Inflammation and Depression: Is Immunometabolism the Missing Link?

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16.1 Introduction

The first experimental investigations of a role of inflammation in depression originated from the observation of the marked similarity between the clinical signs of sickness behavior and the symptoms of depression. The concept of sickness behavior encompasses how individuals sick with an infection behave. As pointed out by Yirmiya et al. at the time, "infectious illnesses are often associated with a range of depressive symptoms, including fatigue, psychomotor retardation, anorexia, somnolence, lethargy, muscle aches, cognitive disturbances and depressed mood" [1]. They went on to demonstrate that these behavioral alterations could be reproduced by administration of the cytokine inducer lipopolysaccharide (LPS) or pro-inflammatory cytokines such as interleukin (IL)-1. It was then observed that they are attenuated for some of them by chronic antidepressant treatment. It did not take long for the concept of depression as a brain inflammatory disease to emerge, encouraged by the observation of increased circulating levels of biomarkers of inflammation in depression, an observation originally reported by Maes et al. [2]. Twenty years later, the rest could be history except that the mechanisms by which inflammation induces depression have not yet revealed all their secrets. Preclinical studies conducted on rodent models of inflammation induced by the activation of the innate immune system or by stressors such as chronic unpredictable stress and repeated social defeat have vastly

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contributed to our understanding of some of the pathways responsible for the development of depressive symptoms in the context of systemic or central inflammation. The multiple routes of communication involved in the propagation of inflammation from the periphery to the brain have been elucidated with a particular emphasis on neural afferents and endothelial cytokine receptors. At the behavioral level, it has been possible to identify the main features of inflammation-induced depressive symptoms and to show the relative importance of fatigue and reduced motivation in the behavioral phenotype of inflammation. At the cellular level, the pivotal role of reactive microglial cells in the brain inflammatory response to peripheral inflammation and their possible modulation by immune cells trafficking into the brain parenchyma in response to chronic stress have been evidenced. Further knowledge on the reciprocal interactions of microglia with other brain cell types including endothelial cells, astrocytes, oligodendrocytes, and neurons has been slowly emerging. At the molecular level, the main cytokines that induce depressive symptoms and their receptor signaling mechanisms have been identified. At the neurochemical level, inflammation has been demonstrated to interfere with brain neurotransmission and in particular to down-regulate dopaminergic neurotransmission and activate glutamatergic neurotransmission. However, all of this still has proven to be insufficient to drive novel drug therapies for inflammatory-liked depression, suggesting something—possibly in plain sight—is still missing.

Inflammation-induced depression does not develop *ex nihilo*. It slowly emerges on a background of symptoms of sickness represented by fatigue, sleep disorder, and reduced appetite [3]. These symptoms are still present in depressed patients with a low-grade inflammation and are part of the somatic symptoms of depression. In all the enthusiasm that has built up since the discovery of the profound behavioral effects of immune activation, we seem to have forgotten how inflammation-induced sickness behavior contributes to the reorganization of the organism's priorities in face of an infectious agent. The initial description of sickness behavior insisted on the adaptive value of this response to infection with regard to the necessity of sparing energy metabolism for allowing a full development of the fever response and meeting the energy requirements of immune cell proliferation [4]. The fitness-enhancing value of sickness behavior for the infected individual and the population in which it belongs has received considerable interest in the field of ecoimmunology [5–7]. However, with very rare exceptions [8] it has totally escaped the attention of biological psychiatrists who have been more interested in finding out how inflammation intersects with classical neurotransmitters, despite the limitations of the monoaminergic theory of depression.

An obvious question not sufficiently addressed by immunopsychiatry is: how does the energy-demanding process of inflammation affect brain function when this peripheral process propagates to the brain? In line with a Jacksonian perspective of brain functions during disease, the dissolution induced by the inflammatory process will first impact the higher mental processes before impacting the lower levels of sensory-motor processing [9]. Translated in the language of network analysis of human brain connectivity, highly structured brain hubs with rich elements of neural architecture that are characterized by expensive energy consumption will be more

likely to be affected than less expensive "small world" networks in which information flows along short communication paths. How this corresponds to the major alterations in the brain connectome reported in major depressive disorder (MDD) remains to be determined. Based on a meta-analysis of resting-state functional connectivity [10], MDD appears to be characterized by hypoconnectivity within the frontoparietal network that is involved in cognitive control of attention and emotion, the dorsal attention network that is involved in attention to the external environment, the neural systems that are involved in processing emotional salience, and the midline cortical regions that mediate the top-down regulation of these functions. In contrast, there is hyperconnectivity within the default network that supports internally oriented and self-referential thought processes. These findings have been interpreted to suggest that MDD cognitive and affective symptoms are the result of an imbalanced connectivity among networks involved in regulating attention to the external versus the internal world together with a reduced connectivity between networks involved in regulating and responding to emotion or salience. It would certainly be interesting to determine whether this pattern of connectivity is a feature of a conserved mode of energy for the brain of an inflamed organism that has to process information arising from physiological changes within the body [11, 12] while having, at the same time, limited resources to do so. While all these issues remain to be addressed, important progress has been made at the mechanistic level as the reasons for the high metabolic cost associated with the inflammatory response have been elucidated at the molecular level. A new research field known as immunometabolism has emerged at the intersection between immunology and metabolism during the last decade, and it provides a new perspective on the relationship between inflammation and depression.

In this chapter we will first describe what we have learned from immunometabolism before examining the evidence for a relationship between immunometabolism and MDD and discussing possible neuronal networks involved in metabolic sensing and regulation of mood.

16.2 An Introduction to Immunometabolism

The field of inflammation has seen three successive waves of research. The first wave focused on the cellular aspects of inflammation. As inflammation is characterized by migration of leukocytes to the site of inflammation, it was important to understand (1) the mechanisms that allow this migration including vasodilatation and increased permeability of endothelial cells and (2) the characteristics of migratory leukocytes and their role at different stages of the inflammatory response. The second wave focused on the molecular events that are necessary to coordinate the different stages of the inflammatory response by allowing subsets of leukocytes to communicate between themselves and with other cell types, including endothelial cells. This second wave benefited from progress in molecular biology and the ability to produce relatively large quantities of recombinant proteins for in vitro and in vivo experiments using engineered strains of *Escherichia coli*. This research led to the

functional characterization of cellular communication molecules and their receptors. The molecular factors allowing immune cells to communicate with each other within the immune system were initially labeled as interleukins. However, their pleiotropic activity and in particular their ability to act outside the immune system on non-immune cells quickly led to a shift to the more general term: cytokines. This wave of research is still very active as new cytokines are still being discovered and their signaling mechanisms are not yet fully elucidated. An important outcome of this second wave is the replacement of the morphological description of the different subsets of inflammatory cells by their functional profiling, which is based on the cytokines they produce. The third wave of research has emerged only recently. It builds on the observation that the proliferation of innate immune cells at the site of inflammation and their engagement in the production and release of multiple communication signals require a reprogramming of their energy metabolism from oxidative phosphorylation to aerobic glycolysis.

Oxidative phosphorylation is an important part of the cellular respiration process by which cells use oxygen to metabolize nutrients. This process takes place in the mitochondria and involves a series of multiple enzymatic steps allowing the transport of electrons across the inner mitochondrial membrane. Oxidative phosphorylation generates energy that is ultimately used by adenosine triphosphate (ATP) synthase to phosphorylate adenosine diphosphate (ADP) into ATP. The amount of energy released by oxidative phosphorylation is high in that it produces 36 molecules of ATP for one molecule of glucose converted to carbon dioxide and water and 14 ATP for each cycle of beta-oxidation of fatty acids.

This is in sharp contrast to glycolysis that occurs in the cytosol and converts one molecule of glucose into two molecules of pyruvate and H+. The amount of energy released by glycolysis generates only 2 ATP. Pyruvate needs to be decarboxylated to enter the Krebs cycle in the form of acetyl-coenzyme A. As the Krebs cycle takes place in the mitochondrial matrix, this requires the transport of pyruvate from the cytosol across the inner mitochondrial membrane. The problem with glycolysis is that it consumes NAD+ that is reduced into NADH. The easiest way to regenerate NAD+ is to oxidize NADH. However, this requires the conversion of pyruvate into lactate. This process produces 2 more ATP. The advantage of glycolysis is that it is much faster than oxidative phosphorylation. However, it cannot be sustained for long. This is what takes place for instance in skeletal muscles during a short, intense exercise. Lactate accumulation does not occur as the liver takes up excess lactate to convert it back into pyruvate and glucose via gluconeogenesis. Glucose can then be fed back to the muscles. The problem for this metabolic pathway is that it consumes 6 ATP for only 2 ATP gained from glycolysis, which results in a net consumption of 4 ATP per molecule of glucose.

Although glycolysis has mainly been studied in anaerobic conditions with reference to fermentation, interest in this metabolic pathway has surged recently in cancer biology based on the observation that glycolysis is the main metabolic pathway used by rapidly proliferating tumor cells. The German scientist Otto Warburg was the first to describe the ability of tumor cells to rely on glycolysis rather than on oxidative phosphorylation even in the presence of oxygen. He got the Nobel Prize

in physiology in 1931 for his work. The so-called Warburg effect was originally proposed to be due to mitochondrial defect in cancer cells. The advantage of aerobic glycolysis over oxidative phosphorylation is that it facilitates the uptake and incorporation of nutrients (mainly glucose and glutamine) into the biomass, in a manner conducive to cell proliferation [13]. However, this is usually not ensured by mitochondrial deficiency as originally proposed by Warburg but by gain-of-function mutations in enzymes of the glycolytic pathway. Whether the Warburg effect takes place in cancer cells or in supporting cells of the tumor microenvironment such as stromal fibroblasts that can in this way feed lactate and other energy-rich nutrients directly to cancer cells leading to the reverse Warburg effect is still a matter of controversy.

Aerobic glycolysis is not restricted to cancer cells. Immune responses and wound repair also require a rapid proliferation of effector cells as the time factor becomes critical when microorganisms invade the body via breakage of the skin or epithelial barriers. The ability of immune stimuli to cause metabolic reprogramming of immune and non-immune cells has become a major focus of immunometabolism research [14]. Aerobic glycolysis has been found to be crucial for the ability of macrophages to engage in phagocytosis and production of pro-inflammatory cytokines. It is also necessary for the functioning of natural killer cells, Th1, Th2, and Th17 cells, as well as regulatory T cells. The link between metabolism and the phenotype of immune cells is so important that it is possible to switch macrophages from a pro-inflammatory phenotype to an anti-inflammatory phenotype just by blocking glycolysis and re-initiating the Krebs cycle. Like macrophages, microglia increase aerobic glycolysis and decrease oxidative phosphorylation when activated [15]. In both macrophages and microglia, the predominance of glycolysis over oxidative phosphorylation should not be seen as absolute. During macrophage activation the Krebs cycle is rewired rather than inhibited [16]. This results in the accumulation of the Krebs cycle intermediates succinate and citrate, and Krebs cycle-derived metabolite itaconate. These immunometabolites have important immune modulatory activities on their own. In addition, the electron transport chain becomes altered during macrophage activation and generates radical oxygen species from Complexes I and III.

The main limitation of these recent developments in immunometabolism is that they are based on the results of in vitro studies, which makes the generalization of these results to in vivo conditions difficult. A few ex vivo studies based on isolation of microglia from inflammatory brains of mice and humans have confirmed that microglia activation is associated with increased glycolysis [17, 18]. Conversely, attenuation of microglia activation by exercise in aged mice was found to decrease the glycolytic capacity of microglia [19]. Another important limitation is the absence of data on the impact of immunometabolism on neighboring organs. In the context of cancer, the metabolic reprogramming that fosters tumor cell proliferation has been proposed to extend to other organs including liver, fat tissue, and skeletal muscles as complementary sources of nutrients for rapidly developing tumors. This is at the origin of the cancer metabolism syndrome which culminates in cachexia [20]. Futile cycles that regulate handling of energy substrates between and within organs

play an important role in this process [21]. For instance, the high levels of lactate produced by metabolically active tumors enter the hepatic Cori cycle for reconversion into glucose that is avidly taken up by tumor cells. This hepatic gluconeogenesis can also be fueled in part by amino acids derived from skeletal muscle protein degradation. Even when oxidative phosphorylation continues to take place, its efficacy can be compromised due to proton leak across the mitochondrial inner membrane caused by changes in content and fatty acid composition of the major phospholipid constituent of the mitochondrial inner membrane cardiolipin [22]. Recruitment of metabolically active organs by the tumor can take place via different modalities, including cancer metabolites such as lactate, cytokines (e.g., IL-6 and TNFα, but also MIC-1/GDF15, a transforming growth factor-beta superfamily cytokine), danger signals such as high-motility group box 1, and tumor produced factors such as activins and parathormone-related peptide. Similar mechanisms are likely to take place in the context of chronic inflammation with the important difference that the original inflammatory response can propagate from the initial organ or body site to other parts of the body including the brain, giving rise to systemic inflammation.

Although this section is focused on what is known concerning the metabolic aspects of inflammation, it is important to examine how the effects of inflammation are modulated by glucocorticoids in view of the potent metabolic effects of glucocorticoids and the intricate interactions between pro-inflammatory cytokines and the hypothalamic pituitary-adrenal (HPA) axis [23]. Pro-inflammatory cytokines activate the HPA axis by acting centrally whereas glucocorticoids released by the adrenal cortex are classically seen as having potent immunosuppressive properties. However, there is also evidence that glucocorticoids can enhance inflammation and immunity. Whether an immunosuppressive or an immunoenhancing effect is observed depends on both the levels of glucocorticoids—immunosuppressive effects are observed at high doses of glucocorticoids—and the temporal relation between the event that triggers HPA axis activation and the one at the origin of inflammation. In rodents, stress occurring before LPS enhances the inflammatory response whereas a decrease is observed when the glucocorticoid response takes place after the stressor. In terms of metabolism, the stress response is well known to be associated with a catecholamine-dependent increase in glucose production and use followed by a glucocorticoid-dependent increased gluconeogenesis from proteins and lipids. Glucocorticoids inhibit glucose uptake and utilization in peripheral tissues such as the liver and muscles [24] by inducing insulin resistance, allowing in this way more glucose to be available to the brain. In addition to these effects, nongenomic actions of glucocorticoids on mitochondrial respiration, calcium mobilization, and apoptosis have been described more recently in neurons [25]. These actions involve the translocation of glucocorticoid receptors into mitochondria and their modulation of mitochondrial genome. In response to acute stress, glucocorticoids enhance mitochondrial function to provide cells with more energy while the organism tries to cope with stressors. Glucocorticoid receptors form a complex with the anti-apoptotic protein B-cell-lymphoma (Bcl-2) and translocate into mitochondria of neurons [25]. This results in upregulation of mitochondrial calcium levels, membrane potential, and oxidation. In contrast, chronically elevated levels of

glucocorticoids reduce expression of the glucocorticoid receptor and Bcl-2, with an opposite action to that of acute glucocorticoids on mitochondrial calcium levels, membrane potential, and oxidation.

At the whole organism level, the way the brain can efficiently compete for limited energy resources with the rest of the organism has been debated. According to the selfish brain theory, the brain maintains constant fluxes of large amounts of glucose to itself by regulating food intake and glucose allocation via ATP-sensitive potassium channels that function as "energy sensors" by coupling bioenergetic metabolism to membrane excitability [26]. The possibility that this trade-off between the brain energetic requirements and those of the rest of the body is so much compromised by chronic inflammation that it can result in the development of symptoms of depression has been presented already [27] at the same time as the metabolic programs associated with inflammation have been better delineated [28]. However, a critical assessment of this conceptualization requires both a minimum understanding of brain metabolism and the consideration of the evidence in favor of a role for metabolic dysfunction in depression. In the next section we will examine how the energy requirements of the brain are met and review the evidence for an involvement of metabolic dysregulation in depression.

16.3 Evidence for Metabolic Dysregulation in Major Depressive Disorder

16.3.1 Brain Metabolism

Glucose is the major oxidative fuel for the brain [29]. The brain is also able to oxidize fatty acids and amino acids, but these compounds make minor contribution to brain metabolism compared to glucose. In resting conditions, glucose oxidation provides most of the ATP consumed by the brain. However, when the brain is activated, glucose consumption increases much more than oxygen consumption, and this is made possible by a switch of brain metabolism from oxidative phosphorylation to aerobic glycolysis. Neuronal signaling accounts for most of the energy expense of the brain (about 70%) while nonsignaling activities account for the remainder. In particular, the ionic pump Na+,K + -ATPase consumes about 50% of the brain's ATP. Excitatory neurotransmission is much more expensive, accounting for 80–85% of brain ATP usage, compared to the expenses of inhibitory neurotransmission and baseline glial activity, which only account for a combined 15–20% of brain ATP. As such, gray matter has a much higher metabolic rate than white matter. Astrocytes have high oxidative capacity, similar to neurons, but their importance in glucose oxidation is limited due to their smaller volume fraction. Despite its high oxidative capacity, the brain preferentially uses glycolysis rather than oxygen consumption to sustain most of its function when activated. As pointed out by Dienel, "although the brain is a highly oxidative organ, it preferentially upregulates nonoxidative metabolism of glucose during activation" [29]. Not surprisingly the brain is highly sensitive to glucose availability as evidenced by the rapid degradation of

brain functions that culminates in coma in response to hypoglycemia. Aerobic glycolysis involves three major pathways: (1) glycolysis with lactate production; (2) the pentose phosphate shunt which is an important pathway for the generation of NADPH, ribose-5-phosphate, a precursor for the synthesis of nucleotides, and erythrose-4-phospate, a precursor for the synthesis of aromatic amino acids. Increased pentose shunt activity is likely a response to oxidative stress; (3) astrocytic glycogen turnover made possible by the storage of glucose as glycogen in astrocytes. In the brain glycogen is not just a storage depot. Glycogen turnover plays an essential role in sensory processing, memory, and neurotransmission even in the presence of normal glucose levels. In particular, glycogen appears to be part of the carbohydrates consumed during neuronal activation.

There has been some controversy about the cellular site at which glycolysis takes place with brain activation. The astrocyte-to-neuron lactate shuttle proposes that glutamate released by neurons induces glycolysis in astrocytes that results in lactate shuttling to neurons where it is converted into pyruvate before entering the Krebs cycle [30]. However, this model has been challenged based on the observation that neurons upregulate glycolysis more than oxidation when activated and release lactate, rather than being fueled by extracellular lactate from astrocytic origin [31]. This increase in neuronal glycolysis would allow neurons to meet the increased energy demands of neuronal activation. Lactate produced by glycolytic neurons would then be taken up by astrocytes which help with dispersing and clearing it from the brain [32]. Of note, lactate is not a waste product as it has various signaling functions in the brain, including its ability to increase blood flow and to downregulate neuronal activity. Astrocytes have high oxidation capacity that is primarily used with the glutamate/GABA-glutamine shuttle which allows neurons to synthesize glutamate and GABA from astrocytic glutamate- and GABA-derived glutamine. This metabolic flux captures about 80% of glucose oxidation in glutamatergic neurons. The synthesis of glutamate in neurons requires the phosphate-activated glutaminase that is a mitochondrial enzyme. In addition, it requires cell-to-cell transfer of ammonia as the formation of glutamate from glutamine in neurons releases ammonium that is needed by astrocytes to form glutamine from glutamate [33, 34].

16.3.2 Preclinical Evidence for a Relationship Between Depression and Mitochondrial Dysfunction

A role for mitochondrial dysfunction in the pathophysiology of depression can be deduced from the examination of the negative impact of inflammation and stress on mitochondrial function and from intervention studies targeting metabolic factors. Most studies in the field are essentially correlative. For instance, mice treated with low doses of LPS display reduced maximum oxygen consumption in their hippocampus 3 h later and increased levels of the inhibitory neurotransmitter GABA, as measured by proton magnetic resonance spectroscopy [35]. In the same manner, induction of sickness behavior by the administration of LPS at the dose of 0.1 mg/kg

increased glycolytic fluxes in the hippocampus 6 h later as measured by the mRNA expression of two key glycolytic enzymes (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 [*Pfkfb3*] and hexokinase 2 [*Hk2*]) in the hippocampus of mice and reduced levels of pyruvate and oxaloacetate [36].

Rats submitted to repeated immobilization stress for 21 days were found to display decreased activities of complexes I to III of the electron transport chain in the brain [37]. These alterations are not the same depending on the model and the brain areas under investigation. For instance, exposure of rats to chronic unpredictable stress for 40 days decreased complex I, III, and IV but had no effect on complex II [38]. In addition, these effects were observed in the cerebral cortex and cerebellum but not in the hippocampus, striatum, and prefrontal cortex. These earlier studies on the effects of stress on mitochondrial function did not try to relate the observed alterations to the most likely causal factor represented probably not by inflammation but by chronic activation of the hypothalamic pituitary-adrenal axis. As mentioned previously, there is evidence that chronic activation of the HPA axis or repeated administration of glucocorticoids induces similar signs of mitochondrial dysfunction in naïve rodents [39]. In addition, a complicating factor for the interpretation of chronic stress studies is that the brain mitochondrial alterations that are reported in chronic stress models might just represent another facet of the negative energy balance induced by stress, as evidenced by body weight loss, which is aggravated by stress-induced decreases in food intake.

More recent investigations are more mechanistic thanks in part to the progress in techniques for assessing mitochondrial function ex vivo and in vivo. Studies on inflammation-induced depression-like behavior have confirmed that the development of depression-like behavior is associated with mitochondrial dysfunction and decreased brain ATP levels. In addition, there is evidence that mitochondrial protectant agents can prevent inflammation-induced depression and, conversely, that mitochondrial toxicants can induce depression-like behavior in healthy naïve mice. As a typical example of this type of study, mice injected with the cytokine inducer lipopolysaccharide (LPS) at the dose of 0.8 mg/kg developed depression-like behavior measured 24 h later by increased immobility in the forced swim test and decreased sucrose preference [40]. These effects were associated with increased production of superoxide by mitochondria isolated from the hippocampus, reduced ATP levels, and decreased mitochondrial membrane potential. Intracerebroventricular administration of the mitochondrial targeted antioxidant Mito-Tempo blocked these effects in LPS-treated mice whereas administration by the same route of rotenone, an inhibitor of complex I of the mitochondrial respiratory chain, increased duration of immobility in the forced swim test and reduced sucrose preference in healthy naïve mice.

Similar approaches have been used for studies based on models of chronic stress. In one of these studies, mice that responded to chronic social defeat by social avoidance in a subsequent test of social exploration had lower levels of ATP in their hippocampus and prefrontal cortex than control mice or mice exposed to chronic social defeat but were not deficient in social exploration [41]. Repeated intraperitoneal administrations of ATP normalized the social behavior of mice susceptible to

chronic social behavior. The same results were obtained on decreased sucrose preference of mice submitted to a model of chronic unpredictable stress.

At the cellular level, astrocytes have been investigated as the possible cell type involved in the effects of chronic stress. Genetic or pharmacological decrease of ATP release from astrocytes in naïve mice induced similar depression-like behavior as that produced by chronic social defeat stress and chronic unpredictable stress [41]. In addition, these effects could be corrected by stimulating ATP release from astrocytes. These findings were interpreted to mean that major depressive disorder is caused by the deficient release of ATP from astrocytes. Of note, the genetic deletion of Calhm2 which functions as an ATP-releasing channel in astrocytes resulted in the appearance of a depression-like phenotype in mice that was rescued by peripheral administration of ATP [42]. The interpretation of these two studies departs from the classical view of ATP as a neurotransmitter as it positions ATP as a communication signal between astrocytes and neurons. Microglial cells could play a role in this communication as they release small amounts of ATP within a few minutes in a toll-like receptor (TLR-)4-dependent manner when activated by LPS, and they do so independently of their ability to produce TNF or NO [43]. The release of ATP by microglia is amplified by astrocytes [43]. These findings point to a partnership between microglia and astrocytes in the modulation of excitatory neurotransmission. If these findings obtained in brain slices apply to in vivo conditions, any event leading to a decrease in the availability of ATP whether it is from astrocytic or from microglial origin will result in a deficient excitatory neurotransmission. This is likely to be the case when microglia undergo aerobic glycolysis to produce inflammatory cytokines. In vitro experiments confirm that LPS exposure is able to induce aerobic glycolysis in primary microglia [44]. This effect is associated with mitochondrial fragmentation as a consequence of increased mitochondrial fission. The addition of the mitochondrial fission inhibitor Mdivi-1 to primary microglia decreased the number of fragmented mitochondria, reduced glycolysis, and attenuated LPS-induced release of cytokines and chemokines, as well as LPS-induced succinate production. Of note, the accumulation of succinate caused by LPS could be responsible for reverse electron transport that would generate excessive mitochondrial radical oxygen species [45]. It is therefore not surprising that Mdivi-1 also inhibits mitochondrial ROS production and attenuates the LPS-induced increase in mitochondrial membrane potential [44].

A systematic study of the effects of stress on mitochondrial function reveals that in general chronic exposure to stress decreases mitochondrial energy production capacity and alters mitochondrial morphology [46]. In contrast, acute stress increases certain aspects of mitochondrial function. Some investigations have been conducted at the genetic level. Most of the mitochondrial proteins are encoded in the nuclear genome, but a few of them are encoded by the mitochondrial DNA (mtDNA) which lacks efficient repair mechanism and is therefore more susceptible to disruption. Mitochondrial DNA codes for a limited number of genes, 37, of which the product is involved in the electron transport chain and the ATP synthase complex, mitochondrial transfer RNAs, and ribosomal RNAs. It is inherited from the mother and it is present in 2 to 10 copies in mitochondria in contrast to nuclear DNA

that is present only in 2 copies. Quantification of mtDNA copy number is carried out by quantitative real-time polymerase chain reaction (qPCR), and alterations in mtDNA copy numbers relative to nuclear DNA copy numbers have been associated with many phenotypes and diseases. In response to chronic stress mtDNA copy number is decreased in the brain but increased at the periphery, which would be due to upregulation of biogenesis and greater mtDNA replication in response to energy deficiency.

In order to determine whether mitochondrial function plays a pivotal role in the response to stress, Picard and his colleagues used mutations targeting either the mitochondrial DNA genes NADH dehydrogenase 6 (*Nd6*) and cytochrome c oxidase subunit 1 (*Coi*) to decrease electron transport chain and respiratory activity or the nuclear DNA genes *Ant1* or *Nnt* to reduce ATP/ADP transport across the inner mitochondrial membrane or reduce a major mitochondrial antioxidant system [47]. There was no evidence for an invariant pattern of response to mitochondrial defects as each mutation gave rise to specific alterations in the neuroendocrine and metabolic responses to a 30 min stress exposure. In particular, *Coi* and *Ant1* mutations were associated with a higher activation of the HPA axis in response to restraint whereas *Nnt* deficiency had the opposite effect. Stress-induced hyperglycemia was more marked in mice with mtDNA defects. However, it was blunted in *Ant1*-deficient mice. Plasma IL-6 reactivity was not significantly altered in mitochondrial mutants. In contrast, there was a tendency for mitochondrial mutations to attenuate the expression of pro-inflammatory genes in the hippocampus in response to restraint [47].

A few studies have investigated possible regional differences in the relationship between depression and mitochondrial activity. In a study carried out in mice submitted to chronic unpredictable stress for 6 weeks, mitochondria isolated from the cortex, hippocampus, and hypothalamus showed a decrease in respiratory rates and in mitochondrial membrane potential, together with the appearance of swollen and vacuolated mitochondria [48]. However, in a study carried out in rats submitted to 24 days of chronic mild stress, there was an indication of a higher rather than a lower mitochondrial activity in mitochondria isolated from the raphe nuclei of stressed rats compared to controls, as measured by respiratory rate, ATP production, superoxide dismutase activity, and glutathione peroxidase activity [49]. These findings indicate that mitochondrial dysfunction in animal models of depression could be region specific.

Non-pharmacological means can be used to improve mitochondrial function and to restore brain ATP levels. The beneficial effects of exercise on brain mitochondrial function have been less well studied than its effects on muscle mitochondria [50–52], but they appear to be robust enough to protect from depression-like behavior [53]. An entirely different approach is the use of low-level laser therapy [54]. Low-level laser therapy has antioxidant and anti-inflammatory properties and can preserve mitochondrial function by increasing cytochrome c oxidase activity and ATP synthesis. Applying low-level laser therapy to the head of mice for 30 min after each restraint session for a minimum of 14 days was sufficient to treat depression-like behavior. This effect was associated with a normalization of ATP levels and an

increase in complex IV activity but only in the prefrontal cortex, not in the hippocampus and hypothalamus. Still another approach represented by deep brain stimulation targeting the nucleus accumbens was found to restore response to imipramine in rats chronically treated with ACTH, and this effect was associated with the normalization of mitochondrial respiration in mitochondria isolated from the prefrontal cortex [55].

Although the previous findings indicate that restoring mitochondrial function or normalizing ATP levels in the brain have beneficial effects on depression-like behavior induced by chronic stress or by inflammation, such a strategy is not without potential drawbacks. ATP is not only a metabolic marker but also an immunomodulator. It increases the production of pro-inflammatory cytokines, and this effect is mediated by the P2X7 purinergic receptor [56]. The pro-inflammatory activity of ATP is counterbalanced by the anti-inflammatory activity of adenosine. This means that it would certainly be counterproductive to increase brain ATP levels in conditions of brain inflammation unless this ATP can be quickly metabolized into adenosine.

Another approach for assessing the relationship between depression and ATP consists of investigating the processes that mediate the metabolism of ATP or those that are responsible for its consumption. CD39 also known as hydrolase ectonucleotide triphosphohydrolase is an important membrane enzyme present on several types of immune cells including macrophages, monocytes, and probably microglia. It regulates the level of extracellular ATP by metabolizing it into AMP that is further transformed into adenosine by CD73. Chronic social defeat was found to increase the hippocampal expression and activity of CD39 [57]. Administration of the CD39 analog, apyrase, mimicked the depression-like behavior induced by chronic social defeat, and this effect was reversed by replenishing hippocampal ATP levels. Conversely, genetic deletion of CD39 blocked the behavioral effects of chronic social defeat.

An article often cited as evidence for a negative relationship between depression and ATP is the study by Gamaro et al. [58]. The authors show that Na+,K + -ATPase activity in hippocampal synaptic membranes was decreased after 40 days of exposure of rats to chronic mild stress. The problem is that chronic administration of fluoxetine blocked this effect but did not normalize the decreased sweet food consumption induced by chronic mild stress.

If mitochondrial dysfunction plays a crucial role in the pathophysiology of depression, it should be possible to treat depression by replacing the deficient mitochondria by new ones. This possibility has been examined in a recent study conducted on LPS-induced depression-like behavior [59]. Mitochondrial transfer by intravenous injection of freshly isolated mitochondria from hippocampi of healthy mice either concomitantly to LPS or 16 h later was able to treat LPS-induced depression-like behavior. It also normalized LPS-induced oxidative stress and activation of microglia and astrocyte while at the same time increasing BDNF and restoring neurogenesis. Mitochondrial transfer was much more effective when administered concurrently with LPS rather than 16 h later. These results clearly

need to be confirmed and expanded in order to determine in which compartment transplanted mitochondria are active, periphery or brain, and why they need to be injected before LPS.

Whether sex differences in the relationship between mitochondria dysfunction and depression could explain the prevalence of depression in females has given rise to some speculation [60, 61]. In general, males utilize mainly proteins and amino acids in mitochondria whereas females predominantly use fatty acids. Sex differences in oxidative/nitrosative stress, mitophagy, mitochondrial quality control, activation of the mitochondrial permeability transition pore, and cell death pathways have been described mainly in the context of brain injury but have not been given much consideration in the context of biological psychiatry.

16.3.3 Clinical Evidence for a Relationship Between MDD and Mitochondrial Dysfunction

Indirect evidence for a relationship between depression and alterations in energy metabolism comes from imaging studies of brain glucose metabolism and blood flow in MDD patients. Despite considerable heterogeneity in the results, depressed patients show a reduced blood flow and glucose metabolism in prefrontal cortex particularly when they exhibit psychomotor retardation. The same abnormalities are also found in anterior cingulate gyrus and basal ganglia whereas the parietal lobe shows increased blood flow and metabolism [62]. A more recent meta-analysis based on the activation likelihood estimate for each brain voxel and including studies carried out in Chinese patients showed that depressed patients have hypoactive glycose metabolism in insula, limbic system, and basal ganglia and an increased activity in the thalamus [63].

More focused studies on the relationship between MDD and mitochondrial dysfunction came originally from the investigation of neuropsychiatric disorders in patients with mitochondrial diseases due to either nuclear or mitochondrial DNA-encoded mutations [64]. As predicted based on the high energy requirements of the skeletal muscles and brain, this population is frequently afflicted with myopathy and neuropsychiatric symptomatology. The risk of comorbid depression is multiplied by 3.9 and the lifetime prevalence of depression is 54%. Of course, this is far from being sufficient to jump to the conclusion that MDD is a form of mitochondrial disease. Instead, the hypothesis proposed by several authors is that MDD could be due to suboptimal mitochondrial function making the energy produced by mitochondrial function unable to meet the metabolic cost of adaptation to psychosocial stressors [65]. Suboptimal mitochondrial function could be due to various genetic or acquired factors, including in this last case low-grade inflammation. If this hypothesis is correct, it should be possible to detect individuals at risk by measuring markers of mitochondrial function. The problem is that there is no gold standard of mitochondrial function and the methods that need to be deployed are fraught with the same pitfalls as those in other fields of biological psychiatry, e.g., the

over-reliance on peripheral markers and the difficulty of running longitudinal studies in sufficiently sized samples unbiased by medication. The few available studies have measured by necessity mitochondrial function in peripheral blood mononuclear cells. In a study carried out in 22 women with MDD age-matched to 22 controls, mitochondrial respiration was assessed using a high-resolution respirometer [66]. MDD patients medicated for two thirds of them had decreased respiratory activity measured by baseline respiration, ATP turnover-related respiration, and spare respiratory capacity. The observed alterations suggested a lower ATP availability at baseline and a reduced efficiency of ATP production that were not related to a decrease in mitochondrial density as citrate synthase activity was not altered. These signs of mitochondrial dysfunction correlated negatively with depression severity measured by scores on the BDI and MADRS symptom scales. At the symptomatic level, items such as loss of energy, fatigue, disturbed sleep, and difficulties concentrating were associated with decreased respiratory activity, but it was also the case for sadness and irritability.

Much progress has been made during the last decade for assessing mitochondrial function thanks to the development of automated assays based on the continuous measurement of oxygen consumption rate of isolated mitochondria, cells, and even tissues exposed to various stress tests to separate the contribution of each complex of the electron transport chain to mitochondrial respiration. However, this specialized equipment is not easily accessible to psychiatrists. This has motivated a search for alternative approaches, including the measurement of mtDNA copy number. Contradictory results have been published, showing either an increase [67] or a decrease [68] as well as no change [69]. In a study carried out on white blood cells of 179 patients in primary health care with anxiety, depression, or stress and adjustment disorders compared to 320 healthy controls, patients were found to have a higher relative mtDNA copy number that correlated with Patient Health Questionnaire scores at baseline and decreased in response to treatment [70]. Complicating the picture, a few studies measured the levels of circulating cell-free mtDNA which comes from the release of mtDNA during cellular stress but does not reflect mitochondrial functional capacity. Cell-free mtDNA was found to be elevated in suicide attempters [71] but decreased in patients with MDD, with this decrease more marked during the depressive episode than during remittance [72]. A direct comparison of mtDNA copy number and cell free mtDNA in the same individuals revealed that MDD patients had higher cell-free mtDNA levels in the absence of any difference in mtDNA copy number measured in peripheral blood mononuclear cells [73]. There was no correlation between cell-free mtDNA and mtDNA copy number, confirming they represent different aspects of mitochondrial biology. Of note, antidepressant treatment normalized levels of cell-free mtDNA but only in patients who responded positively to the treatment. Similar studies on circulating cell-free DNA show that like cell-free mtDNA it is released in response to an acute bout of exercise or to the Trier social stress test in healthy individuals, with exercise being much more effective than the psychological stress [74]. The increase of cell-free mtDNA but not of cell-free DNA in response to psychological stress was confirmed independently [75].

16.3.4 Relationship Between Mitochondrial Dysfunction and Inflammation

From the experimental and clinical studies that examine the role of metabolic inefficiency in depression, it is obvious that there is still a strong tendency to consider inflammation and mitochondrial dysfunction as two separate entities. As we have seen, no more than a handful of studies have investigated the consequences of inflammation on mitochondrial function or the possibility of treating inflammation-induced depression-like behavior by restoring energy balance. In most other cases, mitochondrial function is considered by itself, independently of any connection with either stress hormones or inflammation. This separation between inflammation and mitochondrial function is unfortunate as we know now that psychological stress can induce inflammation in addition to activating stress hormones and in addition that mitochondrial dysfunction can result in inflammation. Several excellent reviews have already been published on the influence of stress on inflammation [76–79]; therefore, there is no need to develop further this aspect. What is less commonly understood is the relationship between mitochondrial dysfunction and inflammation.

While we have learned much about the nature and mechanisms involved in LPS-induced depression, the emphasis on LPS as the inflammatory trigger has likely hindered our progress on the immunometabolic basis of depression. As LPS is derived from bacterial products, it is capable of directly activating inflammation via TLR4. Therefore, we have tended to neglect how other immune sensors and activators may uniquely contribute. In addition to the TLRs, there are numerous other pattern recognition receptors (PRRs), including the cytoplasmic retinoic acid-inducible gene 1 (RIG-1)-like receptors (RLRs) and nucleoid-binding oligomerization domain (NOD)-like receptors (NLRs) as well as the transmembrane C-type lectin receptors (CLRs).

While these receptors are often considered in the context of pathogen-associated molecular patterns (PAMPs), as in the case of viral DNA and RNA, they are also capable of responding to endogenous signals known as danger-associated molecular patterns (DAMPs). DAMPs, also known as “alarmins,” are released by damaged or dying cells and can be actively released in response to cellular stress. Various mitochondrial components can serve as danger signals (mtDAMPS). Upon release, mtDAMPs can initiate inflammatory cytokine production and recruit immune cells to the site of damage through their interaction with PRRs [80, 81].

Mitochondrial-derived DNA (mtDNA) is one of the critical DAMPs tying mitochondrial dysfunction to inflammation. Mitochondria possess a circular, maternally inherited genome that consists of 37 genes that code for the 13 proteins. These proteins form the subunits of the electron transport chain, which is central to the process of oxidative phosphorylation. When mitochondria are damaged or stressed, they release mtDNA into the extracellular space and/or the cytosol. In the extracellular space, mtDNA is agonist of TLR9, which activates MAPK and NF-κB signaling cascades. Intracellular DNA has emerged as a critical activator of the immune

response to sterile inflammation and has been shown to activate a number of various PRRs [81, 82]. The circular structure of mtDNA, which resembles that of bacteria and some viruses, may be what allows it to have such a potent effect on many of the PAMP pathways.

Absent in melanoma 2 (AIM2) is a cytosolic PRR and a component of the inflammasome that can be activated by mtDNA. When activated, AIM2 works in concert with other receptors of the inflammasome (e.g., NLRP1 and NLRP3) to activate caspase 1. Caspase-1 promotes the maturation of pro-IL-1β and pro-IL-18. Higher levels of both of these cytokines have been associated with depressive symptoms [83–85], but a possible role of AIM2 in inflammation-associated depression has not yet been investigated.

Another PRR that acts as a DNA sensor able to respond to cytosolic mtDNA is cyclic GMP-AMP synthase (cGAS) [81]. When cGAS binds mtDNA, it generates cGAMP, which acts as a second messenger to activate the Stimulator of Interferon Genes (STING). STING promotes the production of type I interferon (IFN) via the activation of the IRF3 transcription factor. There is strong history related to the ability of IFN to induce depressive symptoms. It is well accepted that treatment with IFN-α for cancer or infection with hepatitis C virus will increase depressive symptoms in patients [86]. Further, the activation of STING also appears to be capable of activating the NF-κB signaling pathway. However, this activation appears to be in a cGAS-independent fashion, instead relying on the DNA damage sensor ataxia telangiectasia mutated (ATM) [87].

Other mitochondrial-derived DAMPs that may play a role in inflammation-induced depression include cytochrome c (CytC) and mitochondrial transcription factor A (TFAM). Both CytC and TFAM are components of the mitochondrial intermembrane and can be released into the cytosol in response to cellular stress [88, 89]. When released by brain cells, CytC and TFAM can impact inflammation by activating glial cells [90]. As such, these DAMPs may serve a link between mitochondrial damage and neuroinflammation-induced depressive symptoms.

16.3.5 Summary

There is not much evidence yet available on the relationship between the consequences of immunometabolism on brain metabolism and their possible contribution to inflammation-induced depression. A handful of experimental studies support the hypothesis that inflammation-induced depression-like behavior is associated with signs of mitochondrial dysfunction. Conversely, restoration of mitochondrial dysfunction directly or indirectly treats depression-like behavior. Most studies on mitochondrial dysfunction have been carried out in the context of stress biology. There is still a strong disconnect in the literature as the relationship of depression to mitochondrial dysfunction has been studied independently of a possible involvement of inflammation either as a causal factor for mitochondrial damage or as a consequence of mitochondrial dysfunction.

16.4 Neuronal Networks Sensitive to Energy Metabolism Inefficiency

If the hypothesis that depression is caused by inefficient energy metabolism taking place at the periphery or in the brain has some validity, there should be *a minimum* some evidence of sensitivity to variations in energy metabolism within parts of the neuronal networks that mediate symptoms of depression. However, inflammation propagating from the periphery into the brain is a diffuse process that does not target any specific brain area or neuronal network. In contrast, in conditions of acute or chronic stress such as social defeat in which a mouse is defeated by an opponent, microglial activation preferentially occurs in those brain areas that are involved in the processing of the information relative to the dangerous situation, possibly because of a local weakening of the blood-brain barrier facilitating the brain trafficking of peripheral inflammatory monocytes. In the context of a peripheral inflammation relayed to the brain by the vagus nerves or spinal neurons, one could also imagine that neuronal activation in the projection areas of these nerves will be able to increase the level of local microglial activation. This would affect preferentially the insular cortex that substantializes feelings from the body and the cingulate cortex in which interoceptive information conjoins with homeostatic motivations to guide adaptive behavior [91]. Another possibility is represented by the exquisite sensitivity of a certain category of neurons to inflammation, oxidative stress, and mitochondrial dysfunction. This appears to be the case for dopaminergic neurons and more specifically those dopaminergic neurons that project from the *substantia nigra* to the striatum. Alteration of dopaminergic neurotransmission is usually not considered as a landmark of the neurochemical signature of MDD. However, there is much evidence that: (1) inflammation-associated depression is characterized by a predominance of symptoms reflecting hypoactivity of the dopaminergic system, including anergia and reduced motivation, and (2) inflammation impairs dopaminergic neurotransmission.

16.4.1 Inflammation and Motivational Alterations

Epidemiological studies in the general population consistently show an association of inflammation with somatic symptoms of depression, including reduced motivation, psychomotor retardation, and fatigue labeled as anergia in the context of depression, which are relatively resistant to usual antidepressant treatments [92–94]. This symptomatology reflects the consistent observations that innate immune activation preferentially affects midbrain dopamine [95]. The largest population of midbrain dopaminergic neurons are localized in the *substantia nigra pars compacta* (SNc) and the ventral tegmental area (VTA), which have different axonal projections to subcortical and cortical areas and encodes different aspects of motivated behavior [96]. Dopaminergic neurons projecting from the VTA and terminating in the ventral striatum (including the nucleus accumbens (NAc)) appear to play a key role in modulating effort-based decision-making [97–99]. Such observation is

supported by preclinical studies demonstrating that effortful choices can be reduced by 6-hydroxydopamine (6-OHDA) lesions of the NAc and increased by blockade of dopamine uptake. Further, the effort expenditure for rewards can be modulated by increasing or decreasing dopaminergic signaling.

Regarding the impact of inflammation on effort valuation, preclinical studies in rodents and non-human primates demonstrate that administration of inflammatory cytokines (e.g., IL-1β, IL-6, or IFN-α) reduces willingness to work for highly palatable rewards without reducing consumption of freely available but less palatable food [100–102]. However, when both high and low rewards are available simultaneously in a concurrent choice task contrasting high effort/high reward and low effort/low reward options based on the same type of operant responding, LPS not only reduces incentive motivation but also shifts mice behavior toward the most valuable reward despite the higher effort it requires [103]. This effect is also apparent in humans [104, 105], suggesting that in an effort-based decision-making situation, inflammation shifts responding toward the reward that is perceived as most valuable, despite the higher effort it requires [106]. This indicates that inflammation does not just reduce motivation but increases sensitivity to the hedonic value of incentive stimuli, making less valuable incentive stimuli even less worth the effort. This extends to social situations as inflammation increases rejection of strangers' faces and favors positive responding to familiar faces [107].

16.4.2 Inflammation and Mitochondrial Dysfunction in Dopaminergic Neurons

The effects of inflammation on neurotransmission are usually explained in terms of interference with neurotransmitter synthesis, release, and reuptake. However, these effects are not specific to dopamine as they affect all monoaminergic neurotransmitters. In addition to these effects, it has been proposed that dopaminergic neurons receive information from the periphery via the hypothalamus about the metabolic state of the body to guide energy and effort allocation in the face of inflammation [108]. However, dopaminergic neurons have also the peculiarity of being under sustained oxidative stress due to the auto-oxidation of free cytosolic dopamine that results in the formation of dopamine-quinones and superoxide radicals. Dopamine quinones and superoxide radicals can damage the electron transport chain and oxidize mitochondrial proteins and lipids, leading to further generation of radical oxygen species, reduced ATP production, decreased mitochondrial membrane potential, and bioenergetic defects [109]. Importantly, mtDNA is particularly vulnerable to ROS because of its close proximity to the ETC and the lack of DNA repair mechanism. This means that any additional metabolic and bioenergetic burden, such as inflammation, might push dopaminergic neurons over the edge and impair their function if not their structure.

During inflammation, high levels of ROS are generated by activated microglia, which repurpose mitochondria from generating ATP to ROS production [110]. The midbrain dopaminergic pathway has an enriched microglial population as compared

to other brain regions [111], which might contribute to the vulnerability of these neurons to inflammation. Inflammation occurring in the periphery or in the brain is well known to preferentially damage dopaminergic neurons in comparison to serotoninergic or noradrenergic neurons [112, 113], and this is associated with oxidative damage to mitochondrial components and decreased complex III and V respiration [112]. Both celecoxib (an inhibitor of cyclooxygenase-2 activity) and pioglitazone (an agonist of peroxisome proliferator-activated receptor gamma; PPAR-γ) prevented mitochondrial dysfunction, confirming that mitochondrial dysfunction is secondary to inflammation. Together, these data indicate that inflammation activates microglia to generate inflammatory mediators that, combined with the high oxidative burden of dopaminergic neurons, lead to mitochondrial dysfunction. Thus, inflammation, oxidative stress, and mitochondrial dysfunction have the potential to create a detrimental vicious cycle for negatively impacting dopaminergic neurotransmission in depression.

Because defective mitochondria not only produce more ROS but also fail to generate ATP and regulate calcium buffering, their removal by mitophagy is important to maintain cellular homeostasis and allow their replacement by healthier mitochondria. Mitophagy mediated by PTEN-induced kinase 1 (PINK1)/cytosolic E3 ubiquitin ligase (Parkin, PRKN) (PINK1/Parkin) plays a key role in the maintenance of mitochondrial fitness in dopaminergic neurons. *Pink1* or *prkn* gene mutations cause early-onset recessive familial forms of Parkinson's disease (PD) [114]. In damaged mitochondria, PINK1 accumulates on the outer mitochondrial membrane to recruit and phosphorylate Parkin and ubiquitin, leading to lysosomal degradation. Despite the increasing data pointing to mitochondrial dysfunction in depression, few studies have addressed the possibility of impaired or insufficient mitophagy leading to the accumulation of damaged mitochondria and decreased mitochondrial turnover in inflammation-associated depression.

There is evidence that mtDNA leakage into the cytosol and peripheral inflammation facilitate impairment in dopaminergic signaling. While mutations in *Pink1* and *Parkin* in PD patients lead to disease progression, *pink1−/−* and *prkn−/−* mice are healthy and display little motor impairment reminiscent of Parkinson's disease. This observation indicates that factors other than the loss of function of these proteins are required to impair dopaminergic signaling. In chronic models of mitochondrial stress with impaired mitophagy in dopaminergic neurons (double knock out of mutator mice that accumulate high levels of mtDNA mutations with either *pink1−/−* or *prkn−/−*), mtDNA that is released in the cytosol triggers the activation of the cgas-sting pathway to promote inflammation, neurodegeneration, and locomotor defects, while the loss of *sting* abrogates these alterations [115]. Thus, accumulation of mtDNA leading to sting activation creates the necessary condition for a positive feedback loop between inflammation and mitochondrial damage. In addition, intestinal infection of *pink1−/−* mice with Gram-negative bacteria transforms asymptomatic mice into mice with a full PD-like phenotype [116]. Besides their role in mitophagy, PINK1 and Parkin are involved in antigen presentation. They normally suppress antigen presentation derived from LPS-induced mitochondrial degradation. In the absence of PINK1, presentation of mitochondrial antigens to T cells

results in the formation of mitochondria-specific cytotoxic CD8+ T cells. These T cells are able to traffic from the gut into the brain and to attack dopaminergic neurons expressing major histocompatibility complex class I (MCH-I) in an autoimmune manner.

Although mitochondrial dysfunction in inflammation-induced depression remains under-studied, it is likely to represent an important component of the relationship between inflammation, dopamine, and motivational alterations. This opens the possibility that inflammation-induced mitochondrial dysfunction is exacerbated in dopaminergic neurons because of their intrinsic susceptibility to metabolic damage due to sustained oxidative stress and high bioenergetic requirement. Further, inflammation-induced mitochondrial damage leads to cytosolic mtDNA accumulation that activates the cgas-sting pathway and increases the inflammatory insult on dopaminergic neurons. This could explain why reduced motivation and psychomotor slowing are the predominant symptoms in inflammation-associated depression.

16.4.3 Summary

Inflammation-associated depression is characterized by a predominance of somatic symptoms over cognitive and affective symptoms. This could be due to the exquisite sensitivity of dopaminergic neurons to mitochondrial dysfunction caused by the switch of brain innate immune cells from oxidative phosphorylation to aerobic glycolysis and the ensuing metabolic inefficiency it generates. Alterations in mitochondrial structure could lead to mtDNA leakage, which would induce the activation of the cgas-sting pathway and create the condition for a vicious cycle between inflammation and mitochondrial dysfunction. Although not examined in the present section, it can be proposed that the affective and cognitive symptoms of depression in inflamed individuals are a consequence of inflammation negatively affecting mitochondria function in the neurogenic niche, therefore impairing neurogenesis.

16.5 Conclusion and Perspectives

It should be apparent from the literature reviewed in this chapter that inflammation-associated depression is unlikely to be due solely to a direct effect of inflammatory mediators on neuronal function possibly relayed by mediators such as prostaglandins. We have made the case for an involvement of immunometabolism and its consequences on mitochondrial function and structure. This possibility has mainly been studied so far in the context of neurodegenerative diseases rather than psychiatric disorders. Even if there is no common measure between the level of inflammation that is necessary for the progressive loss of neurons in the central or peripheral nervous system and the level of inflammation that is observed in MDD, there is no reason for not accepting the possibility of a continuum in the mechanisms that are triggered by inflammation, with functional rather than structural alterations predominating in the case of inflammation-associated depression. In the assessment of

the nature of this continuum, it is important to remember that in contrast to neurodegeneration that occurs primarily in the brain, the low-grade inflammation that is associated with MDD originates at the periphery before propagating to the brain. This means that the energy requirements of the peripheral immune response are already sufficient for compromising the amount of energy that is available to normal brain functions independently of the propagation of inflammation from the periphery to the brain. Although this has not been investigated specifically, there is evidence that in mice submitted to chronic social stress, the increased energy expenditure at the periphery is associated with a reduced glucose utilization by the brain [117] possibly because of insulin resistance. Not surprisingly, the ability of neurons to sustain the consequences of brain inflammation is reduced and their sensitivity to mitochondrial dysfunction exacerbated. This process is likely to affect preferentially the neurons that are the most sensitive to inflammation and oxidative stress, and we have described how this could explain the association of the somatic symptoms of depression with decreased dopaminergic neurotransmission in the fronto-striatal network. When considering mitochondrial dysfunction, it is important to keep in mind that mitochondria are very dynamic organelles with high motility within the cytoplasm. To increase their metabolic capacity in conditions of low energy they form networks by fusion of their outer and inner membranes. When damaged, they undergo fission to get rid of the damaged part. Damaged mitochondria are ultimately eliminated by mitophagy. Each of these processes involves specific processes orchestrated by GTPases including mitofusin (Mfn)1 and 2 and optic atrophy 1 (Opa1) for fusion and dynamin-related protein-1 (Drp1) for fission. The activation of innate immune cells by LPS biases the balance between fusion and fission toward fission [118]. A similar bias has been described in activated microglia [44, 119] with mitochondria fragmentation being associated with glycolytic shift and production of pro-inflammatory cytokines. This bias can be due to either activation of Drp1 or down-regulation of Mfn1/2 and, as expected, it is corrected by interventions targeting these factors. The same bias toward mitochondrial fission has been reported in neurons undergoing degeneration. Very surprisingly, overexpression of Mfn2 specifically in neurons prevented microglial activation induced by a septic dose of LPS in mice and reduced lethality in addition to protecting neuronal death [120].

Much work is still needed to improve our understating of how chronic low-grade inflammation impacts brain metabolism and mitochondrial function in specific brain networks to ultimately help the development of better approaches for treating symptoms of depression in inflamed individuals. A number of strategies for improving, preserving, or rescuing brain energetics are available [121]. They involve restoring oxidative phosphorylation and repairing the broken Krebs cycle, correcting mitochondrial dysfunction by mitochondrial protectants or mitochondrial transfer to repair damaged mitochondria, recourse to ketogenic strategies, administering hormones or hormone-like molecules that modulate cerebral energetics, and various other interventions that have been presented in this chapter and tested in experimental models. However, it is important to remember that strategies that provide promising results in preclinical studies do not always fulfill their premises when tested in

the real world. A recent example is provided by the failed attempt to target the PI3kinase/Akt/mTOR pathway for the treatment of depression that was initially based on the preclinical observation that the fast-acting antidepressant activity of ketamine, a NMDA receptor antagonist, requires increased production of BDNF and activation of mTOR signaling [122]. This result agrees with the concept that recovery from depression requires the restoration of neuronal plasticity which itself is dependent on protein synthesis orchestrated by mTOR signaling. Blockade of mTOR activation by prior treatment with rapamycin, an antagonist of mTOR signaling, abrogated the antidepressant activity of ketamine in mice [122]. However, contrary to expectation, administration of rapamycin to depressed patients treated with ketamine prolonged instead of inhibited the antidepressant activity of ketamine [123].

In summary, the rapid advances in immunometabolism during the last decade have amply demonstrated that metabolic reprogramming at the cellular and organismic levels is a critical aspect of the host inflammatory response. The possibility that the depressive symptoms that are apparent in inflamed individuals are the outward expression of the response of the brain to this metabolic reprogramming amplified by the metabolic adjustments that take place in the inflamed brain cannot be ignored any longer. New targets for pathophysiology and treatment are emerging from the still sparse research taking place in this field. Their ultimate success will depend on a close cooperation between preclinical and clinical researchers.

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