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A novel approach for dietary regulation of macrophages through mitochondrial energy metabolism

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Abstract

The regulation of macrophages is a major target for dietary immune modulation for their involvement in both innate and adoptive immune responses. Studies revealed that macrophages are unique in their plasticity to polarize into either inflammatory M1 subset or anti-inflammatory M2 cells. Recently, cellular energy metabolism including both glycolysis and oxidative phosphorylation is demonstrated to control macrophage dichotomy. In this review, the differential utilization of glucose, lipids, amino acids, and irons by M1 and M2 cells are discussed in detail. In addition, several dietary approaches for the alteration of inflammatory M1 cells to M2 phenotypes are reviewed for development of functional foods for immune regulation.

Keywords: diet, immunity, inflammation, macrophage, mitochondria

I. Introduction

Macrophages play a crucial role in the immune system with multiple functions in both innate and adaptive immunity (Wang *et al.*, 2021). These cells reside in most tissues of vertebrates and immediately defend against foreign substances (Gordon and Plüddemann, 2017). In innate immune responses, macrophages are involved in controlling

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balance between tolerance and removal through phagocytosis of antigens including microbes, small molecules, and potent neoplastic cells (Hirayama, *et al.,* 2018). Macrophage also mediate adaptive immunity through antigen presentation to both B and T cells and contribute to humoral immunity by releasing wide spectrum of bioactive molecules, such as cytokines, chemokines, enzymes, lipid metabolites and reactive radical compounds (Bowdish, 2016). The activation of macrophage is dichotomically regulated to inflammatory or anti-inflammatory phenotypes depending on micromilieu signals, contributing to tissue homeostasis (Isidro and Appleyard, 2016).

2. Distinct immunophenotypes in polarized macrophages

Macrophages exhibit functional diversity to maintain tissue homeostasis including intrinsic role for recognition and removal of foreign substance from host. This heterogeneity of macrophage stems from cellular plasticity to switch from one specific phenotype to another in response to various micromileu of specific tissues (Sica and Mantovani, 2012). In this regard, several subsets of macrophage with discrete functions have been reported (**Table 1**). Following the subset conceptualization proposed by Mills (Mills *et al.*, 2000), macrophages are generally recognized to polarize to either classically activated (M1) or alternatively activated (M2) macrophages by stimulation of Th1 or Th2 cytokines, respectively. This conversive phenomenon with two distinct phenotypes of macrophages is termed macrophage polarization (Murray and Wynn, 2011).

2.1. Classically activated (M1) macrophages

M1 macrophages induced by Th1 cytokines (interferon-gamma (IFN-γ) and tumor necrosis factor (TNF)-α) or toll-like receptor (TLR) ligands (e.g., LPS, flagellin, CpG DNA, and dsRNA, etc.) exhibit an inflammatory phenotype with a potent phagocytic ability (Takeda and Akira, 2003). These macrophages are characterized by secretion of pro-inflammatory cytokines, including TNF-α, interleukin (IL)-1α, IL-1β, IL-6, IL-12, IL-18 and IL-23 (Murray, 2017). M1 macrophage also produce Th1 cell-attracting chemokines, such as CXC motif chemokine ligand (CXCL)9 and CXCL10 (House *et al.*, 2020). The aforementioned cytokines and chemokines mediate adap-

Table 1. Different phenotypes between M1 and M2 macrophages

Phenotypes	Functions	Stimuli	Expression makers	Cytokines, chemokines and other produced mediators
M1	Pro-inflammatory Th1 response Anti-microbial Anti-tumorigenic	LPS* IFN-γ TNF-α	CD80 CD86 MHC-Ⅱ IL-1R TLR4	IL-1β, IL-6, IL-12, IL-18 IL-23, TNF-α, CXCL9, CXCL10, NO, ROS, RNS
M2	Anti-inflammatory Th2 response Anti-parasitic Tissue remodeling Pro-tumorigenic	IL-4 IL-10 IL-13 TGF-β	CD206 IL4Rα ARG1 Fizz1 Ym1/2	IL-10, TGF-β, CCL17, CCL18, CCL24, PDGF, VEGF

*LPS, lipopolysaccharide; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha; IL-, interleukin; TGF-β, transforming growth factor-beta; CD-, cluster of differentiation; MHC-Ⅱ, major histocompatibility complex class Ⅱ; IL-1R, interleukin-1 receptor; TLR4, toll-like receptor 4; IL4Rα, interleukin-4 receptor alpha; ARG1, arginase 1; Fizz1, resistin-like molecule alpha; Ym-, chitinase-like protein; CXCL, C-X-C motif chemokine ligand; CCL, C-C motif chemokine ligand; NO, nitric oxide; ROS, reactive oxygen species; RNS, reactive nitrogen species; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

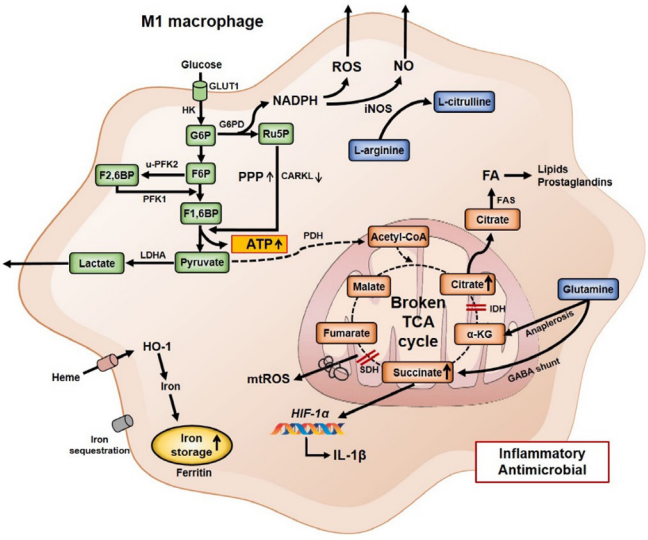

Fig. 1. Metabolisms in M1 polarized macrophages
Black arrows represent activated metabolic reactions and dotted lines indicates blunted metabolic reactions. GLUT1, glucose transporter 1; HK, hexokinase; G6P, glucose 6–phosphate; F6P, fructose 6–phosphate; F1,6BP, fructose–1,6–biphosphate; F2,6BP, fructose–2,6–biphosphate; Ru5P, ribulose 5–phosphate; G6PD, glucose–6–phosphate dehydrogenase; u–PFK2, ubiquitous isoform of 6–phosphofructo–2–kinase; PFK1, 6–phosphofructo–1–kinase; PPP, pentose phosphate pathway; CARKL, carbohydrate kinase–like protein; LDHA, lactate dehydrogenase A; TCA, tricarboxylic acid; PDH, pyruvate dehydrogenase; IDH, isocitrate dehydrogenase; SDH, succinate dehydrogenase; α–KG, alpha–ketoglutarate; GABA, gamma–aminobutyric acid; FA, fatty acid; FAS, fatty acid synthesis; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; NO, nitric oxide; iNOS, inducible NO synthase; mtROS, mitochondrial ROS; HIF–1α, hypoxia–inducible factor–1 alpha; IL–1β, interleukin–1 beta; HO–1, heme oxygenase–1; ATP, adenosine triphosphate.

tive immunity via type 1 T cell responses and tumorigenesis (Osugi *et al.*, 1997; Frostegård *et al.*, 1999; House *et al.*, 2020). In addition, IL-6 or TNF-α-induced M1 macrophages facilitate the expression of major histocompatibility complex (MHC)-II along with the antigen-primed T cell co-stimulatory surface B7 molecules such as cluster of differentiation CD80 (B7-1) and CD86 (B7-2) (Schweitzer, 1998; Gonzalez-Juarrero *et al.*, 2003). M1 macrophages also has potent microbicidal and tumoricidal activity by activating the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system and consequently generating nitric oxide (NO) and reactive oxygen species (ROS) (Wang *et al.*, 2007; Herb and Schramm, 2021).

2.2. Alternatively activated (M2) macrophages

Contrary to M1 macrophages, M2 macrophages are typically polarized by parasitic components or Th2 cytokines such as IL-4 and IL-13 associated with parasitic infections (Mantovani*et al.*, 2005). IL-4/IL-13-induced macrophages up-regulate signal transducer and activator of transcription STAT6 via IL-4 receptor alpha (IL-4Rα) (Saha *et al.*, 2017). IL-10 is another cytokine driving M2 differentiation through the activation of STAT3 (Hutchins *et al.*, 2013). M2 macrophages produce anti-inflammatory cytokine (e.g., IL-10 and transforming growth factor (TGF)-β) and surface molecules such as IL-Ra that are implicated in resolution of inflammation (Torre *et al.*, 2000; Fernandes *et al.*, 2020). Moreover, during the wound healing pro-

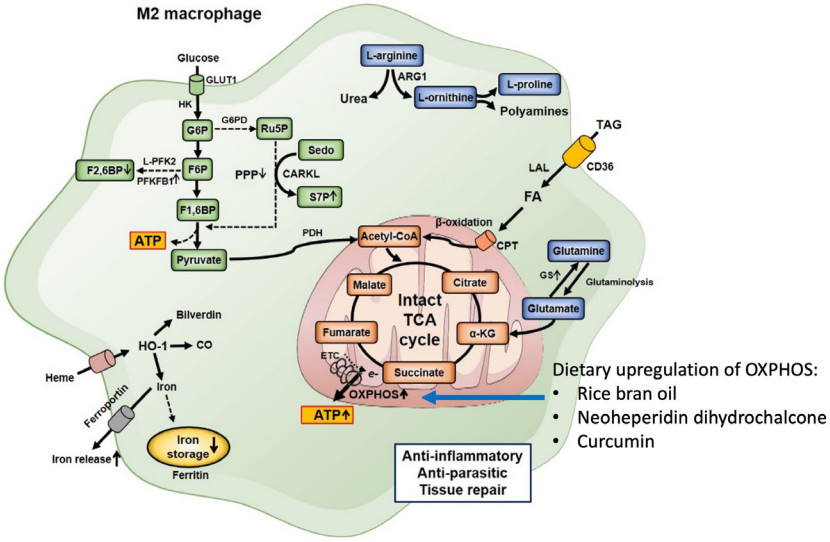

Fig. 2. Metabolisms in M2 polarized macrophages
Black arrows represent activated metabolic reactions and dotted lines indicates blunted metabolic reactions. GLUT1, glucose transporter 1; HK, hexokinase; G6P, glucose 6–phosphate; F6P, fructose 6–phosphate; F1,6BP, fructose–1,6–biphosphate; F2,6BP, fructose–2,6–biphosphate; Ru5P, ribulose 5–phosphate; G6PD, glucose–6–phosphate dehydrogenase; L–PFK2, liver–type of 6–phosphofructo–2–kinase; PFKFB1, 6–phosphofructo–2–kinase and fructose–2,6–biphosphatase; PPP, pentose phosphate pathway; CARKL, carbohydrate kinase–like protein; Sedo, sedoheptulose; S7P, sedoheptulose 7–phosphate; TCA, tricarboxylic acid; PDH, pyruvate dehydrogenase; α–KG, alpha–ketoglutarate; GS, glutamine synthase; FA, fatty acid; TAG, triacylglycerol; LAL, lysosomal acid lipase; CPT, carnitine palmitoyltransferase; ARG1, arginase 1; ETC, electron transport chain; OXPHOS, oxidative phosphorylation; HO–1, heme oxygenase–1; CO, carbon monoxide.

cess, M2 macrophages secrete the growth factors such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) to promote cell proliferation and blood vessel development (White *et al.*, 2021). M2 macrophages also produce CC motif chemokine ligand CCL17, CCL18, CCL22 and CCL24, consequent recruitment of Th2 and regulatory T cells (Tregs) (Tiemessen *et al.*, 2007; Shrihari, 2017). In addition, surface molecules including CD163 (scavenger receptor), CD206 (macrophage mannose receptor, MMR), C-type lectin receptor, CD209 and CD301 are highly expressed on M2 macrophages (Shapouri-Moghaddam *et al.*, 2018; Bhattacharya and Aggarwal, 2019). Therefore, functionally, M2 macrophages are closely linked to resolving process of inflammation and tissue remodeling.

3. Different metabolic profiles of polarized macrophages

The immune function of polarized macrophages is closely related to cell metabolism (Figures 1 and 2). Similar to Warburg effect observed in tumor cells, LPS- and IFN-γ-induced M1 macrophages drive metabolic shift towards aerobic glycolysis with broken tricarboxylic acid (TCA) cycle to react the increased energy demands for synthesizing pro-inflammatory molecules (Soto-Heredero *et al.*, 2020). This metabolic shift enhances glucose uptake and consequently increases conversion of pyruvate to lactate (Mehla and Singh, 2019). Moreover, M1 macrophage display increased pentose phosphate pathway (PPP) flux involved in the production of nicotinamide adenine dinu-

cleotide phosphate (NADPH). In redox reactions of macrophages, NADPH acts as a reducing agent in the generation of ROS and NO by NADPH oxidase and inducible nitric oxide synthase (iNOS), respectively (Ge *et al.*, 2020). Therefore, cells can rapidly obtain energy by these metabolic processes required for microbicidal activity (Covarrubias *et al.*, 2013).

In stark contrast, metabolism in M2 macrophages is characterized by elevated fatty acid oxidation (FAO) and mitochondrial oxidative phosphorylation (OXPHOS) coupled with intact TCA cycle (Saha *et al.,* 2017). IL-4-inducded M2 macrophages enhances fatty acid uptake and β-oxidation related genes through upregulating STAT6 and peroxisome proliferator-activated receptor (PPAR)-γ coactivator (PGC)-1β signaling pathway which are involved in mitochondrial biogenesis (Galván-Peña and O'Neill, 2014; Mou *et al.*, 2015). In addition, M2 macrophages express high levels of arginase 1 (Arg1), thereby facilitating arginine catabolism involved in collagen synthesis required for tissue repairing (Johnson *et al.*, 2016). Thus, these metabolic events facilitate the anti-inflammatory responses of M2 macrophages by acquiring almost energy from FAO and mitochondrial respiration.

3.1. Glucose metabolism in polarized macrophages

Glucose metabolism in macrophages is a main carbon source for energy generation. When cells uptake glucose by transporter, glucose is phosphorylated to glucose 6-phosphate (G6P) by hexokinase (Campbell *et al.*, 2013). It then undergoes cytoplasmic glycolysis to produce pyruvate, NADH and adenosine triphosphate (ATP). Lastly, pyruvate is transported into the mitochondria and converted to acetyl coenzyme A (Acetyl-CoA) by pyruvate dehydrogenase (PDH) to produce energy via TCA cycle and OXPHOS (Love *et al.*, 2016; Curi *et al.*, 2017; Van den Bossche *et al.,* 2017). This metabolic cascade provides cells with a higher amount of energy through OXPHOS compared to glycolysis (36 ATP per glucose versus 2 ATP per glucose, respectively), but is significantly regulated by several factors in the polarization process of macrophages, resulting in a metabolic shift (Kasmi and Stenmark, 2015).

Glucose transporter 1 (GLUT1), a rate-limiting glucose transporter, is upregulated in hypoxia-induced pro-inflammatory macrophages and LPS-primed macrophages. It was demonstrated that the overexpression of GLUT1 in murine macrophage RAW 264.7 cells drives pro-inflammatory phenotype, resulting in increased IL-6, TNF-α, ROS and PPP intermediates production. (Freemerman *et al.*, 2014) In addition, GLUT1 inhibited oxidative metabolism of macrophages by suppressing oxygen consumption rate (OCR), OXPHOS marker, and conversely, upregulated glycolytic rate (Freemerman *et al.*, 2014, 2019). M1 macrophages also enhances the glucose-6-phosphate dehydrogenase (G6PD) expression. G6PD is a key enzyme of the PPP that regulates cellular redox homeostasis involved in regeneration of NADPH (Parsanathan and Jain, 2021). G6PD-overexpressed macrophages stimulate the expression of pro-inflammatory and oxidative genes and molecules accompanied by activated p38 mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) signaling pathways (Lee *et al.*, 2011; Ham *et al.*, 2013).

The increased glycolytic flux of M1 macrophages is related to the accumulation of fructose-2,6-biphosphate by switching from the liver-type expression of 6-phosphofructo-2-kinase (L-PFK2) to more active ubiquitous PFK2 isoform (u-PFK2) by L-PFK2 gene and 6-phosphofructose-2-kinase and fructose-2,6-bisphosphatase (PFKFB3) (Geeraerts *et al.*, 2017). PFKFB3 selectively promotes the extrinsic antiviral functions of macrophage by enhancing glycolysis (Jiang *et al.*, 2016). Conversely, M2 macrophages primarily express PFKFB1, an isoform of PFK2 vice PFKFB3 (Zhang *et al.*, 2021). PFKFB1 has the higher bisphosphatase activity compared to u-PFK2, and it freely degrade fructose-2,6-biphosphate to fructose-6-phosphate,

resulting in lower glycolytic levels (Kelly and O'Neill, 2015). This reduced glycolytic flux compensatively enhances OXPHOS.

LPS stimulation in macrophages promotes production of ribose-5-phosphate (R5P), xylulose-5-phosphate (X5P) and sedoheptulose-7-phosphate (S7P) by PPP (Yang *et al.*, 2021). This increased intermediates of PPP are regulated by carbohydrate kinase-like protein (CARKL) involved in production of S7P. Overexpression of CARKL in M1 macrophages suppresses PPP flux and results in impaired inflammatory capacity in accordance with M2-like phenotype. Conversely, CARKL loss by RNAi enhances glycolysis and induces M1-like metabolic states (Haschemi *et al.*, 2012).

TCA cycle in M1 cells is broken by two reactions catalyzed by isocitrate dehydrogenase and succinate dehydrogenase, resulting in the accumulation of citrate and succinate (O'Neill, 2015). Accumulated citrate is used for fatty acid biosynthesis involved in membrane biogenesis and metabolized to generate reactive oxygen intermediates and prostaglandins for inflammatory responses (Mills *et al.*, 2017). Itaconate is converted from citrate by *cis*-aconitate decarboxylase enzyme coded immunoresponsive gene 1 (IRG1) and possesses microbicidal activity (Németh *et al.*, 2016). Itaconate also regulate succinate level by inhibiting succinate dehydrogenase which are involved in ROS production (Hooftman and O'Neill, 2019). Succinate, another intermediate metabolite from broken TCA cycle, is closely related to pro-inflammatory functions of macrophages. Succinate can be accumulated by inhibition of succinate dehydrogenase involved in LPS stimulation and lead to modification of proteins such as lysine through succinylation (Jiang and Yan, 2017; Wu *et al.*, 2020). Succinate involves in production of IL-1β by stabilizing hypoxia-inducible factor (HIF)-1α (Tannahill *et al.*, 2013).

3.2. Lipid metabolism in polarized macrophages.

Lipid metabolism of macrophage is controlled by transcription of sterol receptor element binding protein (SREBP) and liver X receptor (LXR) which are essential for synthesizing fatty acids and cholesterols (Oishi *et al.*, 2017). LPS stimulation enhances SREBP-1 activity, resulting in the production of IL-1 β by supporting nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome. In addition, deficient SREBP-1a blocked LPS-primed macrophages from producing IL-1β (Im *et al.*, 2011). On the other hand, overexpression or activation of LXRα inhibits the activity of NF-κB and AP-1, thereby attenuating the M1 response and inflammation (Hong *et al.*, 2011; Spann and Glass, 2013).

Differential induction of fatty acid synthesis (FAS) and FAO induces macrophage polarization towards M1 and M2 profiles, respectively. FAS represents a key pathway for energy production and prostaglandin biosynthesis in M1 cells (Batista-Gonzalez *et al.*, 2020). On the other hand, IL-4 induces lipolysis of glycerol and inhibition of lysomal acid lipase (LAL) encoded gene suppresses M2 markers, such as CD206 and CD301 (Huang *et al.*, 2014). Moreover, CD36, a scavenger receptor increased by M2 polarization enhances FAO by promoting triacylglycerol (Feng *et al.*, 2000). The lipid metabolism controlled by LAL and CD36 is closely related to the anti-parasitic response of M2 macrophages (Feng *et al.*, 2000). Mitochondrial long-chain fatty acid β-oxidation requires carnitine palmitoyltransferase (CPT) system, which mediates fatty acid translocation within mitochondria (Nomura *et al.*, 2019). In this regard, RAW 264.7 cells forced to express persistently active CPT-1A dampened inflammatory cytokines production, ROS damages (Malandrino *et al.*, 2015). However, recent studies reported that genetic deletion of CPT-2 did not affect the M2 polarization of IL-4-stimulated macrophages both *in vitro* and *in vivo* (Nomura *et al.*, 2016). Thus, the effect of FAO on the polarization of M2 macrophages is still debated.

3.3. Amino acid metabolism in polarized macrophages.

The impacts of arginine metabolism on polarization and function of macrophage have been well established. Arginine metabolism in polarized macrophages is strongly regulated through two enzymes: iNOS and ARG1. LPS-or-IFN-γ-induced macrophages up-regulate the production of iNOS, which metabolizes arginine to NO. NO is a key effector for the anti-microbial activity of M1 macrophages (Green *et al.*, 1994; Salim *et al.,* 2016). In IL-4-induced M2 macrophages significantly upregulate the expression of ARG1, which metabolize arginine to ornithine and urea (Hu *et al.*, 2018). Ornithine is utilized in the generation of polyamines and proline. These metabolites are essential for collagen synthesis, cell growth and other tissue remodeling function (Witte and Barbul, 2003). ARG1 competes with iNOS for the common substrate arginine, and it can limit arginine availability, resulting in decreased NO production (Mori *et al.*, 1998).

Glutamine is utilized for amino acid and nucleotide acid synthesis, energy production and biosynthetic pathways, which are crucial in cell growth and function (Mori *et al.*, 1998). In M1 macrophages, glutamine is used to promote succinate synthesis via γ-aminobutyric acid (GABA) shunt, by pass of TCA cycle (Mori *et al.*, 1998). Glutamine also participates in NO production in macrophages through conversion to arginine (Mori *et al.*, 1998). In contrast, glutamine metabolisms are closely related in M2 polarization by affecting various levels. α-Ketoglutarate generated from glutaminolysis is necessary for oxidative metabolism and promotes anti-inflammatory gene and mediator expressions by inhibiting HIF-1α (Viola *et al.*, 2019). Unlike M1 macrophages, M2 macrophages express higher amounts of glutamine synthetase (GS), which is essential to acquire the anti-inflammatory phenotype of cells upon IL-10 stimulation. Indeed, ablation of GS suppressed IL-10-induced M2 markers while increasing inflammatory mediators via HIF-1α stabilization (Viola *et al.*, 2019).

3.4. Iron metabolism in polarized macrophages.

Macrophage polarization is closely related to the distinct modulation of iron metabolism by differentially expressing of molecules involved in iron transport system. M1 macrophage display high expression levels of ferritin, an iron-storage protein, and low expression levels of ferroportin, an iron exporter (Biswas and Mantovani, 2012). Depletion of intracellular iron in macrophages inhibits the secretion of pro-inflammatory cytokines and NO (Wang *et al.*, 2009; Johnson *et al.*, 2010). Conversely, increased iron levels in macrophages facilitate TNF-α secretion via NF-kB signaling pathway (Ward *et al.*, 2002). These metabolic differences can be associated with the function of polarized macrophages. Since iron is necessary to the survival of bacteria, iron sequestration of M1 macrophages contributes to host defense by bacteriostatic effect. In contrast, the release of iron from M2 macrophages support tissue remodeling (Gaetano *et al.,* 2010). Moreover, iron is required for the degradation of HIF and iron deficiency leads to HIF activation (Peyssonnaux *et al.,* 2008). IL-10-induced macrophages upregulated the amount of heme oxidase (HO)-1 (Lee and Chau, 2002). HO-1 contributes to the anti-inflammatory function of M2 macrophages by degrading heme to produce ferrous and anti-inflammatory biliverdin (Sophie Mokas *et al.*, 2009; Gozzelino *et al.,* 2010).

4. Dietary approaches for anti-inflammatory alteration of energy metabolism in macrophages

The concept of macrophage dichotomy and differential energy metabolism attracts growing interest for the dietary modulation of immune system due to their safety and lack of adverse effects. In various dietary approaches, edible rice bran oil (RBO) was investigated for its anti-inflammatory effects (Lee *et al.*, 2019) for dietary lipids are major energy

substrates to cells through β-oxidation and subsequent mitochondrial respiration. Briefly, RAW 264.7 macrophages were activated by LPS treatment followed by a treatment of RBO or isocaloric control palm oil (PO). Interestingly, RBO treated cells exhibited up-regulated OCR which was in correlation with reduced inflammatory cytokine production. The authors also reported that oral administration of RBO to mice recapitulated the reciprocal regulation of OCR and inflammatory markers in M1-polarized bone marrow-derived macrophages. These data support the concept that dietary lipids are modulators of immune functioning through energy metabolism.

In a discrete study, the effect of neohesperidin dihydrochalcone (NHDC), a sucrose replacer, and its physiologic metabolite dihydrocaffeic acid (DHCA) on immune cells and their energy metabolism were studied (Choi *et al*., 2021). In this regard, high fat diet-induced obese C57BL/6J mice were fed 45% of total calorie as fat *ad libitum* for 11 weeks, in which NHDC was supplemented to the diet. Dietary supplement of NHDC suppressed the high calorie-induced body weight gain of mice in a dose-dependent manner. Furthermore, the M2 BMDM of NHDC fed mice secreted increased IL-10, the anti-inflammatory cytokine. In a mechanistic approach, RAW264.7 cells were treated with NHDC or DHCA resulting in upregulation of mitochondrial respiration as observed in elevated OCR, indicating that NHDC, and its metabolite DHCA, modulates immune response through regulation of macrophage energy metabolism.

Curcumin in turmeric is an well-accepted food component for its anti-inflammatory properties. In an effort to enhance its bioavailability and functions, a novel physical process by using puffing was applied (Kim *et al.*, 2020). Interestingly, puffing of turmeric increased the degradation of curcumin into smaller bioactive molecules, which further aided in regulation of inflammatory responses in LPS-induced RAW 264.7 cells. Extracts of puffed turmeric also exhibited upregulated oxygen consumption in a puffing pressure-dependent manner.

These studies strongly support that mitochondrial oxidative phosphorylation is regulated by dietary components, which further affect functioning of immune cells including macrophages. Therefore, fine-tuned studies are required for the development of functional foods for regulation of immunity.

5. Summary and implications

Macrophages, a key component of innate immunity, play a pivotal role in inflammation and host defense against foreign substances. They adopt to the tissue in which they reside and serve specialized functions. Accordingly, the response of macrophages to disparate stimuli perquisites complicated genetic and metabolic rearrangements. These dramatic changes termed "polarization" can be divided two distinct types, inflammatory M1 versus anti-inflammatory M2. Since the phenotypic classification of macrophages by different activators such as Th1 and Th2 cytokines was suggested, further grouping and nomenclature of intermediate types based on stimuli and transcriptional profile have been proposed (Mantovani *et al.*, 2004; Rőszer, 2015), but still have limitations. In this regard, advanced transcriptomic and metabolic studies have been focused on interrelation between intracellular metabolic rewiring and functional flexibility based on metabolic heterogeneity of polarized macrophages. These different metabolic profiles in M1 and M2 macrophages are essential for proper cell function. In M1 macrophages, enhanced glycolysis and PPP while blunting OXPHOS enable rapid ATP and biosynthetic molecule production required for the generation of pro-inflammatory mediators in response to infection. Conversely, M2 macrophages depend on OXPHOS coupled with FAO and glutamate oxidation for sustained energy supplement involved in consecutively activation required for tissue repairing.

In this regard, it is clear that detailed metabolic pathway

involved in function of macrophages remain to be clarified. Identification of novel molecular regulatory mechanisms and characteristics related metabolic reprogram will make a significant contribution to our understanding macrophage functions in health and disease, even though several dietary approaches ensure the potency of its application.

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