;98(12):2009-18.

79. Gazzaniga S, Bravo AI, Guglielmotti A, Van Rooijen N, Maschi F, Vecchi A, Mantovani A, Mordoh J, Wainstok R. Targeting tumor-associated macrophages and inhibition of MCP-1 reduce angiogenesis and tumor growth in a human melanoma xenograft. Journal of Investigative Dermatology. 2007 Aug 1;127(8):2031-41.

80. Lin EY, Li JF, Bricard G, Wang W, Deng Y, Sellers R, Porcelli SA, Pollard JW. Vascular endothelial growth factor restores delayed tumor progression in tumors depleted of macrophages. Molecular oncology. 2007 Dec 1;1(3):288-302.

81. Lin EY, Li JF, Gnatovskiy L, Deng Y, Zhu L, Grzesik DA, Qian H, Xue XN, Pollard JW. Macrophages regulate the angiogenic switch in a mouse model of breast cancer. Cancer research. 2006 Dec 1;66(23):11238-46.

82. Kaplan RN, Riba RD, Zacharoulis S, Bramley AH, Vincent L, Costa C, MacDonald DD, Jin DK, Shido K, Kerns SA, Zhu Z. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature. 2005 Dec;438(7069):820-7.

83. Hiratsuka S, Watanabe A, Sakurai Y, Akashi-Takamura S, Ishibashi S, Miyake K, Shibuya M, Akira S, Aburatani H, Maru Y. The S100A8–serum amyloid A3–TLR4 paracrine cascade establishes a pre-metastatic phase. Nature cell biology. 2008 Nov;10(11):1349-55.

84. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nature reviews cancer. 2009 Apr;9(4):239-52.

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85. Zorro Manrique S, Duque Correa MA, Hoelzinger DB, Dominguez AL, Mirza N, Lin HH, Stein-Streilein J, Gordon S, Lustgarten J. Foxp3-positive macrophages display immunosuppressive properties and promote tumor growth. Journal of Experimental Medicine. 2011 Jul 4;208(7):1485-99.

86. Gligorijevic B, Kedrin D, Segall JE, Condeelis J, van Rheenen J. Dendra2 photoswitching through the mammary imaging window. Journal of visualized experiments: JoVE. 2009(28).

87. Ingman WV, Wyckoff J, Gouon-Evans V, Condeelis J, Pollard JW. Macrophages promote collagen fibrillogenesis around terminal end buds of the developing mammary gland. Developmental dynamics: an official publication of the American Association of Anatomists. 2006 Dec;235(12):3222-9.