

## Metabolites-Mitochondria-Microglia (Mmma): Therapeutic Strategy for Treatment of Neural Inflammation and Neurodegeneration

Corrado Angelini\* and Arianna Di Stadio

Department of Neurology, Fondazione IRCCS San Camillo Hospital, Venice, Italy

### Description

We consider the modulation of mitochondrial metabolism to change polarization of the microglia state. Patients with mitochondrial disease often present with prominent neurologic symptoms; the alteration of mitochondrial metabolism produces an excess of ROS and cytokines that appeared implicated in the activation of microglia; similar considerations apply to Amyotrophic Lateral Sclerosis (ALS) and other neurodegenerative disorders.

The microglia polarization by mitochondrial dismetabolism modulation could be considered a possible therapeutic target to treat the neuroinflammation and neurodegenerative disorders, similar to macrophage action in case of muscle inflammation and atrophy.

Since skeletal muscle, heart and brain are the tissues with the highest metabolism in the body, with a staggering 50-100-fold increase in oxygen consumption from rest to maximal exercise, myopathic symptoms in mitochondrial disease is a common presentation of the conditions. Myopathic symptoms can present as limb weakness, bulbar weakness with dysphagia, ptosis, external ophthalmoplegia, and exercise intolerance.

Reactive Oxygen Species also attack and denature a number of components within the mitochondria, including the protein components of the Electron Transfer Complex (ETC), membrane lipids (particularly cardiolipin), and mtDNA. In particular, the denaturing of cardiolipin has been associated with abnormal morphology of the inner mitochondrial membrane (IMM), less association of the ETC complexes within that membrane, a decline in activity of the ETC (ATP production), and the release of cytochrome c which initiates apoptotic signaling.

Upon lipo-poly-saccharide (LPS) stimulation, macrophages in mice [1] change to a pro-inflammatory state, shifting ATP production from oxidative phosphorylation (OX-PHOS) to glycolysis pathway. This demonstrates that increased mitochondrial oxidation of succinate through succinate dehydrogenase (SDH) brings high mitochondrial membrane potential and increases production of reactive oxygen species (ROS). Blocking ROS production with rotenone, a complex I inhibitor and uncoupling mitochondria, results in an inhibition of this macrophagic pro-inflammatory phenotype.

We might extrapolate consequences that apply to human diseases, for instance, it is interesting to note that dimethyl-fumarate, a cell penetrating fumarate ester, has been recently approved by FDA as a front-line drug for the treatment of relapsing-remitting multiple sclerosis [2], since it boosted both LPS induced IL-1beta expression and TNFalpha production. It is well known that fumarate can stabilize hypoxia inducible factor (HIF-1alpha) and this is the likely mechanism by which it is induced IL-1beta.

Complex I can produce large amount of ROS by the regulated process of reverse electron transport when the CoQ pool is highly reduced. ROS signal is sensitive to uncoupling, achieved through an inhibitor of succinate oxidation, dimethyl-malonnate [1]. The central role of mitochondria in immune signaling and in innate immune

response fits the function of this organelle in cell death and signaling. Infact, the endosymbiotic origin of mitochondria may reflect not only the requirement of eukaryote to evolve their respiratory oxidation but also the idea that mitochondria might have a role as "signaling hubs", which can influence the phenotype of immune cells and possibly of other cell types (i.e. T and B lymphocytes and other circulating cells) to respond to infections, since succinate oxidation is an important regulator of signaling in inflammation, opens a great number of new therapeutic opportunities, since it can be also modulated by a series of metabolites such as dimethyl-malonnate, itaconate [3], which modulate succinic dehydrogenase. Inhibitors of SDH might prove useful shifting microglia away from pro-inflammatory gene expression towards anti-inflammatory gene expression within an inflammatory environment.

We aim to cover the key-possibilities that are opened by these experimental observations in the neuromuscular disorders field, where the mechanism of inflammation is part of myositis, Amyotrophic Lateral Sclerosis (ALS) necrotizing autoimmune myopathy, muscular dystrophies, autoimmune neuropathy (both chronic and acute) [4]. Down-regulation of mitochondria might occur in common muscle diseases, such as muscle ischemia due to peripheral vascular diseases, "intensive care unit" weakness (4). Another condition that has probably a role for mitochondria down-regulation is atrophy and cachexia of muscle, which corresponds to a fast atrophy of type 2 muscle fibres due to unknown factors released by tumours (such as pancreatic or stomach cancer). In this condition, muscle fibres loose OX-PHOS capacity, patients undergo fast muscle atrophy. Whether this is a metabolic effect that occurs for remote cancer effect or a paracrine myopathy, remains to be studied.

Metabolic reprogramming in macrophages/microglia has been recently observed; in particular authors identified that an altered mitochondrial metabolism can polarize microglia in its neuro degenerative phenotype (M1) [5,6]. Pro-inflammatory stimuli, such as LPS, cause microphage alteration and a switch away from oxidative phosphorylation towards glycolysis, similar to Warburg effect in tumour cells [7].

Succinate is a TCA-cycle intermediate and activates HIF-1alpha [8] which promotes inflammatory gene expression; on the contrary, endogenous itaconate regulates metabolic remodeling, succinate levels by inhibiting SDH and mitochondrial respiration in inflammatory

**\*Corresponding author:** Corrado Angelini, Department of Neurology, San Camillo Hospital IRCCS, Via degli Alberoni 70 Venice, Italy, Tel: +39 041 220 7111; E-mail: [corrado.angelini@unipd.it](mailto:corrado.angelini@unipd.it)

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Name	Resting microglia	
	M1	M2
	Pro-inflammatory	Activated
Glycolysis	High	Low
OX-PHOS	Low	High
NOS production	High	Low
Fatty acids oxidation	Low	High
Anti-Inflammatory cytokines production	Low	High
Pro-Inflammatory cytokines production	High	Low

M1 microglia: Pro-inflammatory and activated M2 microglia: Anti-inflammatory

Table 1: Characteristics of different classes of microglia.

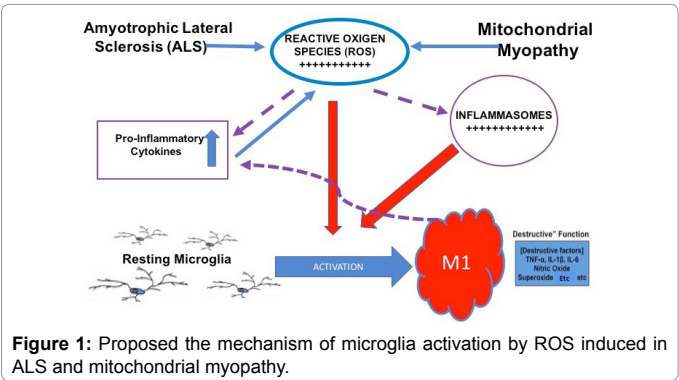


Figure 1: Proposed the mechanism of microglia activation by ROS induced in ALS and mitochondrial myopathy.

macrophages. Figure 1 shows the characteristics of ROS activation of microglia, denominated M1.

It has been recognized that macrophages switch as a potential therapeutic target from M1 (pro- inflammatory macrophage) to M2 (anti-inflammatory macrophage) state. This can happen through an action of drugs such as metformin, and rotenone (a complex I inhibitor). While M1 macrophages metabolism features high i-NOS expression and NO production, M2 macrophages have high levels of oxidative phosphorylation and fatty acids oxidation.

Similar to macrophages, microglia assume different phenotype (M1 and M2) in relation to metabolic state [6]. Microglia, as resident innate immune cells in the brain, belongs to the macrophages family but derives from vitellin sac, has long been implicated in the pathology of neurodegenerative diseases. Under normal condition microglia is present in staying state but, metabolic changes can activate it. Two phenotypes of microglia have been identified the M1 form, the aggressive phenotype, that induces neuro-degeneration by increasing of pro-inflammatory cytokines and direct aggression versus neural cells and the M2 form. M2 is the antagonist of M1 and it has a regenerative and neuroprotective action. Table 1 summarizes the characteristic of microglia in M1 and M2 phenotype.

Here we consider the effect of the mitochondrial metabolic shift and ROS effect on the microglia state/phenotype, in particular on the activation and increasing concentration of M1 phenotype.

We assume that mitochondrial overexpression of ROS might induce the change in state of microglia in M1 pro-inflammatory phenotype, in directly way or by inflammasomes modulation (Figure 1).

M1 phenotype activates different ILs (IL4, IL10) that have been correlated with neurodegenerative condition and mitochondrial encephalomyopathies, and at the same time increases the concentration of ROS; then LPS, HIF1, SOD, indirectly by glutamate increasing (SLA), or at least by an increased ROS production are able to activate microglia

from its staining state as happen in mitochondria myopathy. When the inflammatory process is activated, the concentration of microglia M1 is self-sustained until an inversion of metabolism happens reducing the production and concentration of ROS (Figure 1). Can this be exploited therapeutically in chronic inflammatory states and neurodegenerative disorders?

Here we consider that reprogramming macrophages and microglia with tricarboxylic acid cycle (TCA) intermediate metabolites or metabolic inhibitors might be a novel therapeutic avenue for the treatment of inflammatory and neurodegenerative conditions (“MMM” strategy). Metabolites might shunt M1 macrophages and microglia cells by changing from a metabolism similar to that described in tumour cells with the Warburg effect [7], i.e. high glycolysis with low aerobic metabolism, to utilization of fatty acids and production of reactive oxygen species (ROS).

Mitochondrial derangement occurs frequently when immune-mediated cells undergo a drastic metabolic change during an inflammatory process. Infact, inflammation does not only produce a response to infection or inflammation, but also a number of metabolites and cytokines. This response occurs in neuromuscular tissues, for instance, when in muscle increased macrophages are seen in two possible autoimmune inflammatory disorders, i.e. inflammatory myopathies, where macrophages destroy the muscle fibers in necrotizing auto-immune myopathy. A similar reactive inflammation might be seen in muscular dystrophies where macrophages might stimulate muscle regeneration after necrosis. Microglia, as macrophages, might stimulate neuro-regeneration when is active in M2 phenotype.

In several animal models, myotoxins are used to study regeneration after the necrosis they induce: therefore, one can follow release by macrophages of a series of metabolites and interleukins; Amato [9] in the calpainopathy disease has demonstrated an eosinophilic inflammation and active macrophages clusters might appear, where increased ROS production is likely to occur.

After mitochondrial dysfunction, they are recruited to phago-lysosomes and the production of nicotinamide-di-phosphate by the pentose phosphate pathway occurs. NADPH is the electron donor for NADPH oxidase, finally transferring electrons to molecular oxygen, thus producing the superoxide ion, a potent ROS species. On the other hand, activated macrophages (M2) generate ATP mainly through oxidative phosphorylation. Pharmaceutical companies are highly interested in the production of exogenous itaconic acid, which function as an inhibitor of various enzymes including SDH. After metabolic intervention, these compounds lead to accumulation of succinic acid, fumaric acid. At present itaconic acid acts as a specific anti-microbial metabolite that supports the cellular metabolic immune response, but we have to explore if it has an important role in neuro-inflammation and acts in addition to TCA-cycle intermediate and their endogenous production [3].

Another clinical consequence of the influence of mitochondria on microglia action and on B-, T- lymphocytes sub-populations is that in mitochondrial disorders it is likely that common infections are prevalent and dangerous. Mitochondrial disorders are a heterogeneous group of diseases, that might be due to defects in ETC respiratory chain or to a nuclear DNA mutation. Mitochondrial dysfunctions have a role both in Parkinson syndrome, and ALS. For their treatment, drugs combination composed of vitamins, cofactors and anti-oxidants are used. If a susceptibility to infections and inflammatory state should be present in mitochondrial patients, this would require further therapeutic approaches, such as “MMM strategy”.

Another relevant question is related to the exposure hypoxia exposure, especially in older individuals or in obese sedentary subjects with sarcopenia or in cachexia, due to the critically regulatory role of HIF-1 $\alpha$ , which might show an abnormal response; on the contrary, high intensity exercise seems to reverse both the possible adverse factor of exposure to hypoxia [10,11] and in sarcopenia.

Due to the similarity between microglia and macrophages in state modification, handling mitochondrial metabolism in order to reduce the production of ROS could change the M1/M2 states, by increasing M2 protective/regenerative form. The microglia polarization by mitochondrial metabolism modulation could be considered an option to treat the neuroinflammation and neurodegenerative disorders, similar to macrophage action in case of muscle inflammation and atrophy. Furthermore, thanks to the availability of several biomarkers including mitochondrial microRNAs it should be possible to monitor metabolic state and microglia mitochondrial metabolic shift.

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