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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 with minimal 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 [1,2].

Macrophages are heterogenic which reflects 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 [3,4].

Types of macrophages

1. *Alveolar macrophages:* They phagocytized dead cells, bacteria, and induce immunity against respiratory pathogens.
2. *Kupffer cells:* Presents in Liver, and control immunity to respiratory pathogens.
3. *Microglia:* Presents in central nervous system; eliminate dead neurons.
4. *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 foe the repair of damaged tissues and also in the regulation of 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 is related to a number of immunological diseases [11, 12]. Development of 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 ornithine and urea [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, CCL1, CCL17, CCL18, CCL22, and CCL24, can polarize macrophages into its M2 state [27-30]. M2 macrophgaes 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]. The main differences of M1-type from M2-type of macrophages.

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 showed that both M1 and M2- type of macrophage cells can activate NK cell degranulation, but only M1-macrophages infected with the human cytomegalovirus can trigger NK-cell-mediated IFN-*γ* production [36-38]. Interestingly, Savage et al. (2008) [39] have shown that M2, but not M1, macrophages can cause differentiation of Treg cells with a strong suppressive phenotype, and which involved the cell-cell contact and the expression of membrane-bound TGF-β1. Thus, macrophage polarization is involved in multiple aspects of both the adaptive and 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 broad view of human macrophage polarization [34].

A prominent feature of macrophage polarization is the modulation of cellular metabolic gene(s), such as apolipoproteins (APOL1, APOL2, APOL3, and APOL6) that are involved in cholesterol transport [34]. However, it was noticed that while M1-type macrophages polarization was associated with the changes in the transcriptome profile, M2-type macrophages polarization are associated with minimal alterations in gene expression. Epigenetic studies open up the question how polarized macrophages acquire and maintain their activation phenotype. It was shown that epigenetically regulation of transcription 6-(STAT6-) can modify the induction of the H3K27 demethylase Jmjd3 M2-macrophages genes in mice [41,42]. More recently, Zhang et al. (2011) have shown that an alteration of expression of genes, IFN-*γ*, IFN-*α*, and IL-4, after macrophage polarization are involved with cytokine-induced H4 acetylation (H4ac), a marker of increased transcriptional competence [43]. Thus, systems biology will keep us providing a broader-views on macrophage polarization, it's mechanistic for having heterogeneity and plasticity.

Macrophage Polarization in Cancer Progression

All solid tumors are highly associated with monocytes and local macrophages into their microenvironment, and it is being increasingly convincing that tumor-associated macrophages (TAMs) play several roles, sometimes "foe-to-friend" during

tumor development [44]. Originally it was believed that macrophages kill tumor cells *in vitro* [45], however, later on it became evident that TAMs promote rather than counteract tumor progression, including their metastatic phase [46,47]. Both, clinical and experimental evidence indicates that human tumors loaded with TAMs correlates with 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 supporting the hypothesis that macrophages can facilitate the tumor progression and invasion.

Macrophage Polarization in Viral Diseases

The role of macrophage polarization in 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 circulating monocytes to chemoattractants [49,50], down-regulation of C5α chemotactic receptors and the bacterial tripeptide f-MLP [51,52]. However, HIV^+ monocytes and alveolar macrophages showed a reduced phagocytic activity [53,54], decreased phagosome-lysosome fusion, and decreased intracellular killing of pathogens [55,56]. It was reported that *in vitro* polarization of macrophages to M1 or M2-type, strongly inhibited HIV-1 replication and affects at the different steps of 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) signaling pathway and thereby reduces the inflammation in obese rats [59]. Consistent with this, Xu et. al. (2011) also showed the anti-inflammatory effects of exercise training 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 toward the M2-state [62].

Intense Physica 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 has been shown to induce the expression of IL-4, a cytokine that triggers the alternative macrophage phenotype [63].

Physical exercise induces a decrease in circulating levels of LPS

LPS (Lipopolysaccharides) can regulate macrophage polarization [59,64]. Both mild to intense aerobic physical exercises can induce a decrease in circulating levels of LPS, and there after reduces an alternative M2 activation of macrophages. Physical activity, in haman, positively impacts on both monocytes and macrophages, causing the polarization of macrophages in skeletal muscles, and in adipose tissues [65-67], elicit a transient immune response [65], and prevents from coronary artery disease [68].

Discussion

Regular, even moderate-type aerobic exercise was shown to induce a polarization M1 macrophages in to M2-type in obese rats [62]. In addition, acute exercise promotes reduced expression of TNF-α, IL-1β, and MCP-1, some pro-inflammatory cytokines in rat adipocytes, and also improves insulin signaling there [62]. These suggest that exercise can improve insulin signaling at least in part by inducing macrophage polarization towards the M2-type (anti-inflammatory state). 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 PPARδ was found to be associated with M2-macrophages in rat adipose tissues [63]. Accordingly, cytokines IL-4 and IL-13, 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 is known to be accompanied by 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 minimal side effects.

CRediT

Author contributions: Conceptualization; Data curation; Formal Analysis; Investigation; Methodology; Project administration; Supervision; Writing - original draft; Writing-review & editing- All authors.

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Ethical Approval

Not applicable.

Informed Consent

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Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to participant privacy and institutional ethical restrictions but are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate[@].

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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