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Microglia metabolism in health and disease

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ABSTRACT

In the last decade tremendous progress has been made in understanding how the immune system reacts to insults. During this progress it became obvious that those immune responses are tightly regulated and cross-linked with distinct metabolic changes in immune cells. Extensive research has been conducted mainly on subtypes of T cells, which use different metabolic pathways during differentiation processes and activation states. In addition, it has also been established later, that the innate immune cell lineage of myeloid cells includes a variety of different subsets of bone marrow-derived as well as tissue-specific macrophages, which elicit much more functions than simply killing bacteria. To execute this high variety of functions, also macrophages use different metabolic pathways and are tightly regulated by key metabolic regulators, such as the mechanistic target of rapamycin (mTOR). Upon activation, metabolic changes within the cell occur to meet the requirements of the phenotypic switch. In addition, metabolic changes correlate with the ability of innate immune cells to show hallmarks of adaptive immune responses.

Little is known about specific metabolic changes of myeloid cells and specifically microglia *in vivo*. Microglia are key players in neurodegenerative and neuroinflammatory diseases and have become a major target of medical research. Here, we review the existing data on microglia metabolism and the connection of microglia phenotypes with neuroinflammatory and neurodegenerative diseases. Lastly, we will discuss how our knowledge about the cellular metabolism might be used to develop new treatment options for neurological diseases.

1. Microglia as tissue macrophages of the CNS

Microglia are the brain-resident macrophages, which seed the brain prenatally and sustain without external input by self-renewal-related proliferation (Hagemeyer et al., 2016; Kierdorf et al., 2013; Schulz et al., 2012; Bruttger et al., 2015; Prinz et al., 2017; Tay et al., 2017; Askew et al., 2017; Gomez Perdiguero et al., 2015; Alliot et al., 1991, 1999; Ginhoux et al., 2010; Ajami et al., 2007). They are epigenetically and transcriptionally distinct from other tissue-resident macrophages as well as bone marrow-derived macrophages (Gautier et al., 2012; Butovsky et al., 2014; Hickman et al., 2013) and elicit multifaceted functions during brain development and homeostasis, such as synapse pruning and clearance of dead cells (Li and Barres, 2018; Paolicelli et al., 2011; Colonna and Butovsky, 2017). Furthermore, upon pathogenic insults they initiate immune responses (Kettenmann et al., 2011; Vasek et al., 2016). During homeostasis microglia are rather immunosuppressive, survey their environment, and display a branched morphology, whereas upon activation microglia change their morphology to an amoeboid structure and increase phagocytic activity (Kettenmann et al., 2011; Davalos et al., 2005; Nimmerjahn et al., 2005; Koizumi et al., 2007). All macrophages, including activated microglia are functionally heterogeneous and highly plastic. Therefore, several states of activation have been described eliciting either neurotoxic or neuroprotective functions. Activation is facilitated by intrinsic as well as extrinsic factors and the phenotype can be reprogrammed in new microenvironments (Lavin et al., 2014; Bennett et al., 2018; Holtman et al., 2017). Potentially “neurotoxic” microglia produce pro-inflammatory mediators such as nitric oxide, interleukin (IL)-1β, and tumor necrosis factor (TNF)-α (Hanisch, 2002; Block et al., 2007). In contrast, the neuroprotective phenotype is characterized by increased uptake of dead cells or abnormally accumulated proteins and production of neurotrophic factors such as insulin-like growth factor-1 (IGF-1), glial cell-derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF) (Diaz-Aparicio et al., 2016; Thored et al., 2009; Lu et al., 2005; Batchelor et al., 1999). Consequently, microglia have been implicated in a variety of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinsons's disease (PD), and multiple sclerosis (MS) as well as recovery from brain injury and maintenance of

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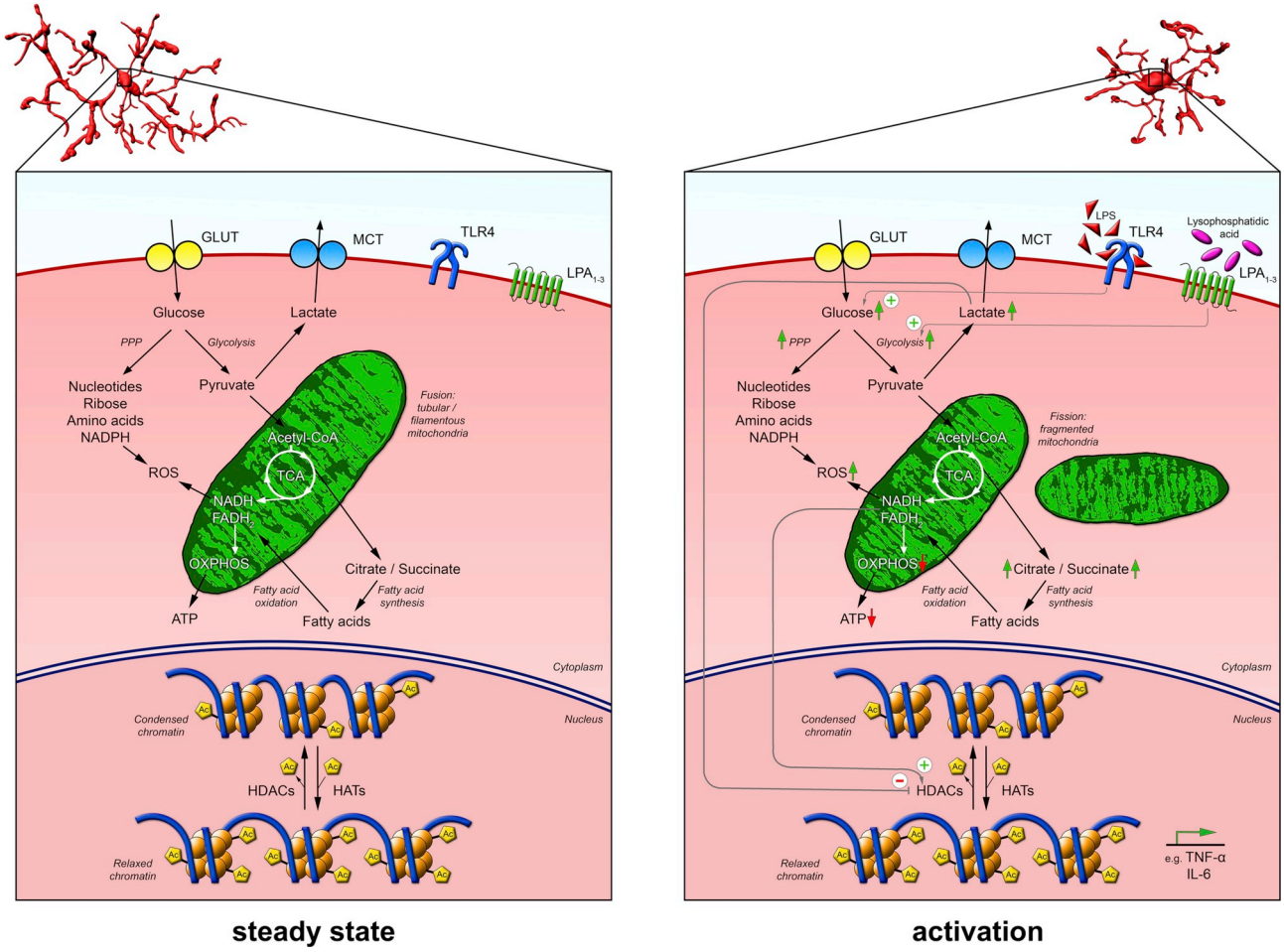

Fig. 1. Microglia express glucose transporters (GLUT), monocarboxylic transporters (MCT), as well as lipoprotein lipase (LPL). Glucose can be converted via glycolysis into pyruvate, which can be a substrate for the tricarboxylic acid (TCA) cycle or feed the pentose phosphate pathway (PPP). Furthermore, fatty acids can be a substrate for the TCA. The TCA produces electrons in form of nicotinamide adenine dinucleotide phosphate or flavin adenine dinucleotide (NADH/FADH2), which are needed for oxidative phosphorylation (OXPHOS) and reactive oxygen species (ROS) production. Upon activation via e.g. TLR ligands (LPS) or lysophosphatidic acid, glycolysis is increased, resulting in increased levels of lactate, products of the PPP and TCA intermediates (citrate, succinate). Such products can regulate histone acetylation/deacetylation, which leads to specific gene transcription (e.g. TNF-a, IL-6).

homeostasis (Colonna and Butovsky, 2017; Salter and Stevens, 2017; Prinz and Priller, 2017).

2. Macrophage metabolism and metabolic reprogramming

It has been previously recognized that activated macrophages change their metabolism. Homeostatic macrophages use the tricarboxylic acid (TCA) cycle located in the mitochondria to produce electrons in form of nicotinamide adenine dinucleotide phosphate or flavin adenine dinucleotide (NADH/FADH2) from various energy sources (pyruvate, fatty acids, amino acids) (Fig. 1). Those electrons are needed for mitochondrial oxidative phosphorylation (OXPHOS) to generate high amounts of adenosine triphosphate (ATP) as well as mitochondrial reactive oxygen species (mtROS) (Mehta et al., 2017; O'Neill and Pearce, 2016). Upon lipopolysaccharide (LPS)/interferon γ (IFN-γ) stimulation, proinflammatory macrophages show enhanced glycolytic metabolism and impaired OXPHOS (Van den Bossche et al., 2017; Pearce and Pearce, 2013; Tannahill et al., 2013; Jha et al., 2015; Huang et al., 2016), whereas IL-4 stimulated anti-inflammatory macrophages show increased OXPHOS (Van den Bossche et al., 2017; Vats et al., 2006; Van den Bossche et al., 2015). Such proinflammatory macrophages use this anabolic metabolism, which yields much lower amounts of ATP then OXPHOS, to balance energy production and synthesis of macromolecules, which are needed for protein production (Rambold and Pearce, 2018). Furthermore, glycolytic metabolism also feeds the pentose phosphate pathway (PPP). The PPP supports the generation of amino acids for protein synthesis, ribose for nucleotides, and NADPH, which is needed for the production of reactive oxygen species (ROS). In inflammatory macrophages the TCA is interrupted and its intermediates (acetyl conenzyme A (acetyl-CoA)) induce the synthesis of fatty acids, lipids, prostaglandins or are used to induce cytokine production (Tannahill et al., 2013; Jha et al., 2015; Infantino et al., 2011, 2013; Wei et al., 2016). Additionally, TCA interruption leads to accumulation of citrate and succinate (Jha et al., 2015). These TCA intermediates influence ROS production as well as proinflammatory cytokine production (Lampropoulou et al., 2016; Mills et al., 2016, 2018). Glucose as well as fatty acid oxidation (FAO) can fuel OXPHOS and both substrates have been shown to effect macrophage polarization (Van den Bossche et al., 2017). Specifically, acetyl-CoA promoted TLR4 positioning into lipid rafts of the cell membrane, connecting fatty acid synthase with proinflammatory activation of macrophages (Carroll et al., 2018). Evidently, bioenergetic changes involve mitochondria, since the electron transport chain is located in the mitochondria. Activated macrophages change their mitochondrial morphology. Those changes are called fusion and fission and impact immune cell metabolism and function (Rambold and Pearce, 2018). Furthermore, the serine/threonine kinase mechanistic target of rapamycin (mTOR) is a key metabolic sensor, which reacts to extracellular

as well as intracellular signals and regulates metabolic reactions including cell growth and proliferation (Laplante and Sabatini, 2012). Extracellular signals include hormones, growth factors, pattern recognition receptor (PRR)-signaling, and cytokines, while intracellular signals include nutrient abundance and the cellular energy charge (AMP:ATP ratio) (Jones and Pearce, 2017). Interestingly, mTOR is essential for differentiation of macrophages from the BM but not tissue-resident macrophages *in vivo* (Hallowell et al., 2017).

Another important option to adjust immunological responses and metabolic pathways is reversible lysine de- and acetylation, which is facilitated by histone deacetylases (HDACs) and histone acetyl-transferases (HATs) (Fig. 1). HDACs include classical zinc-dependent HDAC as well as NAD^+-dependent HDACs, also known as silent mating-type information regulator 2 homolog (sirtuins or SIRTs) (Shakespear et al., 2018). Lysine acetylation regulates key metabolic enzymes, which thereafter regulate immune processes. HDACs and SIRTs can act as transcriptional repressors of genes, which regulate glycolytic enzymes and their activity has been linked to inflammatory responses but it is not clear, whether they are connected by metabolic changes (Shakespear et al., 2018; Das Gupta et al., 2016). Of note, in cell culture lactate inhibits HDAC activity, linking a metabolic intermediate with epigenetic regulation (Latham et al., 2012). Importantly, reported metabolic changes were dependent on the cell type or subset of myeloid cells. It is therefore crucial to analyze metabolic changes in specific myeloid subsets further to confirm results reported in cell lines and specific cell types.

3. Microglia dysfunction and brain energy metabolism

Many CNS disorders are accompanied by changes in brain energy metabolism (Ghosh et al., 2018). Under most conditions, the blood-brain barrier prevents influx of alternative substrates (fatty acids, amino acids, ketons), therefore, the brain needs a continuous supply of glucose. With reduction of blood glucose levels, ketones produced via peripheral fatty acid metabolism, can supplement glucose as an energy source (Ghosh et al., 2018). Microglia have been implicated in a variety of neuropathological diseases, however, surprisingly little is known about microglia bioenergetics.

First studies were performed using microglia cell lines. Thereby, it was established that activation of microglia leads to a decrease in mitochondrial and cellular function via nitric oxide (NO) induction (Moss and Bates, 2001; Chenais et al., 2002). Furthermore, lysophosphatidic acid (LPA) receptor triggering leads to alterations in glycolysis, morphology and motility of C13NJ microglia cells (Bernhart et al., 2010). Another study showed that the mitochondrial glucose-regulated protein 75 (Grp-75) regulates glycolysis and metabolism upon lipopolysaccharide (LPS) stimulation of the murine microglia BV-2 cell line (Volobouéva et al., 2013). LPS stimulation increased glucose uptake, anaerobic glycolysis, and PPP induction, thereby increasing nucleic acid production for gene transcription (Gimeno-Bayon et al., 2014). Chen et al. showed that adenosine monophosphate (AMP)-activated protein kinase (AMPK) activation reduced LPS-induced inflammation in BV-2 cells (Chen et al., 2014a). Furthermore, two studies analyzed the role of autophagy, which is an important process of cell metabolism, *in vitro* in microglia. Autophagy modulated LPS-induced or Aβ-mediated inflammation in BV-2 cells or primary microglia cultures, respectively (Bussi et al., 2017; Cho et al., 2014). In primary microglia cultures 2-Deoxy-D-glucose (2-DG), which blocks glycolysis, blunts TNF-α and IL-6 production by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling and leads to microglia death (Wang et al., 2014; Vilalta and Brown, 2014).

However, basically, no *in situ* data are available yet, which analyzed whether microglia use glycolytic or oxidative ATP production. Recently, intensive transcriptional profiling of microglia was conducted and these studies show that microglia express genes related to both pathways, indicating that microglia might be able to also use both pathways (Zhang et al., 2014). Microglia express the passive glucose transporter (GLUT) 3 (Kalsbeek et al., 2016) and interestingly, GLUT5, a passive fructose transporter, which is only expressed in microglia in the brain (Payne et al., 1997). However, since fructose levels are low in brain, the function of GLUT5 in microglia remains unknown (Douard and Ferraris, 2008). Glucose is needed for the generation of ROS by fueling the mitochondrial electron transport chain or by NADPH production which is needed for enzymatic production of NO and superoxide by inducible nitric oxide synthase (iNOS) (Possel et al., 2000). Microglia predominantly express the NADPH oxidase NOX2, use superoxide to kill invading pathogens (Kauppinen et al., 2008; Schieber and Chandel, 2014) and glucose metabolism was shown to controls microglia activation via the NADH-sensitive transcriptional co-repressor termed C-terminal binding protein (CtBP), which influences NF-κB signaling and iNOS expression (Ghosh et al., 2010; Shen et al., 2017). Furthermore, microglia express monocarboxylic transporters (MCT) 1 and MCT2 to take up ketons and lactate and ketonic dieting has been correlated with inhibition of microglia activation (Moreira et al., 2009; Longo and Mattson, 2014; Gasior et al., 2006). The cellular mechanism proposed is that ketonic bodies inhibit HDACs, which attenuates NF-κB signaling (Fu et al., 2015; Huang et al., 2018; Newman and Verdin, 2014). Furthermore, it was shown that lipoprotein lipase (LPL) controls lipid uptake in microglia and induces neuroinflammation via microglia activation (Gao et al., 2017).

One interesting *in vivo* model, which was used to analyze changes in microglia metabolism and its functional consequences are triggering receptor expressed on myeloid cells 2 (TREM2) knock out mice. TREM2 is highly expressed by microglia and recognizes phospholipids, apoptotic cells, and lipoproteins (Yeh et al., 2017). Upon triggering TREM2 facilitates phagocytosis, survival, proliferation and cytokine production (Colonna and Butovsky, 2017). Interestingly, in a model of AD, $TREM2^{-/-}$ mice showed increased AMPK phosphorylation and autophagy, while mTOR activation was impaired, indicating that TREM2 signaling influences microglia metabolism (Ulland et al., 2017). Elevated mTOR signaling was also shown to induce a reactive phenotype in microglia leading to epileptogenesis and death, indicating that mTOR signaling affects the phenotype of microglia *in vivo* (Zhao et al., 2018). In contrary, in a mouse model of stroke, inhibition of mTOR signaling increased autophagy in microglia, thereby increasing neuronal inflammation injury (Yang et al., 2015). Another study analyzed the influence of HDACs in microglia *in vivo* (Datta et al., 2018). Interestingly, ablation of HDAC1/2 impacted microglia development and their function during neurodegeneration, but not their phenotype during homeostasis indicating that in active microglia, epigenetic changes might influence cellular metabolism, which impacts microglia function. Increasing numbers of *in vivo* studies include analysis of metabolic factors in their studies and it will be interesting to see, how specifically metabolic changes in microglia are influencing disease progression and recovery *in vivo* in different disease settings.

4. Microglia polarization

In an attempt to simplify big data sets, the concept of M1 and M2 macrophage polarization was adapted earlier to the microglia research field (Sica and Mantovani, 2012; Colton, 2009). However, it is now apparent that the over-simplification of the diversity of microglia rather inhibits research progress and should be discarded (Colonna and Butovsky, 2017; Ransohoff, 2016). In fact, Xue et al. were the first to show that human macrophages adopt a whole array of different gene expression profiles depending on the stimulus (Xue et al., 2014). Since then, tremendous progress has been made using new techniques such as time of flight mass cytometry (CYTOF), single-cell RNA-Sequencing and epigenetic analyses, in defining activation specific gene-expression signatures in microglia during homeostasis as well as during different disease settings (Gautier et al., 2012; Butovsky et al., 2014; Hickman et al., 2013; Chiu et al., 2013; Crotti and Ransohoff, 2016; Friedman

et al., 2018). The homeostatic phenotype of microglia is TGF-β-dependent (Butovsky et al., 2014; Gosselin et al., 2014) and they express PRR as well as immune receptors, such as TREM2, SIRP1A, CX3CL1, CSF-1R, CD200R (Wright et al., 2003; Kierdorf and Prinz, 2013; Labzin et al., 2018). Such receptors recognize DAMP or Neurodegeneration-associated molecular pattern (NAMP) (Deczkowska et al., 2018). Upon stimulation microglia loose their homeostatic phenotype and become activated with a common signature for neuropathology. This gene signature has been named microglial neurodegenerative phenotype (MGnD) or disease-associated microglia (DAM) and has been found in mouse models of ALS, MS, AD and humans suffering from AD (Deczkowska et al., 2018; Krasemann et al., 2017; Keren-Shaul et al., 2017). DAMs and MGnD downregulate homeostatic genes, and upregulate genes involved in lysosomal, phagocytic and lipid metabolism pathways. Some of these genes have been shown to be human AD risk factors and key regulators found in those signatures were identified and are now being analyzed in detail (Lambert et al., 2013). TREM2 and APOE are major regulators of microglia phenotypes and are the major focus of research at the moment (Yeh et al., 2017). Contradictory results can be found on the impact of those two pathways during neurodegeneration, depending on the time point and mouse model used for analysis. A recent study of Jay et al. found that TREM2 regulates AD pathology in a time-dependent manner, indicating that these pathways play distinct roles during disease progression (Jay et al., 2017). Recently, metabolic changes in the expression level of genes towards catabolism were found in sorted hippocampus microglia from an epilepsy model (Bosco et al., 2018). Supporting gene expression studies mentioned above, Flowers et al. were the first to analyze the influence of aging on microglia at a global-scale proteome level (Flowers et al., 2017). Pathways, which showed upregulated proteins included oxidative phosphorylation, mitochondrion, generation of precursor metabolites and energy, and immune effector processes. Aged microglia showed a bioenergetics shift from glucose to fatty acid utilization and involved mTOR signaling. Another recent study compared freshly isolated microglia from healthy, LPS-treated and AD mice and pathway analysis in this study showed that microglia are highly metabolically active cells, which change their metabolism upon stimulation and during neurodegeneration (Rangaraju et al., 2018).

5. Metabolic switch in trained immunity

Classically, the innate immune system reacts to insult rapidly and antigen-independently, while the adaptive immune system reacts much slower, but more specifically and builds memory. In recent years this classic view has been challenged by studies showing that innate immune cells can react quicker, stronger, and qualitatively distinct to a re-challenge, introducing the idea that also innate immune cells can build memory (Netea et al., 2016; Bowdish et al., 2007). This phenomenon of memory formation in innate immune cells is called “trained” immunity and is connected to cell type-specific PRR expression (Mills, 2011). One specific and special phenotype of trained immunity is LPS-induced tolerance. When pretreated with LPS, macrophages react less inflammatory instead of stronger upon re-challenge with specific stimuli. Silencing of genes of inflammatory mediators was associated with gene-specific chromatin modifications, indicating that priming of macrophages changes their response upon second triggering (Foster et al., 2007). Of note, chromatin modifications were facilitated by the deacetylases SIRTs (Liu et al., 2012). The phenomenon of trained myeloid cells was further confirmed in studies of fungal, parasitic, bacterial and viral infections (Foster et al., 2007; Quintin et al., 2012; Saeed et al., 2014; Barton et al., 2007; Chen et al., 2014b). Homeostatic macrophages harbor inflammatory genes in a repressed configuration. Upon stimulation, stimulation-responsive transcription factors (e.g. NF-kB) regulate the recruitment of co-activators, such as histone acetyltransferases (HATs) to modify chromatin structure to increase accessibility (Smale et al., 2014). Major immunological and metabolic pathways have been found to play a crucial role in trained immunity (Netea et al., 2016; Saeed et al., 2014; Cheng et al., 2014). However, little is known about trained immunity in microglia.

6. Trained immunity in microglia

In the periphery, trained immunity is important for people lacking adaptive immunity, such as infants or immunosuppressed patients. However, during chronic infections or in patients suffering from autoimmune diseases, trained immunity can have a detrimental effect. In the brain, trained microglia might be detrimental during aging. In the periphery, monocytes are short-lived and also most tissue-resident macrophages can be replaced by bone marrow-derived macrophages upon insult. However, microglia are long-lived and proliferate locally, which makes them an especially interesting cell type to analyze trained immunity.

The first and only study on trained immunity and metabolic changes in microglia so far could show that even 6 months after LPS training, microglia showed different reactions than untrained microglia in an AD model (Wendeln et al., 2018). In addition, using different regiments of repetitive LPS treatment, the authors could show that training and tolerance represent different facets of the same phenomenon. Both, training and tolerance were dependent on HDAC-mediated chromatin remodeling and activation of inflammatory signaling pathways (e.g. NF-κB), but had distinct effects on AD pathogenesis as well as the neuronal damage after cortical stroke. Trained microglia showed increased metabolic activity and glycolysis, while tolerogenic microglia were more phagocytic and more sufficient in clearing plaques and showed reduced activation and neuronal damage after stroke. In line with those results, systemic inflammation has been associated with increased risk for developing dementia and microglia priming (Heneka et al., 2015; Perry and Holmes, 2014). Additionally, it was previously shown that training can be passed on from progenitor cells (Ng et al., 2013; Burgess et al., 2014; Mitroulis et al., 2018). It would be interesting to see whether training can also be passed on when microglia proliferate.

7. Manipulation of microglia metabolism as treatment option

To date, available medication for treatment of neurodegenerative diseases is incapable of repairing or regenerating damaged neurons. Manipulating the phenotype of microglia could be an interesting treatment option for a variety of neurodegenerative diseases in order to slow down, stop or even reverse disease progression. However, it is unknown which microglia phenotype would be beneficial during different stages of disease. So far, the available data are inconclusive. For example, while Krasemann et al. suggest that restoring a homeostatic phenotype in microglia might be protective in AD, others suggest that boosting DAM differentiation may present a promising strategy to fight neurodegeneration (Krasemann et al., 2017; McDade and Bateman, 2017).

One major task is to specifically target microglia without inducing severe side effects by targeting bystander cells. The first obstacle is the blood-brain barrier (BBB). Not every drug can be easily delivered into the brain. However, small molecules can pass the BBB and are therefore interesting targets to be delivered to microglia. One promising option to deliver drugs specifically to microglia would be to pack drugs into nanoparticles, which are readily phagocytosed by microglia but not other cells in the brain. One has to keep in mind though, that depending on the application route, also other macrophages would be targeted and it is unclear how much of the drug would end up in the brain with the right macrophages. Another interesting option would be to use prodrugs, which only become pharmacologically activated upon microglia-specific entry and pharmacological processing (Van den Bossche et al., 2017).

The metabolic switch towards a neurotoxic phenotype in microglia

is inhibited by AMPK and IL-10 and AMPK activation has been shown to be neuroprotective after stroke and during PD (Jin et al., 2014; Venna et al., 2014; Patil et al., 2014). Also cyclic AMP (cAMP) is a regulator of microglial function and activation and several studies showed that inhibitors of negative regulators of cAMP increase neuroprotective phenotypes in diverse CNS disease settings (Song and Suk, 2017; Moretti et al., 2016; Ghosh et al., 2012, 2015, 2016). Furthermore, NOX inhibitors induce a neuroprotective phenotype in microglia, which has been shown to be beneficial in several disease settings (Choi et al., 2012; Zhang et al., 2015; Yao et al., 2015). In contrast, inhibition of mTOR signaling in microglia leads to an increase of iNOS expression and decrease of IL-10 expression and has been shown to be beneficial in treating glioblastoma, the most common and aggressive primary CNS tumor-type (Lisi et al., 2014). Furthermore, the epigenetic regulators HDACs and Sirtuins could be targeted for microglia reprogramming. Interestingly, inhibition of such has been shown to induce the transcription of neuroprotective genes und inhibit the expression of pro-inflammatory cytokines in microglia (Lazo-Gomez et al., 2013; Kannan et al., 2013; Wang et al., 2015). HDAC inhibitors are already approved clinically for oncological treatments and they show promising results in experimental models of inflammatory diseases (Sweet et al., 2012). Very recently, it was shown that the immunomodulatory drug Dimethyl fumarate (DMF), which is used to treat MS, downregulates aerobic glycolysis in activated macrophages, thereby mediating anti-inflammatory effects (Kornberg et al., 2018).

8. Conclusions

Immunometabolism is a fast growing field of immunology. A lot of progress has been made in the last years on understanding how metabolic changes in immune cells influence immune responses. However, little is known about microglia metabolism and many studies were conducted in cell culture due to technical constrains. Microglia have become of key interest for the treatment of neurological diseases and targeting the metabolism of cells in order to change their immunological phenotype is one major treatment approach in research. Though, it will be of utmost importance to better understand microglia metabolism *in vivo* in health and disease before targeting of microglia-specific metabolism will be a useful treatment option in the clinics.

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