ACTA ABP BIOCHIMICA POLONICA

Vol. 68, No 3/2021
457–476
https://doi.org/10.18388/abp.2020_5683

Review

Metabolic evolutionary roots of the macrophage immune response in amoeba-bacteria interactions: The conserved role of hypoxia-induced Factor and AMP kinase*

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The bacteria Legionella, being able to infect both macrophages and protozoans, reduce oxidative phosphorylation and induce glycolysis, which allows pathogens to grow and replicate in these cells. In amoeba-like inflammatory macrophages (M1), the phagocytizing cells of the primary immune defense, an increase in the rate of glycolysis is followed by a decrease of oxidative phosphorylation. The opposite takes place in anti-inflammatory macrophages (M2). They change from glycolysis to oxidative metabolism when AMP-dependent kinase (AMPK) is activated by a high ratio of AMP/ATP. Stimulation of macrophages with anti-inflammatory cytokines causes activation of AMPK. Infection of macrophages with the parasitic flagellate Leishmania infantum induces a switch from an initial glycolytic phase to oxidative phase with the essential role of AMPK in this change. Activated AMPK induces catabolic pathways effectively producing ATP as well as processes requiring the energy supply. AMPK regulates the migration of cells and enhances the phagocytic activity of macrophages. In macrophages, bacterial products activate TLRs and NF-κB signaling, causing an increase of transcription of hypoxia-induced factor HIF-1α (a subunit of HIF-1). This brings about induction of the enzyme and transporter expression essential for glycolysis and the pentose phosphate pathway to proceed and makes biosynthetic processes and ROS production in macrophages possible. Hypoxia augments macrophage phagocytosis in a HIF-1α-dependent manner. Multicellular parasites experience changes in the availability of oxygen in their life cycle. In the nematode Ascaris suum, HIF participates in the pre-adaptation to hypoxic conditions after infection of their hosts. Also, the freshwater and marine invertebrates meet changes of oxygen concentrations. In the anaerobic branch of the respiratory chain of these invertebrates, fumarate serves as the terminal electron acceptor that is reduced to succinate in complex II of the ETC. In mammalian cells, accumulation of succinate under hypoxic conditions suggests that the mammalian complex II may reduce fumarate to succinate, too. The data reviewed here show that the ability to shift the cell metabolism towards glycolysis observed in activated macrophages can be traced back in evolution to metabolic changes characterizing protozoans infected with bacteria. Anabolic needs of multiplying bacteria direct host metabolism to glycolysis that produces, aside from ATP, precursors of the amino acids used by the pathogen for its protein synthesis. M1-activated mammalian macrophages behave in the same way. Regulation of metabolism in M1 and M2 macrophages is further enhanced by HIF-1 and AMPK, respectively. These archaic functions of AMPK and HIF, important also to control phagocytosis and cell migration were extended to embryonic development in multicellular organisms.

Keywords: adaptation to hypoxia, bacterial infection, glycolysis, oxidative phosphorylation, parasite infection

Received: 03 May, 2021; revised: 24 June, 2021; accepted: 28 June, 2021; available on-line: 08 August, 2021

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#Retired

***This paper is dedicated to Professor Wacław Tadeusz Szybalski on the 100th anniversary of his birth**

NATURE OF ENERGY AND BUILDING ELEMENTS PRODUCTION IN THE CELL IS UNIVERSAL

Last years have introduced significant changes to our understanding of metabolic aspects of the immune cell's activation. The phagocytic macrophages of mammals have a long evolutionary history and are believed to preserve primary mechanisms of an immune response, found already in the sponge amoebocytes (ref. in Dzik, 2010). This review aims to show that the metabolic processes accompanying macrophage activation are evolutionary conserved and that homologous mechanisms act in all cells of multicellular organisms from embryogenesis to maturity.

The main metabolic demand necessary for surviving of all organisms is nutrient supply providing energy and building elements. The energy providing mechanisms depend on availability of the oxygen and fuel, mainly glucose, that degradation pathways are central throughout all domains of life. The two main metabolic routes for providing the energy in cells include anaerobic glycolysis (Embden-Meyerhof-Parnas pathway, EMP) and aerobic oxidative phosphorylation (oxphos), comprising citric acid cycle and respiratory chain complexes, with much higher efficiency than the former one. With limited oxygen supply cells depend on glycolysis for providing energy from carbohydrates. Without oxygen, glycolysis supplies 2 molecules of ATP and 2 pyruvates per one molecule of glucose. To recover the NAD^+ necessary for proceeding of glycolysis, pyruvate is reduced to lactate by lactate dehydrogenase in the lactic acid-producing bacteria, erythrocytes, and during exhaustive muscle cell contraction. Instead, in yeast, pyruvate is metabolized to ethyl alcohol by a two-step reaction catalyzed by pyruvate decarboxylase and alcohol dehydrogenase to obtain NAD^+. In aerobic organisms in the presence of oxygen glycolysis is suppressed and oxidative phosphorylation enhanced. The main switch between both pathways depends on oxygen availability that is required to complete the oxphos processes. This phenomenon was named the Pasteur effect because it was Louis Pasteur who found in

1857 that butyric acid fermentation is arrested when air is introduced to the fermenting fluid. The Pasteur effect is considered the most archaic autonomous adaptations of the cell to hypoxia during the anaerobic fermentation. Otto Warburg in 1947 found that cancer cells maintain a very high rate of glycolysis even in the presence of oxygen. The so-called Warburg effect can be considered as a loss of ability to use the Pasteur effect (Amoêdo *et al.*, 2013).

Metabolic flow through glycolysis is controlled at three steps. Hexokinase is inhibited by its product glucose-6-P. Fructose-2,6-bisphosphate, AMP, and ADP are allosteric activators of phosphofructokinase whereas ATP, citrate, and H^+ inhibit the enzyme. Pyruvate kinase is activated by fructose-1,6-bisphosphate and inhibited by acetyl-CoA, ATP, and alanine. Overall, glycolysis slows down when the energy charge is high or the intermediates of the Krebs cycle are abundant. It is noteworthy that glycolytic intermediates give rise to several amino acids: Ser, Gly, Cys, Ala, Val, Leu, Try, Phe, Tyr, and glycerol, a precursor of triacylglycerols and glycerophospholipids.

Under conditions of lack or limitation of carbohydrates, glucose can be synthesized from noncarbohydrate compounds such as lactate, amino acids, and glycerol in the process of gluconeogenesis that is identical in all organisms (Romano & Conway, 1996).

Glycolysis and gluconeogenesis are controlled reciprocally. The difference between glycolysis and gluconeogenesis concerns three steps regulated by substrate cycles. Glycolysis is regulated primarily by reactions catalyzed by hexokinase, phosphofructokinase, and pyruvate kinase. The opposite reactions in gluconeogenesis catalyzed by glucose-6-phosphatase, fructose-1,6-bisphosphatase, and the combination of pyruvate carboxylase and phosphoenolpyruvate carboxykinase control synthesis of glucose *de novo*. Fructose-1,6-bisphosphatase is inhibited by fructose-2,6-bisphosphate, AMP, and citrate. Pyruvate carboxylase is inhibited by ADP and stimulated by acetyl-CoA. The remaining reactions of gluconeogenesis are catalyzed by the glycolytic enzymes that drive reversible reactions in either direction according to mass action. Thus, the rates of glycolysis and gluconeogenesis depend mostly on the energy charge and nutrient status of the cells.

Ronimus and Morgan (Ronimus & Morgan, 2003) have reviewed the present knowledge concerning the distribution and phylogeny of enzymes involved in the Embden-Meyerhof-Parnas pathway. The main metabolic pathway of glycolysis is found in all three domains of life, Archaea, Bacteria, and Eucarya, although a significant variability of enzymes, especially in the hyperthermophilic bacteria and in the Archaea occur. The genes encoding the enzymes of the lower portion of glycolysis (the trunk pathway), including triosephosphate isomerase, glyceraldehyde-3-phosphate dehydrogenase, phosphoglycerate kinase, and enolase, were all present before the divergence of the archaeal and bacterial domains, i.e. in the presumed last universal common ancestor (LUCA). The trunk pathway is essential for amino acid, pentose phosphate, and purine synthesis, therefore it is under rigorous evolutionary maintenance.

The enzymes of the trunk pathway are also common to the Entner-Doudoroff (ED) route that is widely distributed in bacteria where it can be a major pathway of glucose catabolism under aerobic conditions (Romano & Conwey, 1996). In this pathway, glucose-6-phosphate is oxidized to 6-phosphogluconic acid with a concomitant reduction of NADP to NADPH. The 6-phosphogluconate is then dehydrated and split into glyceraldehyde-3-phosphate and pyruvate. Glyceraldehyde-3-phosphate is catabolized, as in glycolysis, which results in the production of NADH and ATP molecules. Thus, glucose molecule catabolized through the ED pathway is degraded to two pyruvates finally yielding one ATP plus one NADPH and one NADH.

The universal occurrence of enzymes of the trunk pathway, in conjunction with their phylogeny, supports the concept that the glycolysis pathway evolved from the bottom up, following the direction of gluconeogenesis. In addition, sequence analysis of compartment-specific isoforms of triosephosphate isomerase and glyceraldehyde-3-phosphate dehydrogenases supports the idea that glycolytic enzymes of Eukaryota have been acquired from mitochondrial genomes (ref. in Liaud *et al.,* 2000). Hexokinase, glucose phosphate isomerase, 6-phosphofructokinase, the enzymes of the upper portion of the EMP pathway, probably derived from various gene families occurring in hyperthermophiles and other Archaea (ref. in Ronimus & Morgan, 2003).

Parallel to glycolysis is the pentose phosphate pathway (PPP) of glucose catabolism, which branches from the glycolysis at the glucose 6-phosphate step and operates in two phases; oxidative and nonoxidative. The oxidative phase results in the production of ribulose-5-phosphate, CO_2, and 2 moles of NADPH per glucose 6-phosphate molecule. In a nonoxidative phase, some ribulose-5-phosphate is converted to ribose-5-phosphate. The synthesis of 5-carbon sugars is provided by a complex series of sugar interconversions**.** The enzymatic rearrangements in the non-oxidative phase with the participation of transketolase and transaldolase give two fructose 6-P molecules and one glyceraldehyde 3-P from the three pentose phosphates. The most important regulatory factor is the intracellular concentration of $NADP^+$. NADPH competes with $NADP^+$ in binding to glucose 6-phosphate dehydrogenase (catalyzing oxidation of glucose-6-P to 6-phosphogluconolactone) and inhibits that enzyme. This reaction is rate-limiting for the pentose phosphate pathway and serves as the control point. The pentose phosphate pathway competes with glycolysis for glucose-6- phosphate. Whereas glycolysis is regulated chiefly by the energy status of the cell and fuel availability, flux through the PPP depends on the cellular $[NADP^+]/[NADPH]$ ratio. The pentose phosphate pathway is regulated also due to sedoheptulokinase (SHPK) activity (Kardon *et al.*, 2008; Wamelink *et al.*, 2008). The enzyme was known earlier under the name carbohydrate kinase-like (CARKL). SHPK phosphorylates sedoheptulose on the C7. The enzyme balances the S7P from the non-oxidative part of PPP and G3P from glycolysis. SHPK creates a second rate-limiting step in PPP aside from glucose-6-phosphate dehydrogenase. The PPP supplies NADPH and ribose 5-phosphate that are vital for the survival and proliferation of cells. NADPH acts as a reductant required for the synthesis of fatty acids, sterols, nucleotides, and non-essential amino acids, and the ribose-5-P is a building compound for nucleic acid synthesis. The PPP is recognized as a central player in controlling and maintaining the redox homeostasis of cells since NADPH serves as a cofactor for the reduction of oxidized glutathione (GSSG) to reduced glutathione (GSH) *via* glutathione reductase. NADPH takes part in reactions of NADPH oxidase and nitric oxide synthase which produce reactive oxygen and nitrogen species respectively.

The oxidative branch of the PPP is not universal since it has not been found in many thermophilic and aerobic organisms (Bräsen *et al.*, 2014). The oxidative branch is

highly active in the majority of eukaryotes (Miclet *et al.*, 2001). Reactions of the non-oxidative phase of PPP may have derived from pre-biotic metal-catalyzed interconversions of sugar phosphates in sequences that resemble glycolysis and the phosphate pathway. However, the interconversion of glucose 6-phosphate to 6-phosphogluconate, delineating the oxidative PPP, was not likely in the conditions of the prebiotic ocean (Keller *et al.*, 2014). This suggests that the non-oxidative branch is older than the oxidative branch of the PPP pathway. Reactions of the non-oxidative PPP (with the overlapping Calvin Cycle and Entner-Doudoroff Pathways), take place nearly ubiquitously, and fulfill a central role to provide ribose 5-phosphate for the nucleotide and nucleic acid synthesis, as well as erythrose 4-phosphate for the synthesis of aromatic amino acids.

In eukaryotic cells, pyruvate obtained from glycolysis is oxidized in mitochondria in the Krebs cycle, and NADH is reoxidized in the electron transport chain (ETC). Oxidative decarboxylation of pyruvate by the pyruvate dehydrogenase (PDH) complex in mitochondria gives acetyl-CoA entering the CAC. Acetyl-CoA condenses with oxaloacetate to form citrate. After one turn of the cycle, oxaloacetate is regenerated and the process takes place anew. During the citric acid cycle, reduced electron carriers (NADH and FADH2) are produced and their reoxidation in the ETC supplies energy for ATP synthesis. The citric acid cycle may supply biosynthetic intermediates as well. Oxaloacetate and α-ketoglutarate are the α-keto-acid analogs of the amino acids, that is aspartate and glutamate, and are used in the synthesis of these and other amino acids by transamination. In the cytosol, citrate transported from mitochondria is cleaved to oxaloacetate and acetyl-CoA, the latter being needed for the fatty acid biosynthesis. To replace these intermediates, anaplerotic reactions balance the loss of carbon from the cycle. Regulation of the citric acid cycle takes place at the level of fuel entry into the cycle (at the pyruvate dehydrogenase and the citrate synthase steps) as well as at the level of isocitrate dehydrogenase and α- ketoglutarate dehydrogenase reactions within the cycle. In mammals, the activity of the pyruvate dehydrogenase complex depends also on the phosphorylation/dephosphorylation of the pyruvate dehydrogenase subunit. Allosteric interactions and concentration of substrates control flux through the cycle. The most important factor controlling the activity of the citric acid cycle is the intramitochondrial ratio of $[NAD^+]$ to [NADH]. When $[NAD^+]$/[NADH] ratio decreases, because of reduction of the oxygen supply, the low concentrations of NAD^+ may restrict activities of isocitrate dehydrogenase and α-ketoglutarate dehydrogenase. Also, a high level of ATP slows down the activity of the Krebs cycle.

The tricarboxylic acid cycle is widespread among α-proteobacteria, from which the mitochondria had derived (Thrash *et al.*, 2011). The same version of the citric acid cycle characterizes virtually all organisms, including also anaerobic chemotrophs. Chemotrophs do not oxidase glucose for energy production but use an incomplete citric acid cycle both as a fermentative pathway and for biosynthesis. For these purposes, the last four reactions of the citric acid cycle are reversed in the direction from oxaloacetate to succinate. NADH for reduction of oxaloacetate to malate derives from the glyceraldehyde-3-phosphate dehydrogenase reaction of glycolysis. In turn, as a result of the first three steps of the citric acid cycle, α-ketoglutarate, an essential precursor to biosynthesis, is obtained. However, there is no enzyme for the conversion of α-ketoglutarate to succinate in anaerobic chemotrophs. Molecular phylogeny suggests that the citric acid cycle originated as a reductive pathway used by early autotrophs to bind CO_2 at the stages of pyruvate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase (Mathews *et al.* 2013; Wood *et al.* 2004).

MACROPHAGES, THE PHAGOCYTIZING CELLS OF THE INNATE IMMUNE SYSTEM OF VERTEBRATES

In all mammalian cells, signals provided by nutrient availability and growth factors are recognized by specific cell surface receptors (Ward & Thompson, 2012). In cells of the immune system, the metabolic stimulation of TCR/CD28 receptors on T cells (Frauwirth *et al.*, 2002), surface immunoglobulin receptors on B cells (Doughty *et al.*, 2006), and Toll like receptors (TLR) on macrophages and dendritic cells (DCs) (Krawczyk *et al.*, 2010; Haschemi *et al.*, 2012) trigger changes in cell metabolism characteristic of the Warburg effect.

The homology of macrophages, the phagocytizing cells of the innate immune system of vertebrates, can be traced back to phagocytes of invertebrates (Hartenstein, 2006). The recognition of foreign agents in invertebrates and vertebrates occurs through pattern recognition receptors. These receptors, such as Toll-like receptors (TLR), recognize infection with fungi or Gram-positive bacteria in *Drosophila* and activate the Toll pathway comparably to the mammalian Toll pathway (ref. in Dzik, 2010). Although the ways of activation of TLR in *Drosophila* and mammals are different, the proteins of these signaling pathways are homologs to each other (Akira *et al.*, 2006). The canonical Toll/TLR pathway can be found on the animal phylogenetic tree since the branching off the anthozoan cnidarians (Miller *et al.,* 2007). Activation of macrophages by evolutionarily ancient Toll-like receptors or intracellular bacteria is a phenomenon that may provide a hint why the metabolic change from oxidative phosphorylation to glycolysis occurs in inflammatory macrophages.

Newsholme *et al.* (1986) have shown the enhancement of glycolysis accompanied by a high hexokinase activity in inflammatory mouse macrophages. The rate of glycolysis and glutamine metabolism rose significantly during phagocytosis or secretory activity. The enzymes of pentose phosphate pathway, glucose-6-phosphate dehydrogenase, and 6-phosphogluconate dehydrogenase were also very active. Resting myeloid dendritic cells (a subpopulation of monocytes/macrophages) use mainly oxidative phosphorylation to produce ATP but after stimulation of TLRs by microbial products a switch to glycolysis was observed (Krawczyk *et al.*, 2010). This increased rate of glycolysis was accompanied by a diminution of oxidative phosphorylation and allowed to maintain a high level of ATP. The inflammatory subtype macrophages (M1) produce reactive oxygen species (ROS) and pro-inflammatory cytokines as a part of their antibacterial activity. The signals coming from the macrophage microenvironment stimulate transcriptional programs to enforce macrophage activation (Murray & Wynn, 2011; Davies *et al.*, 2013). Lipopolysaccharide (LPS) from the cell membrane of Gram-negative bacteria activates TLR4 what results in the activation of transcription factors such as nuclear factor-κB (NF-κB) and interferon regulatory factors (IRFs). These factors stimulate the transcription of pro-inflammatory cytokines: IL-1β, IL-6, and TNF-α. These cytokines appeared in evolution in the teleost fishes (ref. in Dzik, 2010).

In response to parasites, allergy, and long-term tissue repair macrophages present anti-inflammatory behavior (subtype M2) (Murray & Wynn, 2011). These macrophages are very active and able to proliferate, and they rely mostly on oxidative metabolism for their energetic and biosynthetic needs. M2 macrophages produce anti-inflammatory cytokines. They are, connected with humoral immunity and are characterized by diminished expression of major histocompatibility complex (MHC) class II and hence with the low ability for the presentation of antigens (O'Neill & Hardie, 2013). The major inducers of M2 macrophages are IL-4 and IL-13. These cytokines appeared in evolution in teleost fishes (Wang & Secombes, 2015). The binding of IL-4, to its receptor, activates the JAK-STAT pathway. The transcription factor STAT6 is responsible for the induction of several genes including *PGC-1β* (peroxisome-proliferator-activated receptor-γ co-activator-1β) responsible for activation of oxidative metabolism (Kelly *et al.*, 2009), *Arg1* (arginase 1), *Chil3* (Chitinase-like protein 3), and *Retnla* (Resistin-like molecule α or FIZZ1). Retnla represses Th2 response, induced as a result of helminth infection (Murray & Wynn, 2011).

Metabolic adaptation in activated macrophages

Changes in macrophage metabolism are triggered by polarizing signals coming both from the surrounding milieu and pathogens. The rapid shift from a resting state to the active state of macrophages is coupled with the generation of defense factors, enhanced phagocytosis, and antigen presentation. Metabolic changes accompanying these processes in inflammatory cells resemble those in tumor cells, where mitochondrial enzymes are repurposed from the bioenergetic role of ATP generation to a biosynthetic one. However, modified metabolism in tumor cells results from mutated oncogenes and tumor suppressors (Ward & Thompson, 2012).

In TLR4-activated macrophages, the signal from lipopolysaccharide receptor TLR4 induces a shift from the oxidative to glycolytic metabolism of the macrophages. TLR4 pathway causes induction of the glycolytic enzymes, with a change from the expression of the liver isoform of 6-Phosphofructo-2-Kinase/Fructose -2,6-Biphosphatse 1 (PFKFB1) to the 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3 (PFKFB3) isoform, the type also commonly occurring in tumor cells (Rodriguez-Prados *et al.*, 2010). This leads to the accumulation of fructose-2,6-bisphosphate and consequently an increased glycolytic flux. In addition, pyruvate dehydrogenase kinase 1 (PDK1) inhibits the pyruvate dehydrogenase complex, decreasing the oxidation of pyruvate coming from glycolysis in TCA. PDK1 promotes glycolysis and M1 macrophage activation (Tan *et al.*, 2015). As a result of TLR4 activation, oxidative metabolism in mitochondria is partly diminished due to nitric oxide (NO) produced in mitochondria that competitively displaces oxygen from cytochrome *c* oxidase (West *et al.*, 2011). This limits the activity of the electron transport chain, which causes the production of bactericidal reactive oxygen species (ROS). The activity of the pentose phosphate pathway rises because of the decreased activity of sedoheptulokinase (SHPK, CARKL) (Haschemi *et al.*, 2012). As was mentioned earlier, NADPH produced in the pentose phosphate pathway is used for ROS removing and for the reactions producing ROS and NO, the crucial components of the antimicrobial defense (Nathan, 1992; Babior, 1999).

Significant changes in the activity of the Krebs cycle have been identified in proinflammatory macrophages. Strongly decreased expression of isocitrate dehydrogenase caused citrate accumulation in mitochondria. Citrate can be transferred to the cytosol *via* CIC (citrate carrier) in exchange for cytosolic malate. It was found that mRNA and protein of CIC were markedly increased in lipopolysaccharide-activated immune cells (Infantino *et al.*, 2011). Due to the action of ATP citrate lyase, citrate is cleaved to acetyl CoA and oxaloacetate in the cytosol. Acetyl CoA can be used for the synthesis of phospholipids, which are the source of arachidonic acid for prostaglandin production (Wightman & Dallob, 1990). Of note, CIC gene silencing or inhibition of CIC transport activity significantly diminishes the production of NO, ROS, and prostaglandins (Infantino *et al.*, 2011). The second product of ATP citrate lyase, oxaloacetate, is reduced through cytosolic malate dehydrogenase to malate. The malic enzyme converts malate to pyruvate producing NADPH. Again, NADPH is required for NADPH oxidase and NO synthase. Importantly, citrate can be redirected to the generation of itaconic acid (known for its antimicrobial activity). Itaconate is a competitive inhibitor of succinate dehydrogenase (SDH) in the TCA cycle (Cordes *et al.*, 2016). As SDH is a subunit of complex II (CII) of the electron transport chain, itaconate disturbs ETC activity that influences the regulation of mtROS production and inflammatory gene induction. Inhibition of succinate dehydrogenase causes accumulation of succinate that stabilizes the α subunit of HIF (hypoxia-induced factor) what allows induction of proinflammatory cytokine IL-1β, glycolytic enzymes, and glucose transporters (Tannahill *et al.*, 2013).

Depletion of citrate, from the TCA cycle for *de novo* lipid synthesis, requires restoring of the TCA cycle (termed anaplerosis) to go on. Glutamine replenishes the TCA cycle through glutaminolysis, which further results in the production of α-ketoglutarate that enter the TCA cycle (Hensley *et al.*, 2013). As a result of the argininosuccinate lyase activity, fumarate replenishes the cycle. The second product of this enzyme is arginine, the substrate both for arginase and nitric oxide synthase.

In the mouse peritoneal macrophages stimulated either *in vivo* with BCG vaccine or *in vitro* with (LPS + IFN-γ), significant enhancement of nitric oxide production takes place (Dzik *et al.*, 2002). Jha and others (Jha *et al.,* 2015) reported that in (LPS+IFN-γ)-activated macrophages, aspartate, and citrulline are used by argininosuccinate synthase and argininosuccinate lyase to generate arginine, a substrate for NO production by iNOS. *Mycobacterium tuberculosis* infection brings about an import of arginine to macrophages to produce NO. After depletion of extracellular arginine (Qualls *et al.*, 2012), citruline import for arginine regeneration occurs to sustain nitric oxide production.

A shift towards aerobic glycolysis takes place, aside from the LPS-activated macrophages and dendritic cells, also in M1(IFN-γ) inflammatory macrophages, TH17 lymphocytes producing interleukin-17, a pro-inflammatory cytokine. However, in cells that restrict inflammation, such as regulatory T cells, quiescent memory T cells that carry the CD8 antigen, and M2 anti-inflammatory macrophages, oxidative metabolism outweighs glycolysis (ref. in O'Neill & Hardie, 2013).

M2 macrophages demonstrate augmented oxidative phosphorylation and much slower rates of glycolysis (Rodriguez-Prados *et al.*, 2010). They express PFKFB1 but not PFKFB3. IL-4 brings about upregulation of CARKL, which preserves sedoheptulose 7-phosphate

(S7P) levels, diminishing flow through the PPP. Expression of CARKL sensitizes macrophages to M2 polarization (Haschemi *et al.*, 2012). IL-4 signals through STAT6 to induce PGC-1β (Vats *et al.*, 2006). PGC-1β fosters mitochondrial biogenesis and oxidative metabolism, markedly by the enhanced expression of genes, protein products of which play a role in uptake and oxidation of fatty acids (Wu *et al.*, 2010). SIRT1 (NAD-dependent lysine deacetylase) activates PGC-1β (ref. in Chen *et al.*, 2015). On the other hand, SIRT1 inactivates the p65 component of the NF-κB (Kauppinen *et al.*, 2013), restricting the expression of NF-κB-dependent genes that is an anti-inflammatory action. Generation of ATP mainly from oxidative metabolism in mitochondria allows for using various sources of carbon compared with M1 macrophages. This favors M2 macrophages' role in tissue repair and anti-parasitic action. Arginase is active in both of these processes (Allen & Wynn, 2011; Mylonas *et al.*, 2009). It is known that STAT6 and PGC-1β interact directly at the promoter of the ARG1 gene and activate its transcription in M2 macrophages (Vats *et al.*, 2006). In IL-4 activated macrophages, nitrogen from glutamine is used for the hexosamine synthesis and generation of UDP-GlcNAC. UDP-GlcNAC is the substrate for N-glycosylation of proteins found profusely on the surface of M (IL-4) macrophages (Jha *et al.*, 2015).

Metabolic response of protozoan cells and macrophages to bacterial infection

The metabolic programs promoting macrophage activation by inducing glycolysis or oxidative phosphorylation are used already by protozoan cells infected with bacteria. Metabolic reprogramming takes place in amoebas infected with the bacteria *Legionella pneumophila,* an aquatic pathogen that replicates within a wide variety of protist hosts, as well as in the vertebrate macrophages. During infection of amoeba or macrophage, the *Legionella* containing vesicles (LCV) are formed by endoplasmic reticulum-derived vesicles containing also mitochondria (Francione *et al.*, 2009).

The amoeba *Acanthamoeba castellanii* metabolizes glucose largely *via* glycolysis and the pentose phosphate pathway. Pyruvate dehydrogenase transforms pyruvate into acetyl-CoA which enters the TCA cycle. As a result, the carbon backbone of many amino acids is synthesized (Schunder *et al.*, 2014). *L. pneumophila* depends on amoeba's amino acids, mostly serine, from which it acquires carbon and energy for biosynthetic processes from the TCA cycle, throughout early replication (the exponential phase of growth) (Tesh *et al.*, 1983; Price *et al.*, 2011). *L. pneumophila* utilizes a conserved way of eukaryotic proteasomal degradation of Lys48-linked polyubiquitinated proteins to produce amino acids. This way is used for the growth of bacteria in amoebae as well as in human cells (Price *et al.*, 2011). When the amino acid level turns low, the bacteria shift from the replicative phase to the transmissive phase (post-exponential growth phase) (ref. in Best *et al.*, 2018). At this moment, the uptake and utilization of glucose by *L. pneumophila* increase for *de novo* synthesis of amino acids and storage of poly-3-hydroxybutyrate (PHB) (Häuslein *et al.*, 2016). *L. pneumophila* utilizes glucose at least predominantly through the Entner-Doudoroff Pathway (Harada *et al.*, 2010). The glycerol catabolism is also induced (Faucher *et al.*, 2011). Thus, a switch from the replicative phase to the transmissive phase of *L. pneumophila* life cycle is tightly linked to the metabolism and to a life-cycle-specific substrate usage.

Several *A. castellanii* genes, products of which are involved in the oxidation of fatty acids, biosynthesis of carbohydrates, and assembly of complex III of ETC, are downregulated at eight hours after infection and remain at the same level after 24 hours post-infection (Li *et al.,* 2020). A reduction of gene expression involved in ATP production/respiration takes place also during *L. pneumophila* infection of the slime mold *Dictyostelium discoideum* (Kjellin *et al.*, 2019). This corresponds to a reduction of mitochondrial respiration as well as the cellular ATP pool by 6 h post-infection observed in macrophages (Escoll *et al.*, 2017). The dynamics of these metabolic changes in macrophages during *L. pneumophila* infection shows that shortly after infection both glycolysis and oxidative phosphorylation are increased, which peaks one hour post-infection. Then oxidative phosphorylation is severely reduced, while glycolysis remains high. This second phase lasts at least 5 hours post-infection, which precedes bacterial replication and the beginning of the macrophage cell death. The first phase is independent of the type IV secretion system (T4SS) while the second phase is T4SS-dependent (Escoll *et al.*, 2017). T4SS allows injecing effector proteins into macrophages in order to replicate within LCV. *L. pneumophila* mainly activates TLR-2 during infection (Archer *et al.*, 2006), and activation of TLR-2 results in increased glycolysis and oxidative phosphorylation in human primary cells (Lachmandas *et al.*, 2016). Escoll *et al.* (2017) suggested that increased glycolysis and increased oxidative phosphorylation in the first phase is TLR-2-dependent, but T4SS-independent. Further, they propose that bacterial effectors injected through T4SS initiate a Warburg-like program in the second phase, disrupting the mitochondrial network. Infection with *L. pneumophila* causes extended activation of NF-κB in macrophages (Fontana *et al.*, 2011).

Induction of glycolysis and restriction of oxidative phosphorylation allow *L. pneumophila* to replicate due to the biosynthetic role of glycolysis (Escoll *et al.*, 2017). Increased glycolysis and higher level of its intermediates in the infected macrophages can be used for the serine synthesis (like the pathway in proliferating cancer cells), therefore supplying the main amino acid required for the growth of *L. pneumophila*. Also, macrophages infected with *Mycobacterium tuberculosis* show an enhanced glucose uptake and increased glycolysis accompanied by diminished oxidative phosphorylation (Gleeson *et al.*, 2016). The glycolytic intermediates are directed to lipid bodies, fatty acids from which are sources of energy and carbon (Singh *et al.*, 2012). In the case of infection by *Chlamydia trachomatis* bacteria, increased glucose uptake and glycolysis were observed with flux of glycolytic intermediates to the pentose phosphate pathway to provide nucleotides for bacterial replication (Siegl *et al.*, 2014). These examples show that host cell glycolysis seems to be the preferred metabolism for different intracellular bacteria, probably because the intermediates for bacterial growth are produced due to glycolysis. Intracellular bacteria exploit some host-cell-derived substrates as the main energy sources: *Legionella* uses amino acids, *M. tuberculosis* fatty acids, *Chlamydia* malate. Thus, the Warburg-like metabolism, induced in the cell by the bacterial infection, enables the synthesis of metabolites indispensable to complete the development of pathogens and their survival (Escoll *et al.*, 2017; Gleeson *et al.*, 2016). The Warburg-like metabolism found in phylogenetically distant protozoans and macrophages after bacterial infection shows that this strategy is evolutionarily conserved because it protects pathogens from host glucose depletion.

Intracellularly multiplying bacteria, as well as proliferating cancer cells, have extremely large biosynthetic requirements. Only the metabolic program based on glycolysis combined with biosynthetic pathways using Krebs cycle intermediates can fulfill these demands. The aim of the program is the limitation of ATP synthesis through oxidative phosphorylation (Vander Heiden *et al.*, 2009). Thus, the oxidative phosphorylation is relatively inactive in differentiating or proliferating cells, such as stem cells, activated T-cells, or LPS-stimulated macrophages. In these cells, metabolism relies on aerobic glycolysis (ref. in Escoll & Buchrieser, 2018).

AMPK AND TORC KEEP IN BALANCE CATABOLIC AND ANABOLIC PROCESSES

A metabolic shift towards glycolysis was first observed in cancer cells. It takes place during embryonic development, angiogenesis, and in various organs of mature individuals. Hypoxia-induced factor 1α (HIF-1α) and AMP-stimulated protein kinase (AMPK), are key regulators of oxygen sensing and energy balance, respectively. AMPK responds to the low energy level and it promotes cell growth inhibition and stimulation of catabolic processes to enhance nutrient availability and energy level (Hardie, 2014). An antagonist of AMPK pathway signaling is TORC (target of rapamycin complex).

Under favorable energy conditions, TORC promotes protein synthesis and cell growth (Laplante & Sabatini, 2012). Accordingly, enzymes relevant for mitochondrial activity, glucose transport and glycolysis, carbohydrate storage, lipid metabolism, as well as protein translation and the cell cycle are controlled by AMPK and/or TOR. (Angin *et al.*, 2016)

Regulation of AMPK and TORC activity

AMPK exists in virtually all eukaryotic cells, as a highly conserved Ser/Thr kinase. Its composition and regulation were recognized in mammalian cells. This heterotrimeric kinase consists of α, β, and γ subunits. The α subunit contains the catalytic domain and is the main site of enzyme regulation by phospho-dephosphorylation at threonine 172 (Thr 172) in the activation loop (Hawley *et al.*, 1996). The β subunit contains a carbohydrate-binding module (CBM) that associates with glycogen in a phosphorylation-dependent manner (Oligschlaeger *et al.*, 2015). The γ subunit contains four cystathionine-β-synthase (CBS) motifs; these domains create the two binding sites for AMP, the allosteric activator. The enzyme is regulated by the AMP/ATP ratio, a high ratio leading to high AMPK activity. In the most active form of the enzyme, the α-subunit is both phosphorylated (at Thr 172) and bound to AMP at two sites. AMP regulates the AMPK activity by allosteric and covalent mechanisms (Weekes *et al.*, 1994; Hawley *et al.*, 1995; Davies *et al.*, 1995) and importantly, allosterically activates upstream kinase, LKB (liver kinase B1) enhancing its activity towards AMPK. LKB1 possess high basal activity and phosphorylates Thr 172 on AMPK constitutively (Lizcano *et al.*, 2004). In addition, binding of adenine nucleotides to the regulatory γ-subunit of AMPK brings about conformational changes that modulate the phosphorylation state of Thr 172, thus adopting the enzyme activity according to the energy status level of the cell. The binding of ATP (which indicates adequate energy levels) diminishes net Thr 172 phosphorylation, whereas binding of ADP or AMP (which indicates decreased energy levels) enhances net Thr 172 phosphorylation, increasing the kinase activity (Hawley *et al.*, 1995**;** Oakhill *et al.*, 2011). Finally, AMP inhibits dephosphorylation, of the AMPK by human protein phosphatase-2Cα and native bovine protein phosphatase-2AC (Davies *et al.*, 1995).

AMPKα can be phosphorylated also on Thr 172 by kinase TAK1 (transforming growth factor β-activated kinase 1) (Neumann 2018) and by CamKKs (Calmodulin-dependent protein kinase kinases) (Hurley *et al.*, 2005) following the increases of intracellular Ca^{2+} levels. Other protein kinases PKA (Djouder *et al.*, 2010), PKC (Heathcote *et al.*, 2016), PKD (Coughlan *et al.*, 2016), S6K (ribosomal subunit S6 kinase) activated by the MAPK/ERK pathway, Akt (PKB) (Hawley *et al.*, 2014), and glycogen synthase kinase (GSK) (Suzuki *et al.*, 2013) phosphorylate different serine residues in the ST-loop of AMPKα, preventing Thr 172 phosphorylation, thus inhibiting AMPK activity.

AMPK is activated under conditions of reduced generation of ATP such as glucose depletion, ischemia, oxidative stress as well as during muscle contraction (due to increase of ATP consumption) (Hardie, 2007). Due to the phosphorylation of metabolic enzymes and the effects on transcription, AMPK turns on the cellular uptake of glucose and fatty acids, and their oxidative metabolism. On the other hand, AMPK turns off biosynthetic pathways for instance the synthesis of glucose, glycogen, and lipids in the liver (ref. in Hardie *et al.*, 2012).

AMPK activates catabolic processes and inhibits anabolic processes, partially by negative regulation of mTORC1 signaling. TOR is Ser/Thr protein kinase (Wullschleger *et al.*, 2006; Laplante & Sabatini, 2012) that promotes anabolic processes under conditions of high nutrient and energy levels. In mammals, there are two complexes containing mTOR kinase: mTORC1 and mTORC2. Other subunits of these complexes such as Raptor and Rictor are different from each other and are found in mTORC1 and mTORC2, respectively. mTORC1 connects the availability of nutrients (mainly amino acids) and growth factor signaling with anabolic processes in proliferating cells and tumors. Branched-chain amino acids, particularly leucine, are potent nutrient activators of mTORC1. The RAG family of small GTPases is involved in amino acid sensing (Sancak *et al.*, 2008). AMPK phosphorylation of Raptor brings about the inhibition of mTORC1 and the arrest of cell-cycle caused by energy stress (Gwinn *et al.*, 2008). As a result of its inhibitory effect on mTORC1 signaling, AMPK switches off protein synthesis and favors autophagy (Gwinn *et al.*, 2008; Inoki *et al.*, 2012). It also downregulates the expression of HIF-1α (Shackelford *et al.*, 2009).

Evolutionary conservation of AMPK and TORC pathways

AMPK is present in protists, plants, fungi, and animals (Hardie, 2014; Garcia & Shaw, 2017). The general AMPK structure did not significantly change in the evolution of animals, except for duplications of some of the subunits. Amino acids critical for the function of AMPK are either conserved or substituted by biochemically similar residues in other taxa (ref. in Sinnett & Brenman, 2016). These conserved amino acid residues concern those regulating AMPK activity, subunit interactions, and localization of the enzyme. A functional AMPK, as well as an LKB1 (liver kinase B1) homologs, were discovered in the amoebozoan *Dictyostelium* (Bokko *et al.*, 2007, DictyBase accession no. DDB02290349; Bokko *et al.*, 2007). In sucrose non-fermenting fungi, SNF, a homolog of AMPK was found (Hong *et al.*, 2003). Similarly, LKB1, the upstream kinase of AMPK, is an evolutionarily con-

served enzyme, having homologs throughout eukaryotes. Also, reaction of AMPK phosphorylation catalyzed by LKB1 is a conserved substrate-kinase reaction occurring in organisms from yeast to mammals (ref. in Nakano & Takashima, 2012). In addition, expression of acetyl CoA carboxylase, the first enzyme of lipid biosynthesis pathway, that is phosphorylated and inactivated by AMPK (Carling *et al*., 1987), points to the evolutionary significance of this signaling pathway, preserved in both mammals and insects (flies) (Pan & Hardie, 2002).

The animal AMPK enzyme regulates genes and proteins that take part in oxidative fuel selection related to the transition from energy-rich to energy-poor conditions (Hardie, 2014; Garcia & Shaw, 2017). Once switched on, AMPK reestablishes energy homeostasis by induction of catabolic pathways that produce ATP effectively while switching off energy-using processes like biosynthesis and cell-cycle progression (Imamura *et al*., 2001; Jones *et al*., 2005). New functions were developed during the evolution of metazoans so that hormones and adipokines affect AMPK activity regulating energy balance at the whole body level (Hardie *et al*., 2012).

Like the AMPK pathway, the TOR pathway is highly conserved from yeast to humans

Roustan and others (Roustan *et al.,* 2016) have reported that the phylogenetic profiles of the TOR pathway indicate the presence of both TORC1 and TORC2 already in the LUCA (last universal common ancestor). The RAG complex, which regulates TORC1 on the base of the amino acid availability is as old as the eukaryotes. The same also concerns the tuberous sclerosis complex (TSC2), which stimulates mTORC1 (Covarrubias *et al*., 2015) and the pathways such as IκB kinase β (IKBKB), ERK, and AKT, which combine the extracellular and cellular energy level signals. The TORC pathway appears to be significantly stable in the course of evolution. Among several modifications, there is for instance duplication of an ancestral TSC2-like gene at the origin of the opisthokont (fungi and animals) branch, which gave rise to contemporary paralogs TSC1 and TSC2, and to the appearance of REDD1 (regulated in development and DNA damage responses 1), a hypoxia-inducible factor-1 (HIF-1) target gene, which plays a critical role in the inhibition of mTORC1 signaling during hypoxic stress (Katiyar *et al*., 2009). The ancestor of Opisthokontae was probably a heterotrophic organism as a common way of control of energy turnover in response to the availability of nutrients characterizes yeast and mammals. Yeast ferment glucose when it is in large quantities that is a fairly ineffective way for energy production. At that time, the expression of enzymes involved in oxidative metabolism is repressed (Gancedo, 1992). When the supply of glucose is limited, yeast SNF1 is activated (Woods *et al*., 1994; Wilson, *et al*., 1996) and the yeast cell uses other fuels suitable for a more energy-efficient oxidative metabolism. During the yeast adaptation to glucose restriction, upregulation of genes required for oxidative metabolism and downregulation of genes required for glycolysis are observed, and importantly, a SNF1 complex is necessary for most of these changes (Haurie *et al*., 2003).

Activation of AMPK in immune cells

The ancestral function of AMPK inferred from the role of its yeast orthologue was a response to glucose starvation, reflected by a high AMP/ATP ratio. Activation of AMPK in immune cells triggers the shift from a pro-inflammatory to an anti-inflammatory phenotype, in part by bringing a change from rapid glucose uptake and glycolysis to mitochondrial oxidative metabolism, as well as oxidation of fatty-acid (O'Neill & Hardie, 2013). Catabolic metabolism, regulated by AMPK support the anti-inflammatory macrophage functions (O'Neill & Pearce, 2016). Inflammatory response of bone marrow-derived macrophages (BMDM) stimulated by infection with the intracellular bacteria *Legionella pneumophila* is accompanied by the diminished AMPK phosphorylation. This is in agreement with metabolic change observed after infection when a switch from oxidative phosphorylation to glycolysis occurs. (Escoll *et al*., 2017). Similarly, AMPK phosphorylation is also diminished in *L. pneumophila*-infected mouse lungs (Kajiwara *et al*., 2018). Anti-inflammatory cytokines, IL-10, transforming growth factor β (TGFβ) (ref. in Dzik, 2010), and IL-4 (Wang & Secombes, 2015; Li *et al.,* 2007) have appeared in evolution at the vertebrate level in the teleost fishes. The treatment of macrophages with IL-10 or TGFβ causes rapid phosphorylation, thus activation of AMPK, whereas the treatment of macrophages with LPS as a pro-inflammatory stimulus causes AMPK dephosphorylation and inactivation (Sag *et al*., 2008). AMPK prevents LPS-induced IκB-α degradation and stimulates Akt activation. Akt inhibits glycogen synthase kinase-3 (GSK3) by its phosphorylation (Cross *et al.,* 1995). GSK3 is the constitutively active downstream kinase of the phosphatidylinositol-3-kinase (PI(3)K). Inhibition of GSK3 causes the PI(3)K pathway to selectively augment anti-inflammatory cytokine production with simultaneous inhibition of the pro-inflammatory cytokine production resulting from TLR stimulation of macrophages (Martin *et al*., 2005). Zhu and others (Zhu *et al*., 2015) have shown that AMPK is needed both for IL-10 activation of the PI(3)K/Akt/mTORC1 pathway and STAT3-mediated anti-inflammatory pathways regulating functional polarization of macrophages. The Akt-mTORC1 pathway links sensing of amino acids to IL-4 activation of macrophages, so amino acid availability rises, while amino acid insufficiency reduces the induction of IL-4-dependent genes (Covarrubias *et al*., 2016). Akt mediates also enhanced glucose consumption in M2 macrophages, and this contributes to induction of M2 gene expression (Covarrubias *et al*., 2016). Huang and others (Huang *et al.,* 2016) have reported that mTORC2 works parallely with the IL-4Rα/Stat6 pathway to facilitate an enhancement of glycolysis during M2 activation *via* the induction of the transcription factor interferon regulatory factor 4 (IRF4). The IRF4 takes part in metabolic reprogramming to assist M2 activation and influences fatty acid oxidation. The mTORC2 pathway is clearly important for the function of M2 macrophages as its inhibition decreases immunity to the parasitic nematode *Heligmosomoides polygyrus*. Remarkably, AMPK may directly increase the rate of glycolysis. The enzyme is able to phosphorylate PFKFB3 enhancing its kinase activity, which results in an increase of the cellular concentrations of fructose-2,6-bisphosphate (the allosteric activator of phosphofructokinase), and the activation of glycolysis (Marsin *et al*., 2002). Due to this mechanism, macrophages can continue generating ATP in hypoxic regions of the infected or damaged tissue.

The AMPK activation in mammalian cells by parasite infection

Carbohydrate and lipid metabolism in macrophages is strongly affected as a result of infection with parasitic flagellates *Leishmania major*. mRNA levels of glucose

transporters and key glycolytic enzymes (hexokinase, pyruvate kinase M2, and lactate dehydrogenase a are enhanced in infected cells. Also, induction of the PDK1 gene is initiated at the third hour after infection. It is accompanied by a downregulation of genes, products of which are involved in the Krebs cycle and oxidative phosphorylation. All of this suggests that in infected macrophages energy production depends mainly on the increased glycolytic flow. *L. major* infection induces accumulation of cholesterol and triacylglycerols as a source of high-energy substrates for the parasite needs (Rabhi *et al.*, 2012). In addition to inflammatory mediators, *L. major* promastigotes also induce the transcription of genes accompanying an M2 response, such as arginase1.

The observed induction of genes encoding glycolytic enzymes in *L. major* has been confirmed by analysis of bioenergetic fluxes in *Leishmania infantum*-infected bone marrow-derived macrophages (BMDM) (Moreira *et al.*, 2015). An initial transient glycolytic phase is followed by a switch to oxidative metabolism. During the glycolytic phase, a decrease of ATP/AMP and NAD/NADH ratios takes place followed by induction of the AMPK activity. SIRT1 (NAD-dependent lysine deacetylase) and LKB1/AMPK are essential for the shift to oxidative metabolism. At this point, the respiration rate and activation of peroxisome-proliferator-activated receptor-γ co-activator-1α (PGC-1α), the main inducer of mitochondrial biogenesis, increase. The energetic and redox pools of the parasite are restored. In the absence of SIRT1 or LKB1, infected macrophages cannot activate AMPK and initiate the metabolic switch. The need for macrophage AMPK for the successful *Leishmania* infection was demonstrated in mice with a myeloid-specific AMPK deficiency which displayed reduced parasite burden (Moreira *et al.*, 2015). In the liver stage of malaria, *Plasmodium berghei* infection decreases the transcription of glycolytic enzyme phosphofructokinase 1, and in parallel increases transcription of gluconeogenesis enzymes, as well as AMPKα and AMPKγ in hepatocytes (ref. in Mesquita *et al.*, 2016). Increased glucose levels are essential for the survival of sporozoites, their metabolism is strongly dependent on glucose.

The mice lacking AMPKα1 in alveolar macrophages and dendritic cells presented increased Type-1 responses, greater numbers of Th17 cells, and defects in the generation of M2 macrophages when infected with the gastrointestinal roundworm *Nippostrongylus brasiliensis*. Impairment of Type-2 response was manifested by augmented intestinal worm burden. Also, tissue damages caused by the pathogen were poorly regenerated in these mice. It shows that the activity of AMPK in myeloid cells is essential for protection against gastrointestinal nematodes (Nieves *et al.*, 2016).

CELL MIGRATION

Cell migration makes possible embryonic morphogenesis, regeneration, and repair of tissues. It also makes possible the immune response when leukocytes leave the bloodstream and migrate into the surrounding tissue to kill invading microorganisms, infected cells and to clear debris (ref. in Ridley *et al.*, 2003). To migrate, the cell has to become polarized, i.e. the molecular processes at the front of a moving cell should be different from those in the back. The capability of a multicellular organism cell to be polarized is inherited after protists or even bacteria and is well developed in yeast to mammals (Etienne-Manneville, 2004). Migration of cells occurs towards a gradient of the signal from growth factors, chemokines, or extracellular microenvironment (ECM) (Fig. 1). Cell surface receptors respond with the activation of G proteins or receptor tyrosine kinases, stimulation of guanine nucleotide exchange factors (GEFs) for cell division control protein 42 (Cdc42) that is a small GTPase of the Rho family (which includes Rac/CDC42/RhoA), activation of phosphoinositide 3-kinases (PI3Ks), following the recruitment of activated Rac. Signaling through Rho GTPases regulate dynamics of cytoskeleton in several phases of cell migration, including polarity, adhesion, and membrane protrusions (Cain & Ridley, 2009). The local activation of Rac and/or Cdc42, and subsequently a Wiskott-Aldrich Syndrome protein/ verprolin homologous protein (WASP/WAVE) family proteins and the actin-related proteins-2/3 (Arp2/3) complex, trigger the arrangement of a branching actin filament network at the leading edge, which in turn brings about a protrusion in the direction of migration (ref. in Ridley *et al.*, 2003; Fig. 1).

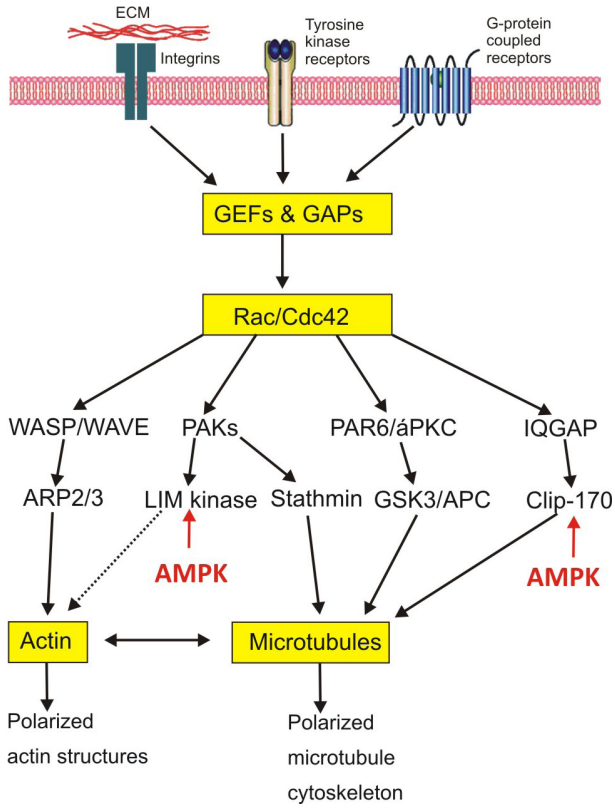

Figure 1. A simplified presentation of signaling pathways for cell migration with the pointing to the pathways which are influenced by AMPK (based on Etienne-Manneville, 2004).
Abbreviations: GAPs, GTPase-activating proteins; GEFs, guanine nucleotide exchange factors; Cdc42, cell division control protein 42); WASP/WAVE, Wiskott-Aldrich Syndrome protein/ WASP verprolin homologous protein; Arp2/3, actin-related proteins-2/3; APC, adenomatous polyposis coli protein; GSK3, glycogen synthase kinase-3 beta; CLIP-170, cytoplasmic linker protein 170.

Cdc42/Rac signal through p21-activates kinase (PAK) that phosphorylates LIM kinase, an actin-binding kinase. PAK and LIM kinase signaling regulates actin depolymerization (Edwards *et al.*, 1999). The interaction of Rac/Cdc42 with PAK causes also an enhancement of the phosphorylated myosin light-chain kinase (MLCK) level

that is essential for anchoring of lamellipodia (Kiosses *et al*., 1999). Cdc42 affects the location of the microtubule-organizing center (MTOC) mainly through the PAR for "partitioning defective" (PAR6), present in a complex with PAR3 and an atypical protein kinase C (aPKC) (Etienne-Manneville & Hall, 2003). This complex is suggested to orient the MTOC through local capture of microtubules at the leading edge *via* adenomatous polyposis coli protein (APC). It binds tubulin and locates on the ends of microtubules (Etienne-Manneville & Hall, 2002). This interaction of APC with microtubules is diminished by phosphorylation of APC by glycogen synthase kinase-3 beta (GSK3 beta) Zumbrunn *et al*., 2001).

The other effector of Cdc42/Rac is IQGAP. This GTPase-activating protein (GAP) is a scaffold protein containing the IQ domain (Cao *et al*., 2015). IQGAP1 catches the plus-ends of microtubules through cytoplasmic linker protein 170 (CLIP-170) (Gundersen, 2002).

Activated Rac1 and Cdc42 also tag the sites where IQGAP1 crosslinks actin filaments (not presented in Fig. 1). There, APC is acquired through IQGAP1 to actin filaments (Noritake *et al*., 2005). Activation of PAKs brings the phosphorylation/inhibition of the microtubule-destabilizing protein stathmin (Daub *et al*., 2001). According to Wittmann and others (Wittmann *et al*., 2003) stathmin could take part in the protrusive activity throughout cell migration.

AMPK function in cell polarity and motility

Activated AMPK increases the motility of the cell through tubulin polymerization and subsequent cytoskeletal reorganization (Nakano *et al*., 2010). AMPK controls cell migration by regulation of microtubule dynamics and directional cell migration through phosphorylation of the microtubule plus end protein CLIP-170 (Fig. 1). According to this, inhibition of AMPK activity prevents cell migration by hyperstabilizing the microtubule cytoskeleton *via* dephosphorylation of CLIP-170 (Nakano *et al*., 2010). AMPK has been also suggested to be involved in controlling of actin cytoskeleton dynamics and reorganization of the plasma membrane (Yan *et al*., 2015). An enhancement of the AMPK activity due to hypoxia suppresses migration of cells by rearranging actin filaments after phosphorylation of PDZ and LIM domain protein 5 (Pdlim5) (Fig. 1). Phosphorylation of Pdlim5 by AMPK inhibits cell migration by repressing the Rac1-Arp2/3 signaling pathway. Both suppression and activation of AMPK cause inhibition of the cell migration, which suggests different mechanisms acting on CLIP-170 or Pdlim5 (Yan *et al*., 2015).

AMPK signaling in cell polarity is evolutionarily conserved

In cultured mammalian cells, both anterior–posterior in migrating cells and apical–basal in epithelial cells polarity demands participation of the PAR-3/PAR-6/aPKC/CDC-42 complex. In the *Caenorhabditis elegans* zygote (Kemphues *et al*., 1988), establishing of anterior- posterior cell polarity demands the expression of the PAR-3/PAR-6/aPKC/CDC-42 complex at the anterior end, but PAR1 and PAR2 at the posterior one. Although setting up the anterior- posterior axis occurs at different stages of development in response to different signals, it was found that the same conserved PAR proteins play the crucial function in the creation of polarity both in *C. elegans* and *Drosophila melanogaster* (Goldstein & Macara, 2007).

PAR-4 is the LKB-1 orthologue in *C. elegans* (Narbonne & Roy, 2006). It is indispensable for the cytoplasmic division during the early stages of embryogenesis. Maternal-effect lethal mutations in PAR-4 result in the loss of intestinal cell ability to differentiate. It has been shown that these mutations influence several facets of cell polarity (Morton *et al*., 1992).

In the human LS174T cell line (colon adenocarcinoma), AMPK (activated due to energy deprivation) causes complete polarization and brush border formation in cells through phosphorylation of myosin regulatory light chain (MRLC) (Lee *et al*., 2007). In *Drosophila,* AMPK controls mitotic cell division and epithelial polarity subsequent to LKB1 through direct phosphorylation of MRLC (Lee *et al*., 2007). Studies on HeLa cells have shown phosphorylation of AMPK during mitosis, and AMPK was restricted to components of the mitotic apparatus apparently independent of the cellular energy levels (Vazquez-Martin *et al*., 2009a). AMPK has been found also to regulate indirectly MRLC phosphorylation, at least in part, by phosphorylation regulatory subunit 12C (PPP1R12C) of phosphatase 1 and PAK2 in human cells during mitosis (Banko *et al*., 2011). For completion of mitosis phosphorylation of MRLC is necessary (Banko *et al*., 2011). Although energy is required to perform mitosis, the process proceeds even under energy stress in order to arrest cells at the G1/S checkpoint and allow them to await more beneficial nutrient conditions. On the other hand, the role of AMPK in mitosis may be independent of the energy status of the cell (Vazquez-Martin *et al*., 2009b). Processes such as completion of mitosis, polarization, and migration could be crucial for various physiological functions. Although AMPK activation is generally linked with reduced energy consumption**,** processes that need energy are also augmented by AMPK.

Phagocytic activity of neutrophils and macrophages is increased as a result of AMPK activity and ingestion of apoptotic cells or bacteria increases AMPK activity in macrophages (Bae *et al*., 2011). *In vivo*, AMPK activation results in enhanced phagocytosis of bacteria in mouse lungs.

Activation of PAK1/2 and WAVE2 (effectors of Rac1) occurs together with activation of AMPK. AMPK activation also causes phosphorylation of CLIP-170, which takes part in the synthesis of microtubules (Fig. 1). Thus, the capacity of activated AMPK to increase phagocytosis is coupled with the cytoskeleton organization, together with augmentation of microtubule and actin polymerization. According to Bae and others (Bae *et al*., 2011), AMPK activation concerns nonselective phagocytosis rather than more specific receptor-dependent mechanisms recognizing individual targets. AMPK is involved also in the regulation of phagocytosis *via* remodeling of the actin cytoskeleton in hemocytes of oysters (He *et al*., 2019).

HYPOXIA-INDUCIBLE FACTOR-1 AS THE MAIN EFFECTOR TURNING ON THE ANAEROBIC METABOLISM

Systemic and cell-autonomous adaptations have been developed in the process of evolution in response to limited oxygen availability. The crucial factors controlling metabolism under hypoxia are heterodimeric transcription hypoxia-induced factors (HIF-1 and HIF-2). Both isoforms contain α subunits that heterodimerize with HIF-1β and bind to the same DNA sequence hypoxia-responsive element (HRE) but induced expression of

certain genes may vary. HIF-1α preferentially induces glycolytic pathway and HIF-2α is involved in the regulation of genes important for tumor growth, cell cycle progression, and maintaining stem cell pluripotency (ref. in Loboda *et al.*, 2012). HIFs activation is crucial for cell growth processes including development, angiogenesis, and vascular injury during hypoxia. The HIF-1 mediates the Pasteur effect. It is also an important mediator of the Warburg effect because of its function in the regulation of glycolysis (Seagroves *et al.*, 2001).

HIF-1 consists of HIF-1α and HIF-1β subunits. Both contain the helix-loop-helix-PAS (PER- ARNT-SIM) domain (Graham & Presnell, 2017). HIF-1β is constitutively expressed and the expression of HIF-1α is sustained at low levels in the majority of cells under normoxia.

The low level of HIF-1α subunit is maintained mainly due to O_2-dependent hydroxylation of proline residues: 402, 564, or both, by prolyl hydroxylase domain protein 2 (PHD2), also named EglN. The oxygen Km values for the hydroxylation of HIFα by EglN hydroxylases are just slightly over those present during normoxic conditions (Hirsila *et al.*, 2003). Hydroxylation of each site makes a binding place for the ubiquitin ligase containing pVHL (von Hippel-Lindau protein), the recognition module of this enzyme that assigns HIF-1α for proteasomal degradation (ref. in Semenza, 2002). These hydroxylases belong to the iron(II)- and 2-oxoglutarate-dependent dioxygenase family generating CO_2 and succinate from O_2 and α-ketoglutarate. In humans, three prolyl hydroxylase isoenzymes (PHD1-3) and asparagine hydroxylase factor inhibiting HIF (FIH) have been recognized (Hewitson *et al.*, 2003). Low concentrations of O_2, high concentrations of tricarboxylic acid cycle intermediates, for instance, succinate, fumarate, also chelators of Fe(II), inhibit the activity of hydroxylases. In addition, O_2-independent ubiquitination and proteasomal degradation of HIF-1α take place (Liu & Semenza, 2007).

Oxygen regulates the ability of HIF-1α to activate gene transcription. Under normoxic conditions, the cooperative binding of VHL and FIH-1 allows recruiting of histone deacetylases that make the DNA less accessible to HIF-1α (Mahon *et al.*, 2001). Furthermore, oxygen-dependent hydroxylation of Asn803 by FIH-1 disturbs the interaction of HIF-1α with the co-activator p300 (Lando *et al.*, 2002) and CREB binding protein (CBP) (Kallio *et al.*, 1998).

Under hypoxic conditions, oxygen is rate-limiting for prolyl hydroxylase reaction (Epstein *et al.*, 2001), which results in diminished ubiquitination of HIF-1α (Sutter *et al.*, 2000) and decreased proteasomal degradation. The HIFα subunit becomes stable, makes a dimer with a HIF β subunit, translocates to the nucleus, and hundreds of genes can be activated in a cell-type-specific manner (ref. in Semenza, 2007). Hypoxia or low oxygen partial pressure cause the expression of genes involved in hematopoiesis, oxygen binding, and delivery. The HIF-1 mediated expression of genes governing energy production results in enhanced glucose uptake, and glycolysis, and diminished oxidative phosphorylation. HIF-1 directly transactivates the PDK1 gene (Kim *et al.*, 2006; Papandreou *et al.*, 2006). It limits the entry of pyruvate into the Krebs cycle. Instead of this, pyruvate is reduced to lactate by the lactate dehydrogenase A and expelled from the cell by monocarboxylate transporter 4. Both proteins are the HIF responsive gene products (Ebert & Bunn, 1998; Ullah *et al.*, 2006). Inhibition of pyruvate dehydrogenase causes attenuation of mitochondrial respiration and excessive ROS generation. Lactate dehydrogenase recovers NAD^+ necessary to maintain glycolysis and ATP production under hypoxia, which is critical for hypoxic cells to survive.

Synthesis of HIF-1α protein depends on growth factor stimulation of receptor tyrosine kinases and a signaling pathway guiding from phosphatidylinositol-3-kinase (PI3K) to the protein kinase B (AKT) and FRAP/mTOR pathway (Laughner *et al.*, 2001). The tumor suppressor phosphatase PTEN inhibits this pathway as it dephosphorylates the products of the PI3K reaction. When the PTEN levels increase, both HIF-1α expression, and HIF-1-mediated gene transcription is inhibited, as was shown to take place in the prostate cancer and glioma cells (Zhong *et al.*, 2000; Zundel *et al.*, 2000).

Evolution of Hypoxia-inducible factor pathway

The core elements of the HIF pathway were formed before the metazoan common ancestor and the pathway has been subjected to further processing and enlargement in each of the successor lineages (Rytkönen & Storz, 2011). All the metazoan genomes, except for that of *Bombyx mori*, contain at least one HIF-α sequence (Graham, & Presnell, 2017). As a result of HIF-α duplication in the vertebrate stem lineage, four paralogs emerged, HIF-1α and HIF-2α being less divergent than the small HIF-3α or the HIF-α-like ones. The two latter paralogs were lost in many vertebrate lineages. Most vertebrate genomes contain between two and six HIF-α genes. Although HIF-α homologs have been found only in metazoans, prolyl hydroxylase homologs are also found in other eukaryotes. In *Caenorhabditis elegans,* the mRNA levels of prolyl 4-hydroxylase (*egl-9*) were enhanced because of hypoxia in a HIF-1-dependent manner (Shen *et al.*, 2005). Regulation of transcription of the prolyl 4-hydroxylase subunits by HIF turns out to be evolutionarily conserved (Takahashi *et al.*, 2000). In humans, three PHD genes (*egl-9* homologs) have been recognized, and PHD2 and PHD3 are induced by hypoxia as well. (Epstein *et al.*, 2001; D'Angelo *et al.*, 2003; Cioffi *et al.*, 2003). On the other hand, homologs of FIH (factor inhibiting HIF) are not as common in metazoans as PHD enzymes.

HIF-β subunit in invertebrates, referred to as ARNTs, is distinct from vertebrate ARNTs. Additional vertebrate-specific ARNT2 is related to other vertebrate ARNT sequences. In humans, three paralogs of the HIF-α subunit (HIF-1α, HIF-2α/EPAS, HIF-3α) and two paralogs of the HIF-β subunit (ARNT, ARNT2) occur (Graham & Presnell, 2017). Over the animal kingdom HIF accumulates in hypoxic cells and operates in a very conserved way (Gorr *et al.*, 2006). The genes strictly linked with HIF-α are absent in nearly all unicellular eukaryotes. This suggests that the appearance of the HIF gene family in metazoan might ensure better regulation of oxygen homeostasis corresponding with the possible higher oxygen requirements in multicellular organisms. Also, given HIF-1α conservation among the majority of metazoans, the appearance of HIF-2α in primitive chimaeroid fish *Callorhinchus* may be connected with the emergence of specialized systems for O_2 delivery accompanying vascularization (Graham & Presnell, 2017). HIF-2α expression was found to be essential for erythropoiesis, vascularization, and pulmonary development in the vertebrates. The primordial role of HIF-1 is the regulation of metabolism (Semenza, 2012).

Role of HIF in macrophages

HIFs promote glycolysis and the pentose phosphate pathway inducing the relevant transporter and enzyme

expression, to provide an adequate amount of ATP for biosynthesis and antioxidant defense in conditions of lowered mitochondrial metabolism (ref. in O'Neill & Hardie, 2013). Stimulation of macrophages with LPS causes a switch from oxidative phosphorylation to the production of ATP by glycolysis. When mitochondria do not produce ATP, their membrane potential increases. This is combined with the altering of metabolism to channel metabolites to succinate. The inflammatory phenotype of the macrophages is governed by succinate oxidation by SDH in mitochondria (Mills *et al.*, 2016). Enhanced oxidation of succinate and increased mitochondrial membrane potential produce a redox signal that can influence HIF-1α activity (Mills *et al.*, 2016). According to Chandel and others (Chandel *et al.*, 2000), mitochondria-derived ROS are both required and sufficient to initiate HIF-1α stabilization during hypoxia. Induction of proinflammatory IL-1β, as well as glycolytic enzymes and glucose transporters in LPS-activated macrophages dependent on HIFs transcriptional activity (Tannahill *et al.*, 2013). HIFs activity is enhanced also due to the upregulation of pyruvate kinase muscle (PKM2) (Palsson-McDermott *et al.*, 2015).

Macrophages that lack HIF-1α have a reduced ability to kill bacteria, and impaired production of antimicrobial peptides and granule proteases (Peyssonnaux *et al.*, 2007; Nizet & Johnson, 2009). HIF-1α is necessary also to control the macrophage inflammatory response and promotes their phagocytic activity in the skin and joints (Cramer, 2003). Skin is a hypoxic organ and HIF-1α is expressed at high levels in the skin epithelium. Peyssonnaux and others (Peyssonnaux *et al.*, 2008) have found that the production of antimicrobial peptide cathelicidin in keratinocytes depends on HIF-1.

During inflammation, both immune cells and pathogens have enhanced metabolic demands which result in local depletion of oxygen and hypoxia (Dehne & Brune, 2012). It was found that when monocytes differentiate under hypoxia, a distinct macrophage phenotype develops with at least partially a higher level of HIF-1α protein (Staples *et al.*, 2011).

HIF-1 plays a role in the M1 polarization of macrophages (Nizet & Johnson, 2009). It has been shown that mouse macrophages overexpressing HIF-1*a* represent a hyperinflammatory state, showing an enhancement of M1 markers and a diminished rate of oxygen consumption. M1 polarization of macrophages caused by HIF-1*a* overexpression occurred *via* enhanced transcription of genes connected with glycolysis. Thus, promoting glycolytic metabolism, HIF-1 induces M1 polarization of macrophages (Wang *et al.*, 2017).

Migration of macrophages and phagocytosis are HIFs-dependent processes

Transcription factors belonging to the HIFs family also play roles in cell fate determination and cell migration (Cramer *et al.*, 2003). In the absence of HIF-1α, macrophages, concomitant with a decreased rate of glycolysis and energy production show impaired motility (Cramer *et al.*, 2003). Hypoxia augments phagocytosis and bacterial killing in macrophages in a HIF-1α-dependent manner. HIF-1α deletion in macrophages hampers the hypoxia-induced increase in phagocytosis (Anand *et al.*, 2007).

In severe hypoxia, HIF-1 mediates induction of pyruvate dehydrogenase kinase (PDK1). As a result, inhibition of pyruvate dehydrogenase complex diminishing oxidation of pyruvate in TCA takes place. Monocyte-derived macrophages experience a gradual decrease in the concentration of oxygen when they migrate into areas of inflammation (Leach & Treacher, 1998). Semba *et al.* (2016) have found that in mild hypoxia (4–6% oxygen), metabolic changes mediated by HIF-1 cause induction of PDK1 even though cytochrome c oxidase activity remains unchanged, a phenomenon named by the Authors glycolytic reprogramming. In mild hypoxia, the migratory activity of macrophages (*in vitro* and *in vivo)* depends on glycolysis. Pyruvate kinase PKM2 produces ATP in the last step of glycolysis. PKM2 co-localizes with F-actin in filopodia and lamellipodia where ATP is quickly consumed during remodeling of actin (Semba *et al.*, 2016). This suggests that even in mild hypoxia glycolytic reprogramming is essential for macrophage migration.

The myeloid-derived phagocytes neutrophils and macrophages circulating in the oxygen-reach blood have low HIFs levels. Migrating into sites of the infection, they cross the endothelium and experience decreasing concentrations of oxygen. In these conditions, prolyl hydroxylase activity is inhibited and consequently, HIF-1α protein is stabilized. Now, HIF-1α is able to form a functional transcription factor molecule with HIF-1β. The heterodimer translocates to the nucleus and activates transcription of innate immune response genes having hypoxia-responsive elements in their promoters. However, the maximal activation can be achieved due to the pathogen activation of TLRs and NF-κB, in order to increase HIF-1α transcription. This transcriptional activity of HIFs results in inhibition of apoptosis, reflected in the increased lifespan of phagocytes, promotes phagocytosis, triggers the release of antimicrobial peptides and pro-inflammatory cytokines (TNF, IL-1, and IL-12), enhances TLR expression, and activates inducible NO synthase for the production of nitric oxide. Nitric oxide aside from its bactericidal activity hinders HIFs degradation, which makes an amplification loop for fast activation of phagocyte response (Nizet & Johnson, 2009). However, the superoxide anion production by NADPH oxidase does not dependent on the transcriptional activity of HIF-1 (Peyssonnaux *et al.*, 2005).

Infection with pathogens induces HIF expression in target cells

An acute infection caused by viruses promotes stabilization of HIFs protein in infected cells.

In the case of the common respiratory syncytial virus (RSV) infection, HIFs stabilization in human bronchial epithelial cells occurs through a NO-dependent pathway. HIFs induce VEGF production and stimulate airway edema (Kilani *et al.*, 2004).

Stimulation of macrophages or neutrophils by a variety of bacterial species as *Staphylococcus aureus*, *Salmonella typhimurium,* and *Pseudomonas aeruginosa*, induces increased levels of HIFs showing that this phenomenon is characteristic of bacterial infection (ref. in Nizet & Johnson, 2009). Such bacterial products as LPS and peptidoglycan, while activating TLRs and NF-κB signaling, cause an increase of HIF-1α transcription (Frede *et al.*, 2006).

Chlamydiaceae, obligate intracellular bacteria, are able to replicate even in 3% concentration of O_2 (Rupp *et al.*, 2007). In hypoxic Human Epithelial type 2 (HEp-2) cells, *Chlamydium pneumoniae* causes stabilization of HIF-1α that promotes glucose uptake in the early phase of infection, important for replication of the bacterium. In the later phase of the chlamydial developmental cycle, uptake of glucose by *C. pneumoniae*-infected cells is radically decreased and further decreases subsequent to fol-

lowing degradation of HIF-1α caused by the chlamydial protease-like activity factor. Degradation of HIF-1α through the mid to late phase of infection may prevent pro-apoptotic signaling in host cells helping the pathogen to persist infectious in hypoxic conditions (Rupp *et al.*, 2007). Remarkably, HIF-1 and/or hypoxia may act either as an anti-apoptotic or pro-apoptotic factor, depending on the cell type and experimental conditions (Piret *et al.*, 2002).

Infection with the parasitic flagellate *Leishmania amazonensis* results in cutaneous lesions. In the later stages of infection, induction of HIF was observed in the cytoplasm and parasitophorous vacuoles of macrophages recruited to these lesions (Arrais-Silva *et al.*, 2005).

The obligate intracellular parasite *Toxoplasma gondii* causes opportunistic infections in fetuses and in immunocompromised individuals. In infected fibroblasts, expression of HIF is induced (Spear *et al.*, 2006). HIFs subsequently activate genes for glycolytic enzymes, glucose transporters, and mevalonate metabolism (Bladder *et al.*, 2001). Under hypoxic conditions in the brain, muscle, and retina, where the parasite causes severe pathology, both *T. gondii* replication and its organelle maintenance are severely impaired in the host cells that lack HIF-1α. According to Spear and others (Spear *et al.,* 2006), two alternative explanations of probable HIFs need for the parasite successful replication: a specific HIFs target gene is important for the growth of the parasite, or activity of HIFs is indispensable for the preservation of homeostasis in the infected cells. The HIF-1 function appears to be a very important mediator of cell resistance to intracellular pathogens (Knight & Stanley, 2019).

Adaptation of metazoan metabolism to changes of the oxygen concentration

A homolog of HIF-1 is necessary for adaptation to hypoxia in the free-living nematode *Caenorhabditis elegans* (Jiang *et al.*, 2001). Studies of Shen and others (Shen *et al.*, 2005) on hypoxia-induced genes in *C. elegans* showed that the glycolytic enzymes: hexokinase, phosphoglucomutase, enolase, and glycerol kinase were induced in an *hif-1*-dependent manner. Also, aconitase and isocitrate lyase involved in the conversion of fatty acids to sugars are induced by hypoxia.

Isocitrate lyase is a part of the bifunctional malate synthase/isocitrate lyase enzyme which transforms isocitrate to glyoxylate and succinate. Malate synthase catalyzes the condensation of glyoxylate with acetyl-CoA, coming from fatty acids oxidation, giving malate, a substrate for gluconeogenesis. This bifunctional enzyme expression at high levels occurs in embryos and L1 larvae. Nematodes are the only animals in which the glyoxylate metabolism has been detected (Liu *et al.*, 1995). Pyruvate carboxylase, the key enzyme of gluconeogenesis, producing oxaloacetate, is induced by hypoxia also, but in an *hif-1*-independent manner.

Parasitic nematodes adapted to the changes in oxygen concentration during their life cycle, as exemplified by free-living and parasitic forms of *Ascaris suum*. Its third-stage larvae (L3) live in normoxic condition but adults live in the small intestine where the oxygen concentration is below 5%. In the L3 larvae, phosphoenolpyruvate (PEP) is converted by pyruvate kinase to pyruvate in the last step of glycolysis, and acetyl-CoA is generated by pyruvate dehydrogenase complex entering the CAC. In adults living in anaerobic condition, carboxylation of PEP by phosphoenolpyruvate carboxykinase (PEPCK) is performed by the enzyme in the opposite direction than in gluconeogenesis, which results in oxaloacetate production. Oxaloacetate is reduced to malate that reaches mitochondria, where it is converted to fumarate by reversible reaction of fumarase, and fumarate is reduced to succinate (Kita & Takamiya, 2002; Sakai *et al.*, 2012). For fumarate reduction, complex II of ETC functions as quinol fumarate reductase (QFR, FRD), not like in aerobic conditions as succinate–ubiquinone reductase (SDH, SQR), to maintain redox balance in mitochondria of adult *A. suum* (Kita *et al.*, 2002). Electrons from NADH are transferred to the rhodoquinone (RQ) *via* the NADH-RQ reductase activity of mitochondrial complex I and then to fumarate through the rhodoquinol-fumarate reductase activity of mitochondrial complex II, with the generation of succinate. This anaerobic electron transfer in complex I is coupled with proton transport through the inner mitochondrial membrane and allows the synthesis of ATP in anaerobic condition.

Roos & Tielens (Roos & Tielens, 1994) have found differences in the expression pattern of two genes coding the B subunit of the complex II between free-living (L3) and adult nematodes *Haemonchus contortus*. All adult parasitic worms examined until now use fermentative pathways for energy production. The major end products of anaerobic metabolism are typically lactate, succinate, acetate, and propionate. Remarkably, the generation of the same range of end products is favored both in the presence and in the absence of oxygen (Barrett, 1991).

Both *hif-1a* and *hif-1β* mRNAs are present at all stages of *A. suum* life cycle, and most profusely in the aerobic free-living L3 larvae. Then their levels slowly diminish after infection of the host (Goto *et al.*, 2013). High levels of *hif-1* mRNAs in third-stage larvae would be a preadaptation to a hypoxic environment in the small intestine. This phenomenon suggests the necessity of a rapid, adequate response resulting in the regulation of genes involved in anaerobic energy metabolism in the face of sudden changes in oxygen concentrations. It shows transcription of *A. suum hif-1* regulated rather at the stage-specific way than in the oxygen-dependent way (Goto *et al.*, 2013). The genes of all subunits of mitochondrial complex II (succinate–ubiquinone reductase/quinol-fumarate reductase), are stage-specific expressed (excluding the adult-type flavoprotein subunit), and have putative hypoxia-responsive elements, which suggests that they are HIF-1 responsible genes (Goto *et al.*, 2013).

Hypoxic conditions induce *hif-1a* transcription in the hypoxia-tolerant mole rat *Spalax*. Even in normoxia, *Spalax* has 2-times higher levels of *hif-1a* mRNA than found in the sensitive to the hypoxia rat *Rattus*, which enable successful responses to hypoxia (Shams *et al.*, 2004).

These examples of *hif-1* mRNAs accumulation under normoxia in the otherwise evolutionarily distant organisms imply that this way of accommodation to changes of oxygen concentrations is conserved among animals. Of note, hypoxia and body temperature interact markedly in the regulation of HIF-1 function. As was shown in a poikilothermic fish crucian carp *Carassius*, the activity of HIF-1 increases at low temperatures (Rytkönen *et al.*, 2007).

Aside from parasitic invertebrates, also freshwater and marine invertebrates experience hypoxic conditions periodically in the intertidal zones. In the early phase of hypoxia, the bivalve *Mytilus* redox balance is sustained due to the formation of opines from pyruvate. After changing conditions to aerobic, the opines are reoxidized (Grieshaber *et al.*, 1994). Opine formation takes place in

the cytosol; it is a fermentation pathway in which pyruvate is condensed with arginine, alanine, or glycine by the dehydrogenase that reduces the Schiff base with NADH derived from glycolysis. As a result, iminoacid derivatives (opines) and NAD are produced. Regenerated NAD can be used for oxidative reactions. Various marine invertebrates, even the most primitive, use opine pathways (ref. in Müller *et al.*, 2012). The amount of ATP generated by these pathways is equal to the amount produced during lactate formation, *i.e.* two moles of ATP per mole of glucose.

mRNAs of *hif-a* and *phd* show the most intense expression in *Mytilus* gills. Both of them were found to be transcriptionally regulated under short-time air exposure. Also, HIF-α and PHD proteins were modulated in a time-dependent manner with a tendency equal to mRNA expression patterns. This suggests an essential role of HIF-α and PHD in the hypoxia tolerance in marine bivalves (Giannetto *et al.*, 2015). Under prolonged anaerobiosis, malate is converted to fumarate in *Mytilus*, like in anaerobically living parasitic nematodes. Electrons are transported from NADH *via* complex I, rodoquinone, fumarate reductase to fumarate, resulting in succinate production (Tielens & van Hellemond, 1998). Complex I pumps protons from the matrix into the intermembrane space, which allows mitochondrial ATPase to produce ATP. Succinate is either excreted as the end-product or may participate in the two mitochondrial ways providing additional ATP through substrate-level phosphorylation with two end-products, acetate or propionate (ref. in Müller *et al.*, 2012; Zimorski *et al.*, 2019). Succinate, acetate, and propionate together with alanine and opines are the major end products of anaerobic energy metabolism both during repression and during regular physiological activity in the majority of free-living marine invertebrates, like in parasitic nematodes (Müller *et al.*, 2012; Zimorski *et al.*, 2019). Aerobic and anaerobic animal lineages do not differ in terms of genes and enzymes involved in the generation of energy. Only the occurrence of rhodoquinone looks to be limited to animals that change their habitat to anaerobic.

The reduction of fumarate through the complex II under hypoxic conditions has its analog in the betaproteobacteria *Rhodoferax fermentans*. The complex II of *R. fermentans* and fumarate reductase located in mitochondria of facultative and anaerobic eukaryotes probably evolved independently (Miyadera *et al.*, 2003). This is supported by the finding that the pathway for rhodoquinone biosynthesis in bacteria and some protists is different from that in *Caenorhabditis elegans* and parasitic helminths (Salinas *et al.*, 2020).

Hypoxia enhances HIF-1α at both mRNA and protein levels in immortalized human renal proximal tubular epithelial cells (HK-2 cells) (Chen *et al.*, 2016). Reduction of fumarate to succinate takes place in kidney proximal tubule cells, and the resultant succinate is accumulated (Weinberg *et al.*, 2000). Also in cancer cells, succinate, fumarate, and malate were found in greater concentrations than in healthy tissues (Hirayama *et al.*, 2009). Lack of glucose and oxygen that imitates the tumor microenvironment, causes a decrease in the SQR activity and an increase in the FRD activity of complex II. These changes in activity are considered to be an effect of the flavoprotein subunit phosphorylation. Thus, complex II may act as a fumarate reductase in mammalian cells adapting to a hypoxic environment (Tomitsuka *et al.*, 2009).

The unity of anaerobic energy metabolism in virtually all major lineages of eukaryotes indicates a single origin and common ancestry of the involved genes, that can be traced back to their common ancestor (Müller *et al.*, 2012).

Hematopoiesis is affected by HIFs

Many physiological processes in developing mammalian embryos proceed in low oxygen concentrations prevailing in the uterus. Hypoxia controls the development of the placenta both through HIF-1α and HIF-2α (Cowden *et al.*, 2005). The likely consequence of a low oxygen concentration (between 1 and 5 percent) in the uterus (Okazaki & Maltepe, 2006), is the stabilization of HIFα, that induces expression of *Vegf* (vascular endothelial growth factor) leading to vascular growth to provide blood and nutrients for developing tissues (ref. in Imanirad & Dzierzak, 2013). Hematopoietic and vascular systems develop in parallel. Hypoxic hematopoietic tissues of early and mid-gestation mouse embryos show expressing HIFs and HIFs downstream targets. Both the development and function of hematopoietic progenitor/stem cells depend on HIFs. In adults, hematopoietic stem cells are maintained in the hypoxic microenvironment that is important for regulation their quiescence. This may be a remnant feature of the hypoxic conditions, in which they were generated in the embryo (Imanirad & Dzierzak, 2013). Genetically modified embryonic stem mouse cells (ES) show that HIF-1α is required for the induction in response to hypoxia of 13 genes encoding glucose transporters and glycolytic enzymes (Iyer *et al.*, 1998; Ryan *et al.*, 1998).

In wild-type ES cells, lack of glucose caused induction of *Vegf* mRNA without induction of HIF-1α protein. Although under hypoxia overall protein synthesis is diminished to preserve ATP, translation of both HIF-1α and VEGF, crucial for the hypoxic response, is continued due to initiation of translation by internal ribosomal entry site (ref. in Liu & Simon, 2004)

In cancers, enhanced cellular proliferation gives rise to greater O_2 use and hypoxia. Most common human cancers show overexpression of HIF-1α. To adapt to a hypoxic environment, neovascularization and increased glycolysis in solid tumors take place. HIF-1 causes an enhanced transcription of genes encoding VEGF and glycolytic enzymes as well as glucose transporters (Zhong *et al.,* 1999). Due to the activation of HIF-1, tumor cells can produce their own energy, becoming less reliant on nutrient supply to the tumor.

CONCLUSIONS

Genes of the enzymes catalyzing reactions of glycolysis, and the citric acid cycle are present in bacteria, archaea, and eukaryotes. Metabolic pathways, producing nutrients and energy, can be traced from protozoans to mammals. Also, regulation of these pathways based on oxygen availability and energy levels has a surprisingly ancient evolutionary history and is similar both in yeast and animal cells. The metabolism specific for activated immune cells of vertebrates has the beginnings in amoeba cells infected with bacteria. Bacteria impose their metabolic demands for survival and reproduction on the host cells similarly in macrophages and amoebas. This strategy, crucial to sustaining a species, led to the preservation of these metabolic regulations in organisms phylogenetically as distant as protozoans and vertebrates (Table 1). The glucose availability influences the energy charge of the cell. Both in yeast and mammalian cells, high AMP levels reflecting low energy charge activate kinase AMP and its yeast orthologue (SNF1) resulting in

Table 1. Metabolic characteristics of amoebas and macrophages after stimuli or infection with intracellular bacteria Legionella or protozoan Leishmania

Cells	M1 macrophages Proinflammatory and bactericidal, TLR-activated	*Acanthoamoeba* infected with *L. pneumophila*	Macrophages infected with *L.* pneumophila	Macrophages infected with *Leishmania*	M2 macrophages Antiinflammatory, tissue repair and anti-parasitic
Hallmarks of metabolic processes	Glycolysis and pentose phosphate pathway	Glycolysis and pentose phosphate pathway	Shortly after infection OXPHOS is reduced, glycolysis remains high	Increased glycolysis. Then a shift to an oxidative metabolism	OXPHOS
Enzymes important for metabolic switching	PFKFB3 and mTORC1, PDK1	Homologs of AMPK and LKB1 found in *Dictyostelium* model organism	Inhibition of AMPK	Induction of *PDK1*; AMPK, SIRT1 are essential for the shift to OXPHOS	PFKFB1, AMPK and SIRT1
Transcription factors	NF-κB and IRFs, HIF-1α	Lack of NF-κB and IRFs in Protozoa**	Prolonged activation of NF-κB, no data for HIF-1 expression	PGC-1α, HIF-1α	STAT6, PGC-1β.
Metabolic description	Citrate build-up, lipid synthesis, ROS and RNS	Elevated levels of amino acids in the amoeba cytosol. Down regulation of genes for carbohydrate synthesis and β-oxidation. Lack of ROS in Protozoa**	Elevated levels of amino acids in the macrophage cytosol. Repression of genes for protein translation, OXPHOS*. Inhibition of ROS production	Accumulation of cholesterol and triacylglycerols for the parasite growth	Increased fatty acid oxidation and biogenesis of mitochondria, *ARG1* induction

The contents of this table is explained in the text, with addition: *Price & Abu Kwaik (2014); **ref. in Dzik (2010). **Abbreviations**: AMPK, AMP-stimulated protein kinase; ARG, arginase; HIF, hypoxia- induced factor; IRF, interferon responsible factor; LKB, liver kinase B; NF-κB, nuclear factor κB; OXPHOS, oxidative phosphorylation; PDK, pyruvate dehydrogenase kinase; PFKFB, 6-phosphofructo-2-kinase/fructose-2;6-biphosphatase; PGC—peroxisome-proliferator-activated receptor-γ co-activator; ROS, reactive oxygen species; RNS, reactive nitrogen species; SIRT1, NAD-dependent lysine deacetylase; STAT —signal transducer and activator of transcription; TLR, Toll-like receptor; TORC, target of rapamycin complex.

inhibition of anabolic processes. In macrophages, catabolic processes enhanced by AMPK activity support anti-inflammatory functions. The transcription factor HIF induces a set of genes that activate anabolic processes. It promotes glycolysis, biosynthesis, and antioxidant defense against pathogens in inflammatory macrophages. Because AMPK and HIF-1 are regulated by glucose levels and oxygen concentrations respectively, they are indispensable to fundamental processes such as cell migration, or embryogenesis occurring in all multicellular eukaryotes.

Acknowledgements

I am very grateful to Elżbieta Wałajtys-Rode (Warsaw University of Technology, Faculty of Chemistry) for constructive criticism and many helpful suggestions how to improve the manuscript in respect to its merits, and Małgorzata Kloc (Research Institute Houston Methodist Weill Cornell Medical College) for critical reading and improving the manuscript.

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