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Molecular regulations of metabolism during immune response in insects

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ABSTRACT

Mounting an immune response is an energy-consuming process. Activating immune functions requires the synthesis of many new molecules and the undertaking of numerous cellular tasks and it must happen rapidly. Therefore, immune cells undergo a metabolic switch, which enables the rapid production of ATP and new biomolecules. Such metabolism is very nutrient-demanding, especially of glucose and glutamine, and thus the immune response is associated with a systemic metabolic switch, redirecting nutrient flow towards immunity and away from storage and consumption by non-immune processes. The immune system during its activation becomes privileged in terms of using organismal resources and the activated immune cells usurp nutrients by producing signals which reduce the metabolism of non-immune tissues. The insect fat body plays a dual role in which it is both a metabolic organ, storing energy and providing energy to the rest of the organism, but also an organ important for humoral immunity. Therefore, the internal switch from anabolism to the production of antimicrobial peptides occurs in the fat body during infection. The mechanisms regulating metabolism during the immune response ensure adequate energy for an effective response (resistance) but they must be properly regulated because energy is not unlimited and the energy needs of the immune system thus interfere with the needs of other physiological traits. If not properly regulated, the immune response may in the end decrease fitness via decreasing disease tolerance.

1. Physiological trade-offs during immune response that requires increased energy supply

The ability to mount an immune response belongs to the most fundamental of evolutionary traits among all organisms, insects being no exception. Organisms are usually equipped with an array of pre-existing, innately present immune mechanisms, ready to take immediate action. These mechanisms quiescently await activation by the pathogen, using no more energy than is needed for their basal functioning (maintenance costs – (McKean et al., 2008)). For example, developing and maintaining hematopoietic cells in *Drosophila* larva, which are important for cellular immunity, requires around 10% of the whole organismal glucose (Bajgar et al., 2015). Activation of the immune system rapidly increases its energy needs, depending of course on the extent of the response; the induction of immune response is associated with so called deployment costs (McKean et al., 2008). Merely triggering immune cell motility and executing, for example, phagocytosis already requires an increased amount of energy (Anderson et al., 1973). Detecting a pathogen however induces a plethora of additional immune reactions, which require the synthesis of many new molecules with signaling and antimicrobial functions, the undertaking of various cellular tasks and often the proliferation of additional immune cells (for example lamellocytes for encapsulation); all this must happen rapidly. Therefore, the energy requirements of immune cells may rise from 10% to almost one third of overall glucose consumption, for example in the case of the mounting of an immune response to parasitoid infection in *Drosophila* larva (Bajgar et al., 2015).

Such an increase in energy consumption by the activated immune system affects other processes within the organism competing for the available resources, which is well documented in eco-physiological studies of insects. During infection, the immune response, as an essential life-preserving process, becomes privileged regarding energy supply over other processes. Therefore, activating the immune response leads to a reduced overall metabolic rate during infection (Arnold et al., 2013; Bashir-Tanoli and Tinsley, 2014; Chambers et al., 2012; Gray and Bradley, 2005; Ibrahim et al., 2018), associated with slower development and reduced growth (Bajgar et al., 2015; Diamond and Kingsolver, 2011; DiAngelo et al., 2009) and can also lead to an extensive loss of energy reserves during chronic infection (Bajgar and Dolezal, 2018; Dionne et al., 2006). The immune response may also compete with another energy consuming process, reproduction. Especially during the acute phase of infection, a decline in fecundity has been observed

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Abbreviations

Ado	adenosine
AMPs	antimicrobial peptides
JNK	c-Jun N-terminal kinase
Dilps	*Drosophila* insulin-like peptides
Grnd	Grindelwald
GBP	growth-blocking peptide
Imd	Immunodeficiency
InR	insulin receptor
LDH	lactate dehydrogenase
OXPHOS	oxidative phosphorylation
PPP	pentose phosphate pathway
PDH	pyruvate dehydrogenase
PDK	pyruvate dehydrogenase kinase
TCA	tricarboxylic acids
Upd	Unpaired

(Bashir-Tanoli and Tinsley, 2014; Gray and Bradley, 2005; Howick and Lazzaro, 2014; McKean et al., 2008; Nystrand and Dowling, 2014). On the other hand, active reproduction may negatively affect resistance to infection (McKean et al., 2008; Siva-Jothy et al., 1998).

Another process, which may compete with the immune response for energy, is the acute stress response (fight-or-flight). They both represent life-preserving reactions and they share certain attributes – they are energy consuming processes and they are associated with a release of energy required for the reaction. Therefore, transient acute hyperglycemia as a marker of energy release is present during both reactions. However, the actual use of energy differs profoundly. In contrast to immunity, the overall metabolic rate during fight-or-flight increases because tissues, such as muscles and the nervous system, which are not negligible on the whole organismal level, need to process the released energy to fight or escape. Stress induces the production of the stress hormones octopamine and adipokinetic hormone, which cause the release of energy required in muscles and the nervous system (Gäde and Auerswald, 2003; Verlinden et al., 2010). These hormones reduce resistance, which may be explained by their activating effects on systemic metabolism, which is not favorable for the immune response (Adamo, 2017; Adamo and Parsons, 2006; Goldsworthy et al., 2005; Ibrahim et al., 2018). This is in agreement with the observation that chronic exposure to predators, which increases levels of stress hormones and metabolic rates, leads to a chronic reduction in disease resistance (reviewed in Adamo, 2017). On the other hand, the immune response increases susceptibility to predation stress (Otti et al., 2012).

The regulation of resource distribution during development and the maintenance of various systems within the organism as well as during the activation of the stress response is a fundamental theme in the evolution of organisms. The trade-offs between different systems have been beautifully demonstrated by the artificial selection of increased resistance to parasitoids (Kraaijeveld and Godfray, 1997). The

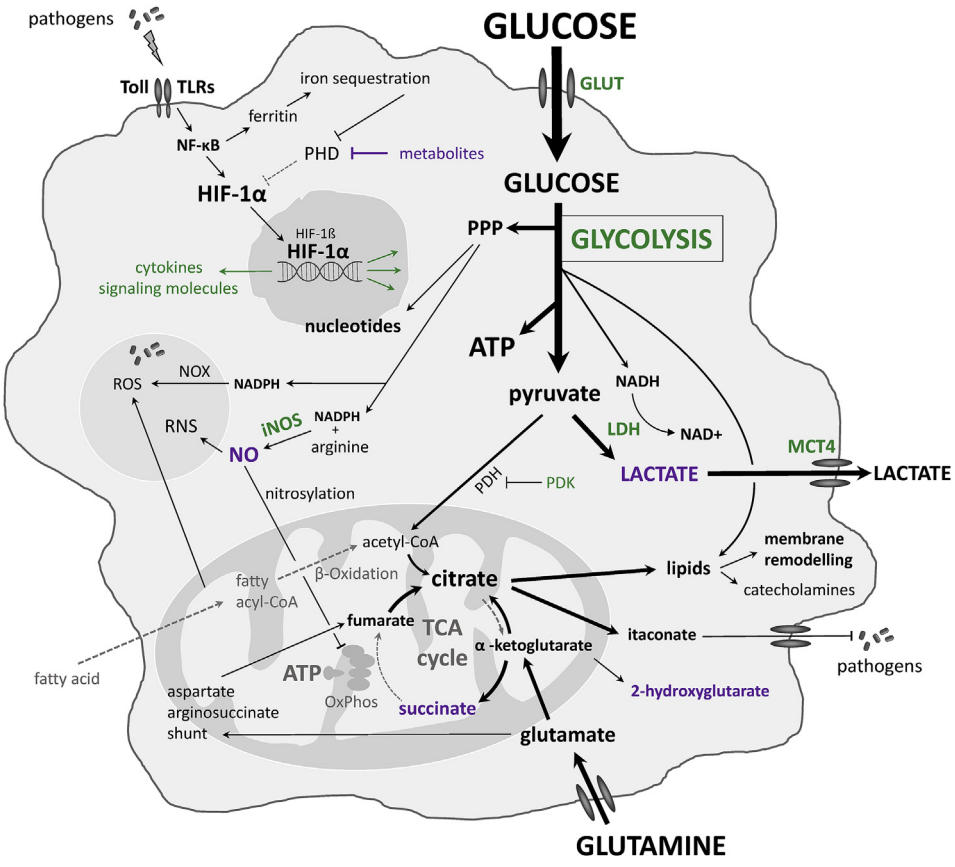

Fig. 1. Metabolic changes in the activated macrophage based on studies of mammalian cells. Grey arrows and letters represent pathways and metabolites that are important in the quiescent immune cell but are rather suppressed in the activated immune cell. Black arrows and black/colored letters represent enhanced pathways, metabolites and enzymes in the activated immune cell. Activation of the Toll-like receptors and NF-κB signaling leads to stabilization of HIF-1α (by the ferritin-mediated inhibition of prolyl hydroxylase dehydrogenase - PHD). The stabilized HIF-1α works as a master switch, which promotes a glucose uptake and increases expression of several glycolytic genes. The green color shows the targets of activated HIF-1α. ATP is generated by increased glycolysis, which also feeds glucose carbons into the pentose phosphate pathway (PPP) for a production of nucleotides and NADPH. By pyruvate dehydrogenase kinase (PDK)-mediated inhibition of pyruvate dehydrogenase (PDH) and by simultaneous increase of lactate dehydrogenase (LDH) and lactate transporter MCT4, HIF-1α diverts pyruvate from mitochondrial metabolism. The mitochondrial metabolism is substantially changed in activated immune cells. Inflammatory macrophages largely reduce OXPHOS via the nitrosylation of the electron transport chain by iNOS-generated NO and by itaconate produced from citrate. In inflammatory macrophages, the TCA cycle is broken when citrate is not converted to isocitrate but is primarily used for fatty acid synthesis, membrane biosynthesis, and the production of antimicrobial metabolite itaconate. When pyruvate is not fed into the TCA cycle and/or the TCA cycle is broken at the citrate step, glutamine is anaplerotically metabolized in the mitochondria to replenish TCA intermediates. It is first converted to glutamate, which is used in mitochondria to produce α-ketoglutarate and either succinate or citrate in a reversed mode, reductively carboxylated by NADPH-dependent isoforms of isocitrate dehydrogenase. Citrate can also be produced, using glutamate, through an aspartate-argininosuccinate shunt. Purple color shows metabolites that increase due to the HIF-1α-reprogrammed metabolism and which further stabilize HIF-1α (by inhibiting PHD) to reinforce changes induced by initial stabilization of HIF-1α. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

increased resistance was associated with an increased number of immune cells and thus with increased maintenance costs, which decreased, on the other hand, the competitiveness of larvae in obtaining food (Kraaijeveld et al., 2001).

2. What are the energy needs of immunity?

The immune system of insects can be divided into the cellular and the humoral components, which are however interconnected at many levels. Insects occupy a wide variety of ecological niches where they inevitably face trauma and frequent attack by pathogens. After a pathogen crosses the first physical immune barriers, integument, or the gut peritrophic membrane, immune cells are usually the first to react to it. They can phagocytose the invading pathogen or they can initiate nodulation, netosis, or the encapsulation response associated with melanization (Rosales, 2017). During nodulation, hemocytes form multicellular aggregates, entrapping groups of microorganisms, and ultimately performing melanization (Satyavathi et al., 2014). It seems that insect hemocytes can also release nucleic acids to facilitate the extracellular trapping of bacteria (Altincicek et al., 2008) similar to mammalian NETosis (Branzk and Papayannopoulos, 2013). Larger objects such as parasitoid eggs, which are too large to be phagocytosed, are encapsulated in the multilayered capsule of hemocytes and destroyed by melanization. This may involve the proliferation and differentiation of specialized cells known as lamellocytes. These cellular responses are accompanied by humoral processes such as the above mentioned melanization, which requires the activation of prophenoloxidases transforming them into phenoloxidases, and acts on tyrosine, forming melanin in multiple steps. Another humoral response involves the production of various antimicrobial peptides (AMPs), which are produced mainly in the fat body and usually follow the cellular response several hours later.

The activation of cellular immunity leads to a metabolic switch within the immune cells, which become dependent on a massive supply of glucose and glutamine (see section 3 below). The energy costs of the humoral arm of immunity are associated with the synthesis of AMPs, whose expressions might increase even several hundred times during the immune response. The question is whether the induced synthesis of numerous AMPs and other immune molecules among all other synthetic processes normally happening in the fat body represents a significant cost to the overall metabolism (Wagner, 2005). For example, flies overexpressing Drosomycin have reduced glycogen and triglyceride stores and reduced activity (Rera et al., 2012) suggesting that the induced expression of AMPs might indeed represent an energy burden upon the organism. In addition, the induction of AMPs expression is directly linked to the suppression of anabolism in the fat body through the switching of MEF2 (Clark et al., 2013). However, the fat body plays a dual role in which it expresses AMPs on the one hand, but on the other hand also provides energy to the rest of the organism, including cellular immunity. The observed metabolic costs thus might be primarily associated with the energy-demanding cellular immunity; it is hard to separate the metabolic costs of the cellular and humoral arms due to this dual role of the fat body. It may also be hard to estimate metabolic costs of the other humoral part of immunity, the melanization cascade, which is often again linked with actions of immune cells. Prophenoloxidases are constitutively present prior to defense activation, so the metabolic costs of mounting the melanization response are mainly associated with the depletion of the amino acid tyrosine (Chambers et al., 2012).

3. Cellular immunity activation leads to a metabolic reprogramming resembling the Warburg effect

3.1. Warburg effect in immune cells is based on studies of mammalian immunity

To understand the metabolic needs of cellular immunity, we must look at mammalian immune cells studies, which describe the process of metabolic reprogramming with sufficient depth (summarized and described with additional details on Fig. 1). However as described below, it is likely for the most part to also be valid for insect cells. As shown on Fig. 1, quiescent immune cells, awaiting immune stimulation, use glycolysis for the production of pyruvate, which enters the mitochondria and is converted into acetyl-CoA. Acetyl-CoA, which is also produced by the β-oxidation of fatty acid, is used in the tricarboxylic acids (TCA) cycle linked to oxidative phosphorylation (OXPHOS) to produce ATP by the most efficient means – theoretically up to 38 ATP molecules are generated per one molecule of glucose. Glycolysis and β-oxidation are thus linked to active OXPHOS and primarily used for effective ATP production to cover the basal maintenance of quiescent immune cells (reviewed in Palsson-McDermott and O'Neill, 2013). Although this is a very efficient metabolism for energy generation, it is too slow for ATP generation during the immune response. Upon immune stimulation, the immune cells switch from this state of low nutrient uptake to the metabolism optimized to a rapid production of ATP and a large amount of newly-synthesized molecules, which are required to mount the immune response. ATP is primarily produced by glycolysis, ineffectively (merely 2 ATP molecules per glucose) but much faster compared to the glycolysis-TCA-OXPHOS axis. Glucose carbons are also used to a much greater extent for the production of new macromolecules, required for the functioning of the activated immune cell, not being lost as CO_2 in OXPHOS. The pentose phosphate pathway (PPP) branches off from glycolysis, generating ribose for nucleotides and NADPH for the production of reactive oxygen species (Bergin et al., 2005; Rybicka et al., 2010). Pyruvate is converted to lactate to regenerate NAD+ from NADH by lactate dehydrogenase (LDH). Lipids are used for a dynamic remodeling of the cellular membrane and for the synthesis of eicosanoids and other lipid based metabolites in lipid bodies (Péan et al., 2017; Remmerie and Scott, 2018).

Metabolic changes in inflammatory immune cells thus resemble a situation where cells prefer glycolysis over OXPHOS even with sufficient oxygen supply, the process known as the Warburg effect. This metabolic adaptation was originally described for yeast and cancer cells (Warburg, 1925), but recently found also in mammalian immune cells in their proinflammatory state (Mills, 2015) and in rapidly proliferating cells (Burns and Manda, 2017). The mitochondrial metabolism is substantially changed in activated immune cells; pyruvate is diverted from the TCA cycle, which is broken at the citrate step and glutamine is anaplerotically metabolized in the mitochondria to replenish TCA intermediates, becoming thus another important metabolite for activated immune cells (Jha et al., 2015). In summary, the activation of the immune cell is associated with massively increased glycolysis (feeding PPP, lipid synthesis, and resulting in lactate production) and the rewired mitochondrial metabolism (broken TCA cycle and suppressed OXPHOS), which make the cell dependent on high doses of glucose and glutamine (Van den Bossche et al., 2017).

3.2. Metabolic reprogramming is present also in insect immune cells

Although the metabolic reprogramming of activated immune cells is studied mostly in mammalian systems and is much less studied in insects, the Warburg effect has also been described in insects both in normal proliferation and cancer (Herranz and Cohen, 2017; Slaninova et al., 2016; Tennessen et al., 2014; Wang et al., 2016) as well as in activated immune cells. For example, the activation of phagocytic cells of *Blaberus* was associated with changes resembling the Warburg effect

(Anderson et al., 1973). The transcriptome profiling of activated hemocytes of mosquitos, fruit flies, and tobacco budworms also reveals changes associated with the increased expression of glycolytic genes and LDH (Bartholomay et al., 2004; Choi et al., 2012; Irving et al., 2005; Johansson et al., 2005; Pinto et al., 2009; Shelby et al., 2012). We have shown that the proliferation and differentiation of lamellocytes during the parasitoid infestation of *Drosophila* larvae were associated with a hemocyte-specific increase in the expression of glycolytic genes, accompanied by increased glucose consumption (Bajgar et al., 2015) and the production of lactate (Fig. 2 and Strasser, 2016). Although it is clear that various insect immune cells significantly increase glucose consumption, glycolysis and lactate production upon activation, further detailed characterization of metabolic changes is necessary to bridge the gap between insect and mammalian studies.

3.3. Myc and hypoxia inducible factor 1α induce the metabolic reprogramming, both in insects and mammals

The above described complex reprogramming of many metabolic pathways, which supports the activated immune functioning of the cell, requires a coordinated change of expression and the activity of hundreds of metabolic enzymes. It is then adaptive to have a master regulator, quickly reacting to the immune activating signals and triggering the whole complex reprogramming (Metallo and Heiden, 2013). The metabolic switch in proliferating immune cells is connected to the activation of Myc, as has been shown, for example, for proliferating T lymphocytes in mammals (Gnanaprakasam and Wang, 2017; Wang et al., 2011). In insects, Myc was shown to be strongly upregulated in highly proliferative *hopTum-l* hemocytes (Anderson et al., 2017). The metabolic changes of activated macrophages and the subsequent pro-inflammatory phenotype are dependent on Hypoxia inducible factor 1α (HIF-1α). Contrary to the proliferating precursors of macrophages, the pro-inflammatory stimulation of macrophages in mammals suppresses Myc while engaging HIF-1α (Gnanaprakasam and Wang, 2017).

The role of HIF-1α was originally described during hypoxia, where it is responsible for changes of cellular metabolism induced by the lack of oxygen which is otherwise necessary for OXPHOS in mitochondria (Wenger et al., 2005). The signaling pathway, activated in response to hypoxia in the insect, is conserved and mediated by a homolog of HIF-1α, known in *Drosophila* as *Similar,* or *Sima* for short (Lavista-Llanos et al., 2002). Without hypoxia, HIF-1α is continuously translated, followed by an immediate hydroxylation by enzyme prolyl hydroxylase dehydrogenase (PHD), which marks HIF-1α for degradation; in *Drosophila*, the respective enzyme is called Fatiga and mutation in the *Fatiga* gene has been shown to lead to an accumulation of the Sima protein in normoxia (Centanin et al., 2005). HIF-1α stabilization leads to nuclear translocation, heterodimerization with HIF-1β (Tango in flies), and the activation of the specific transcriptional program of genes under the control of HRE elements (Dengler et al., 2014; Romero et al., 2008). HIF-1α thus works as a central transcription factor regulating the expression of many metabolic genes leading to the complex rewiring of cellular metabolism.

Various other inputs besides the lack of oxygen may lead to a stabilization of HIF-1α, including immunostimulatory signals, linking the activation of immune cells with metabolic changes. In mammals, activation of the Toll-like receptors and NF-κB signaling results in an increased expression and stabilization of HIF-1α (Jung et al., 2003; Siegert et al., 2015). This mechanism of normoxic stabilization and the expression of HIF factors by NF-κB signaling has also been described in *Drosophila*. Bandarra et al., (2015) and Uden et al., (2011) showed that HIF-1α can be induced by both Toll and Imd-induced NF-κB signaling, either genetically or by infection. Bandarra et al. (2015) showed that the *Sima/Tango* induction during infection is dependent on Imd/IKK/Rel and that the knockout of *Sima* resulted in increased mortality during *Serratia marcescens* infection. Uden et al. (2011) showed that *Sima/Tango* are activated by the overexpression of *Drosophila* NF-κB factor *Dorsal* or by the *cactus* mutation, both mimicking activated Toll signaling.

4. Effects of immune response activation on systemic metabolism

As described above, activated immune cells undergo a metabolic switch associated with increased glycolysis and glucose uptake. The increased demands of activated immune cells for glucose raise a question of the impact on overall metabolism. The impact likely depends on the extent of the response. For example, using radioactively-labeled glucose, we were able to quantify the glucose demands of the activated immune cells during the parasitoid attack – glucose consumption by immune cells raised from 11% to 27% of total glucose (Bajgar et al., 2015). In such cases, immune activation can lead to a significant suppression of the metabolism in the rest of the organism during infection. The generation of energy reserves (triglycerides and glycogen) during larval development was suppressed by wasp infection (Bajgar et al., 2015) and, in adult flies, the reserves decreased during bacterial infection, providing energy to phagocytes (Bajgar and Dolezal, 2018). Larval development slowed down, resulting in slower imaginal disc growth and in developmental delay (Bajgar et al., 2015). The overall metabolism was documented to be suppressed by various types of infection (Chambers et al., 2012; Schlenke et al., 2007). These results demonstrate that the activation of the immune system leads to a systemic metabolic switch redirecting the energy/nutrients flow from growth/storage to the activated immune system.

The fat body plays a dual role in such energy redirection since it is both an immune and a metabolic organ at the same time. The fat body is important for storage and overall metabolic homeostasis on the one hand, but it is also responsible for the humoral immune response on the other. Therefore, the switch from anabolism to immunity also operates within the fat body itself, which is beautifully demonstrated by the dual

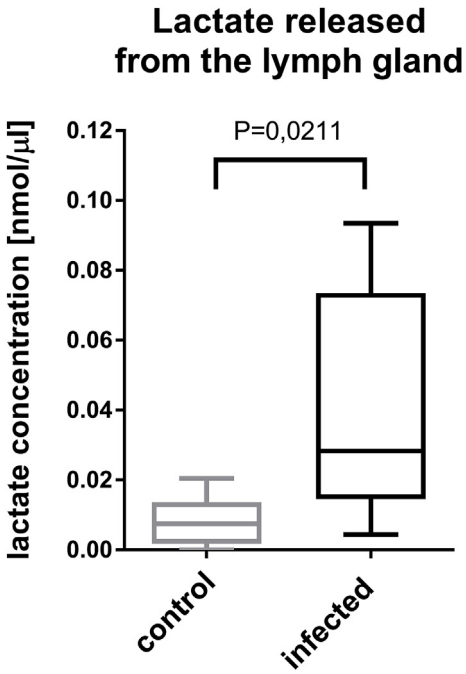

Fig. 2. Lactate production is increased in the lymph glands of *Drosophila* larvae infected by parasitoid wasps. Six lymph glands were dissected from larvae of *Drosophila melanogaster* infected with parasitoid wasp *Leptopilina boulardi* 6 h post-infection (black) and from uninfected control (grey). Lymph glands were incubated *ex vivo* for 50 min in 20 μl of PBS supplemented with 200 μM glucose and 6 mM trehalose. Lactate was determined in supernatant by Lactate Assay Kit (Sigma Aldrich). The difference was tested by Welch's *t*-test (n = 8). Further details can be found in (Strasser, 2016).

role of MEF2. Phosphorylated MEF2 activates the expression of genes involved in anabolic processes, however infection leads to its dephosphorylation, thus lowering anabolic processes and at the same time dephosphorylated MEF2 activates AMPs expression (Clark et al., 2013). Immune system activation is, therefore, linked to the suppression of systemic metabolism and to a redirection of energy flow from the anabolic and non-immune processes towards immunity. Since immune cells require an increased supply of nutrients upon their activation, it seems logical that they obtain nutrients by suppressing their consumption by other processes.

It is not easy to test the importance of such suppression for the effectivity of the response since the manipulations of inducers of metabolic changes often simultaneously affect immune induction. These processes are intricately linked and regulators often suppress metabolism and induce immune response at the same time (Clark et al., 2013; DiAngelo et al., 2009). It is then hard to say whether the resulting reduced resistance is due to the lack of metabolic switch or due to the lack of immune induction. When the processes are manipulated throughout the development, it is hard to say whether the effects are caused by the state of metabolism before the immune response starts, for example by low energy stores as reported in (Clark et al., 2013; Yang and Hultmark, 2017). However, when the inducible knockdown of glycogen phosphorylase (i.e. merely a metabolic manipulation blocking the release of glucose from glycogen) was performed just prior to infection, the glycogen levels in manipulated flies were comparable to the control and the glycogen breakdown was suppressed only upon infection (Bajgar and Dolezal, 2018). In such a case, the reduced resistance to *Streptococcus pneumoniae* in flies with such manipulation clearly demonstrated the importance of the metabolic switch to the effectivity of the immune response.

5. Adenosine mediates the privileged behavior of the immune system

The importance of the systemic metabolic switch for immune response can be demonstrated in the *adoR* mutant with a deficiency in adenosine (Ado) signaling (Dolezal et al., 2005). The *adoR* mutation allows normal development with no effect on metabolism under normal conditions (Bajgar et al., 2015; Bajgar and Dolezal, 2018). However, extracellular Ado mediates the systemic metabolic switch via AdoR during infection and the switch does not occur or is severely delayed in the *adoR* mutant. The mutant simply keeps developing as if there were no infection (Bajgar et al., 2015) and the hyperglycemia associated with glycogen breakdown (markers of the switch) is suppressed (Bajgar and Dolezal, 2018). This inability of the *adoR* larvae or flies to reroute energy from storage and growth towards immunity results in a markedly decreased resistance against parasitoid and bacterial infections. These results demonstrate that the Ado-mediated systemic metabolic switch, associated with hyperglycemia at the expense of stores and with an overall suppression of the metabolism, supplies immune cells with the required energy either for their rapid proliferation and the differentiation of lamellocytes and effective encapsulation of parasitoid eggs, or for their effective phagocytosis of bacteria.

Ado is not only an important metabolite but it also serves as an important stress signaling molecule. It is formed during intracellular metabolic stress when ATP levels drop and AMP increases. Ado is then formed from AMP and is released from a stressed cell to inform the surrounding tissues or the whole organism of the stress (Antonioli et al., 2008). It can also be formed upon tissue damage from leaking ATP by ectoenzymes converting ATP to ADP, AMP, and Ado (Fenckova et al., 2011). A common response at the organismal level to the increased level of Ado is a slowing down of metabolism to overcome the stress. This Ado role is very ancient, being present in “social bacteria” (Shimkets and Dworkin, 1981) to vertebrates (Buck, 2004). The Ado role in the systemic metabolic switch during infection perfectly fits into this ancient role. Interestingly, knocking down the transporter of Ado ENT2 specifically in hemocytes demonstrated that it is actually immune cells themselves that produce this important regulator of systemic metabolism (Bajgar et al., 2015). Therefore we can say that the activated immune system becomes privileged, hierarchically placed above other systems, and the immune cells release Ado to usurp energy from the rest of the organism (Fig. 3).

The privileged behavior of immunity, mediated by Ado, represents an experimental verification of a theoretical concept of the “selfish immune system”, first articulated by Rainer Straub (2014) inspired by the “selfish brain theory” (Peters et al., 2004). These concepts put brain and immune system hierarchically above the rest of the organism in allocating energy. During the fight-or-flight response or trauma/infection, the organism depends vitally on either the central nervous system or the immune system and thus these organs are privileged in energy allocation. According to Straub, insulin resistance, leading to the lower consumption of glucose and hyperglycemia, is a physiological means for the brain or immune system to usurp energy from the rest of the organism during acute stress because the brain and immune cells themselves do not become insulin resistant. Chronic insulin resistance, caused by chronic inflammation or by chronic mental activation, then leads to various pathologies such as diabetes, obesity, metabolic syndrome, or chronic inflammatory diseases.

Such Ado effects clearly demonstrate that the global metabolic switch is crucial for an effective immune response. How this global effect is achieved by Ado signaling in *Drosophila* is not well understood. Ado modulates fat body metabolism, for example the expression of glycogen synthase/phosphorylase (Bajgar and Dolezal, 2018); AdoR is expressed in imaginal discs, the brain, and the ring gland (Dolezelova et al., 2007) and thus it could influence the target tissues directly or via the production of hormones. Hyperglycemia and growth/storage

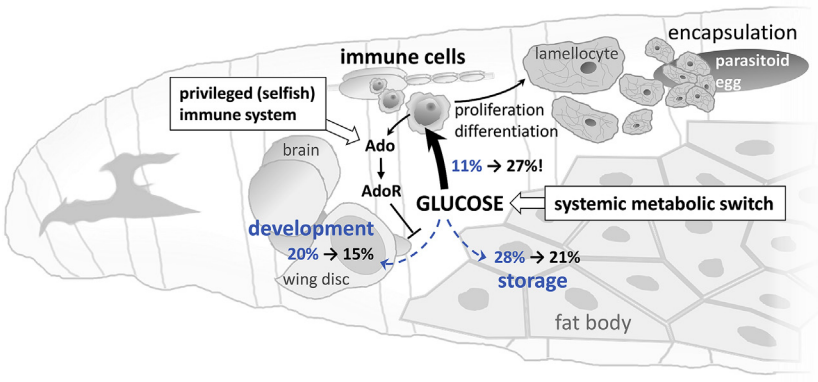

Fig. 3. Adenosine-mediated systemic metabolic switch during parasitoid wasp infection of *Drosophila* larva. Parasitoid egg is first recognized by circulating hemocytes that activate the proliferation and differentiation of specialized immune cells called lamellocytes. Lamellocytes eventually encapsulate and destroy the egg. Activated lamellocyte precursors increase glycolysis and glucose consumption. They usurp glucose from the rest of the organism by releasing adenosine (Ado). The extracellular Ado inhibits the metabolism of other tissues by signaling via the adenosine receptor AdoR and this slows down the larval development. By releasing Ado, which induces a systemic metabolic switch, the immune system becomes privileged over the rest of the organism. Percentage shows changes in overall glucose consumption by different systems from uninfected (blue) to infected (black) state (based on (Bajgar et al., 2015)). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

suppression mediated by Ado resembles a common response observed with different types of infection (Bajgar et al., 2015; Bajgar and Dolezal, 2018; Dionne et al., 2006; Ibrahim et al., 2018). Since insulin signaling is generally pro-growth/pro-storage, the systemic metabolic switch observed during infection is most likely associated with attenuation of insulin signaling, as observed for example in (Dionne et al., 2006). Reduced insulin signaling during the immune response seems to be at the core of the immune-metabolic interaction. In humans, insulin resistance-causing pro-inflammatory cytokines are believed to mediate the systemic metabolic switch (Straub, 2014). Pro-inflammatory cytokines-induced insulin resistance as a means to re-route energy towards immunity in mammals might have parallels in the insect world.

6. Molecular regulations of metabolism during immune response

Various research work, described in detail below, leads us to the following overall picture (Fig. 4) of the molecular regulation of the systemic metabolism during the immune response. Without immune stimulation, insulin signaling allows energy/nutrients to be used for storage, growth, and other non-immune processes. The fat body uses dietary nutrients in part to generate fat and glycogen stores, and releases other amounts for the needs of other tissues. The detection of pathogens activates the immune processes in immune cells and the fat body. The activation of immune cells leads to their internal metabolic switch (Warburg effect) associated with increased energy consumption. Activated immune cells release various signals and some of them suppress systemic metabolism. Others send the information to the fat body and mediate the switch from anabolism to humoral immunity. Many of these proinflammatory signals affect insulin signaling at various levels, from the release of insulin-like peptides (in *Drosophila* known as Dilps such as *Drosophila* insulin-like peptides), to blocking insulin signaling downstream of the insulin receptor (InR) in target tissues. Toll, Imd, Eiger/TNF-α, JNK, and JAK-STAT are the most important signals/signaling cascades for the immune response. They are activated by various immune stimuli and besides being crucial to the induction of immune processes, they also affect metabolism at various levels. Therefore, they can be seen as the key players in immunometabolism. Toll signaling, which is predominantly activated by G-positive bacteria or fungi, was shown to reduce insulin signaling in the fat body. Imd (Immunodeficiency) signaling, activated mainly by G-negative bacteria, induces an MEF2-mediated switch from anabolism to immunity in the fat body. JNK (c-Jun N-terminal kinase) is a master regulator of metabolism during various types of stress. It can be activated by both Eiger and Imd and it can possibly mediate the Imd-induced MEF2 switch in the fat body, it activates FOXO in various tissues and it reduces Dilps expression in insulin-producing cells. JAK-STAT is activated by many different pathogens, including viruses, bacteria, and parasitoids, and it has been shown to interact with insulin signaling in muscles. There is probably a certain degree of redundancy among these signals but they might also be engaged with different strengths and with different impacts on tissues, fine tuning thus both metabolic and immune responses according to the type of infection. Possible molecular interactions are depicted in Fig. 5 and described in details below.

6.1. Toll and insulin signaling

DiAngelo et al. (2009) clearly showed that bacterial/fungal infection reduces insulin signaling at the level of the Akt phosphorylation in the fat body via Toll activation. Imd, predominantly activated by G-negative bacteria, leads to JNK activation in the fat body but it does not affect the Akt phosphorylation. However, G-negative bacteria also activate Toll signaling in the fat body, leading to the suppression of Akt phosphorylation, suggesting that this metabolic regulation by Toll is not restricted to G-positive bacterial or fungal infection but also includes those associated with the activation of the Imd pathway. The activation of Toll in the fat body reduces triglycerides stores and has a global impact on organismal growth, demonstrating that immune activation in the fat body can lead to a systemic metabolic switch via the reduction of insulin signaling. This is further supported by (Roth et al., 2018) demonstrating that Toll-induced growth suppression can be rescued by the expression of the phospho-mimicking version of Akt in the fat body. Such research work thus quite clearly demonstrates that infection can lead to an acute suppression of insulin signaling in the fat body and the global suppression of growth. However, how important this suppression is for the effectivity of the immune response was not tested. The work of Libert et al. (2008) may support the role of the suppression of insulin signaling for the effectivity of the immune response when mutation in InR substrate Chico actually increased the survival of *Pseudomonas aeruginosa* and *Enterococcus faecalis* infections. However, the resistance was tested in the *chico* mutant when its function was lacking throughout the whole development and therefore the effect on resistance cannot simply be attributed to insulin signaling suppressed by infection. *Chico* mutant flies might simply be better prepared for coming infection, for example by the pre-existing expression of AMPs due to lowered insulin activity and increased FOXO activation of AMPs as reported by Becker et al. (2010). Toll activation was also shown to block the S6K-mediated phosphorylation of MEF2, leading to a switch from anabolism to immunity in the fat body (Clark et al., 2013). This work, together with the work of DiAngelo et al. (2009), demonstrates that Toll and Imd

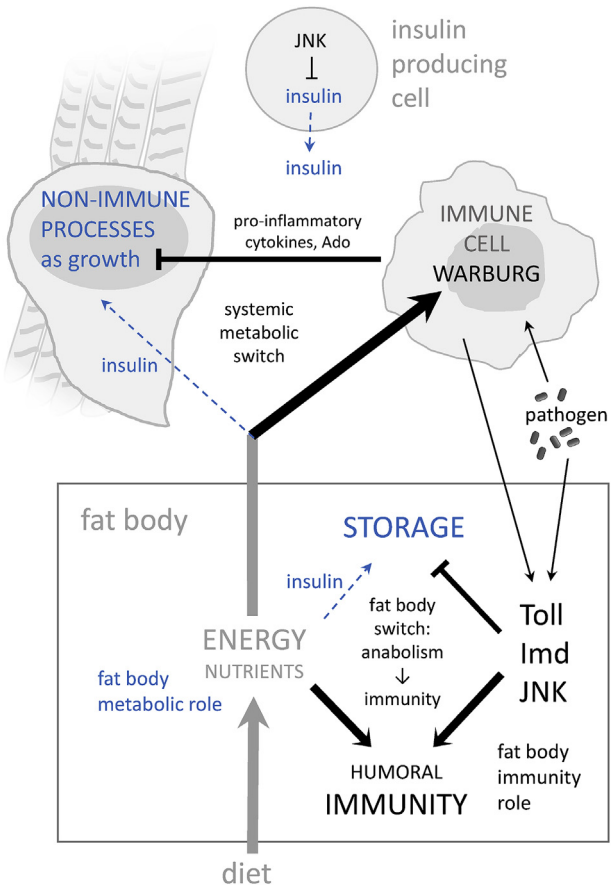

Fig. 4. Overall scheme of change of energy flow during immune response. Normally (blue), insulin signaling directs dietary nutrients towards storage and non-immune processes, such as growth. During immune response (black), immune signaling, as Toll, Imd and JNK, activates humoral immunity in the fat body while reducing insulin signaling, diverting energy flow from storage to humoral immune response and releasing energy for the needs of immune cells. Activated immune cells alter their own metabolism (similar to Warburg effect) and release signals that suppress energy consumption by non-immune processes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

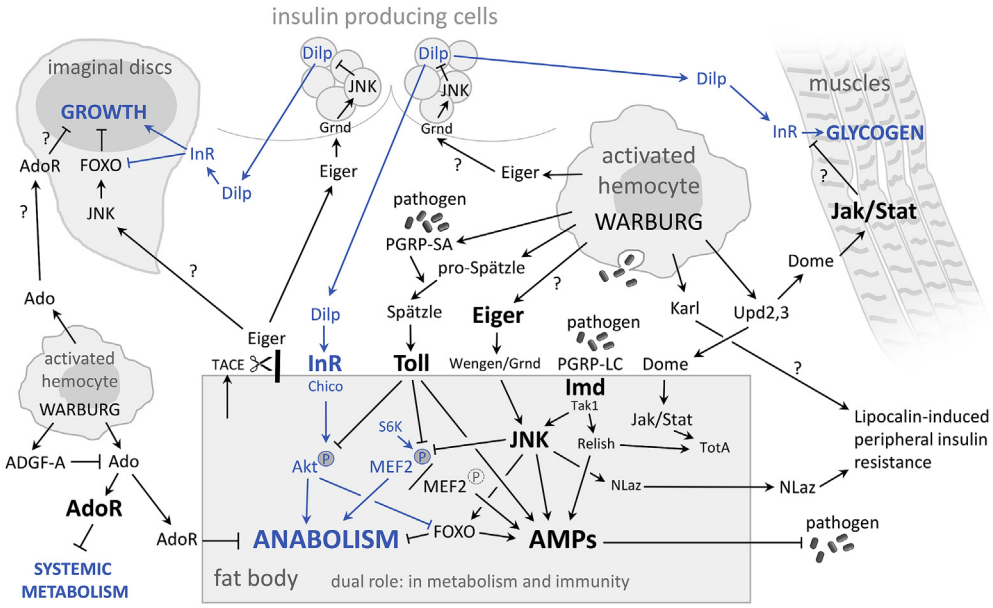

Fig. 5. Scheme of possible molecular interactions between immune signaling and metabolism. Signaling during an uninfected state is shown in blue and during infection in black. Arrows represent a known induction (although not necessarily tested for the suggested immunometabolic interaction), bars represent a known suppression, and arrows/bars with question marks represent suggested induction/suppression. See the text for a detailed description of the depicted interactions. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

signaling, the core immune activators, are directly linked at the molecular level to a switch redirecting nutrients away from anabolic processes. This inevitable switch away from anabolism associated with immune activation means that the immune response is hardwired with the expected metabolic costs of the response in the genetic program.

PGRP-SA and Spätzle are crucial to Toll activation in the fat body. They are expressed by hemocytes and the expression increases upon infection (Boutros et al., 2002; Irving et al., 2005; Shia et al., 2009). Therefore, hemocytes are somehow involved in setting up the magnitude of this crucial activation – the magnitude is determined by the number of bacteria, but also by the pool of molecules able to detect the pathogen (PGRP-SA) and by the molecules mediating the signal (Spätzle). Since activation of Toll leads not only to AMPs expression, but also to the suppression of insulin signaling, it can be said that hemocytes, by expressing PGRP-SA and Spätzle, play a role in the activation of humoral immunity associated with a metabolic switch. In this regard, PGRP-SA and Spätzle resembles the pro-inflammatory cytokines of mammals released by immune cells and causing insulin resistance.

6.2. Eiger, Imd and JNK

Another important signaling for antibacterial response is the Imd pathway, which is primarily associated with the response to G-negative bacteria. Similarly to Toll, Imd was associated with the MEF2-mediated switch from anabolism to immunity (Clark et al., 2013). Although it is not clear how, the likely explanation for the Imd-MEF2 interaction is TAK1-dependent JNK activation (Boutros et al., 2002; Delaney et al., 2006). JNK (c-Jun N-terminal kinase) signaling can influence metabolism and immunity in many different ways and in many different tissues. Besides being activated by Imd, it is also activated by another important pro-inflammatory cytokine Eiger. Eiger is a TNF-α orthologue in insect (Igaki et al., 2002; Tang et al., 2019), which has also been shown to influence both the immune response and metabolism, representing thus another potential link between immune activation and systemic metabolism. TNF-α causes insulin resistance in mammals when the administration of TNF-α can induce cachexia (Moldawer and Copeland, 1997), and the blockade of TNF-α in rats with either cancer or sepsis prevents muscle wasting (Combaret et al., 2002). In *Drosophila* larvae, a low-protein diet induces Eiger secretion from the fat body into the hemolymph, Eiger binds to insulin-producing cells through the Grindelwald (Grnd) receptor, which acts through JNK to inhibit Dilp2/5 mRNA expression and reduces larval growth (Agrawal et al., 2016). Under high-sugar diet conditions, Grnd signaling in the fat body induces a lipocalin NLaz-mediated peripheral insulin resistance by inducing NLaz expression via JNK in the fat body (Agrawal et al., 2016; Hull-Thompson et al., 2009; Pasco and Léopold, 2012). Eiger is thus able to reduce insulin signaling either by lowering Dilps expression remotely in insulin-producing cells or by inducing the expression of lipocalin NLaz.

Eiger was shown to be expressed upon immune stimulation both in hemocytes (Johansson et al., 2005) and in the fat body (Mabery and Schneider, 2010) and was shown to influence the immune response to various infections (Bastos et al., 2017; Brandt et al., 2004; Schneider et al., 2007; Tang et al., 2019). Eiger signaling is required for resistance to extracellular pathogens but may cause complications to the host when infected with intracellular pathogens (Brandt et al., 2004; Schneider et al., 2007). Eiger is required for an effective phagocytosis (Schneider et al., 2007), which could explain the resistance defect regarding extracellular pathogens. Although it is not known why Eiger is important for phagocytosis, one possible explanation is the effect of Eiger on the systemic metabolism being similar to that of AdoR, namely that the AdoR-mediated metabolic switch was shown to be crucial to effective phagocytosis (Bajgar and Dolezal, 2018). Likewise, some of the complications, the reduced survival rate of the host with intracellular infection, may be explained by the wasteful effects of Eiger on metabolism (Brandt et al., 2004; Schneider et al., 2007). In this light, an Eiger-induced systemic metabolic switch (Agrawal et al., 2016) would be required to mount an effective response, for example phagocytosis (Bajgar and Dolezal, 2018). However, it may become counterproductive in the case of intracellular pathogens which have escaped immune destruction, and removing Eiger would rather increase disease tolerance (Schneider et al., 2007) similarly to the blockade of TNF-α in rats with sepsis where it prevents muscle wasting (Combaret et al., 2002). Eiger-mediated effects during intracellular infection have been shown to be dependent on Eiger expressed in the fat body (Mabery and Schneider, 2010). Eiger released from the fat body has beens shown to suppress Dilp2 and Dilp3 expression via Grnd-activated JNK signaling in the insulin-producing cells (Agrawal et al., 2016). Similarly, Eiger released by infection from the fat body or hemocytes upon infection (Johansson et al., 2005; Mabery and Schneider, 2010) may suppress the expression of Dilps in the same way. Since Eiger activates JNK, the effects of Eiger are potentially much broader. JNK activates FOXO and induces insulin resistance in peripheral tissues, as in larval imaginal discs (Wang et al., 2005) and as mentioned above, it might also be

associated with the MEF2 mediated switch from anabolism to immunity in the fat body (Clark et al., 2013). It was shown that activating JNK increased the survival of *Pseudomonas aeruginosa* and *Enterococcus faecalis* infections (Libert et al., 2008) but the potential role of Eiger in metabolic regulation through JNK during immune response has yet to be tested.

A high-sugar diet activates JNK through Grnd in the fat body (Agrawal et al., 2016) which leads to the expression of lipocalin NLaz (Hull-Thompson et al., 2009) and NLaz-mediated peripheral insulin resistance. Although Imd activation in the fat body leads to JNK activation (DiAngelo et al., 2009), Hull-Thompson et al. (2009) showed that NLaz is not important for immune resistance. However, they used G-positive *E. faecalis* to test resistance, which might not lead to a strong activation of IMD-JNK-Nlaz in the fat body; it would be interesting to test the importance of NLaz with G-negative bacteria. Interestingly, they also showed that another lipocalin, Karl, was released from hemocytes and was important for an efficient immune response (Hull-Thompson et al., 2009); it is not clear what activates the secretion of Karl upon infection and whether or not it leads to peripheral insulin resistance similarly to NLaz.

6.3. JAK-STAT

JAK-STAT signaling activated by the Unpaired 3 (Upd3) cytokine in *Drosophila* can be seen as parallel to JAK-STAT activation by type 1 cytokines in mammalian systems, such as for example IL-6 (Vanha-aho et al., 2016; Woodcock et al., 2015). Yang et al. (2015) showed that the activation of JAK-STAT in muscles by hemocytes-derived cytokines Upd2 and Upd3 is required for an effective response against parasitoid wasp infection. Yang and Hultmark (2017) further showed that insulin signaling is reduced both in muscles and the fat body upon this type of infection. This effect of Upd3 cytokine is similar to the effect found by Woodcock et al. (2015) who showed that hemocyte-secreted Upd3 activates Jak-Stat signaling in muscles and the gut, which reduces insulin sensitivity. Although in this case, Upd3 was stimulated by a high-fat diet in adult flies, the potency of Upd3 derived from hemocytes to cause insulin resistance in muscles would nicely explain the results of Yang and Hultmark (2017) and would fit the suggested role of pro-inflammatory cytokine Il-6 in insulin resistance in mammals (Kim et al., 2013; Straub, 2014). Upd3 released from hemocytes upon infection could lower insulin sensitivity in muscles by activating JAK-STAT, lowering thus glucose consumption by muscles and leaving the required energy to hemocytes. Although Yang and Hultmark (2017) tried to explore the relationship of JAK-STAT and insulin signaling during wasp infection, genetic manipulations of both these pathways led to reduced feeding throughout the larval development, which affected the immune response but did not clarify the role of JAK-STAT in insulin signaling post-infection. Thus the role of Upd cytokines and JAK-STAT effects on insulin signaling during the immune response in *Drosophila* remain to be clarified.

(Agaisse et al., 2003) showed that bacterial infection can also trigger the hemocyte-specific expression of upd3 that was necessary for the JAK-STAT + Relish-dependent activation of the TotA-mediated immune response in the *Drosophila* fat body. However the knockdown of stat92E, the transcription factor that mediates JAK-STAT pathway activity, in the fat body did not affect triglycerides storage, suggesting that JAK-STAT does not modulate metabolism in the fat body (Rajan and Perrimon, 2012) and the metabolic role of JAK-STAT might be rather associated with muscles. JAK-STAT effects are quite complicated, having for example both pro-proliferative functions in imaginal discs earlier in development and anti-proliferative effects later in development (Mukherjee et al., 2005). Ectopic activation of JAK-STAT leading to the premature cell cycle arrest in the wing imaginal disc in third instar larva (Mukherjee et al., 2005) offers another possibility of how hemocyte-released Upd3 during infection (Agaisse et al., 2003; Yang et al., 2015) could lead to the redirection of energy by slowing down the development.

6.4. GBP

Although growth-blocking peptide (GBP) signaling through Methuselah-like receptor-10 was shown to influence both the immune response and metabolism (Sung et al., 2017), the role of GBP in this intersection remains unclear. GBP from the fat body increases expression of Dilps (rather an opposite effect to that described above) and this is more likely important for nutritional signaling (Koyama and Mirth, 2016; Sung et al., 2017). The effect of GBP on immunity might be rather associated with a direct effect of GBP signaling on hemocytes, inducing their spreading during activation (Sung et al., 2017; Tsuzuki et al., 2014). It was not distinguished whether the lower resistance associated with systemic Mthl10 knockdown was due to the hemocyte activation defect, or due to the expression of Dilps, or both (Sung et al., 2017).

6.5. Crosstalk and specificities of immune-metabolic pathways

Both Toll and Imd shift MEF2 activity from anabolism to immunity in the fat body, but only Toll reduces phosphorylation of Akt. Both G-positive and G-negative bacteria can activate Toll but G-positive bacteria and fungi are stronger inducers of Toll while G-negative bacteria predominantly activates Imd (DiAngelo et al., 2009; Lemaitre et al., 1997). So although the metabolic effects of Toll and Imd are partly redundant (effect on Mef2), different types of infection can probably differ in the metabolic response they induce. In addition, Eiger can further modulate the response of Toll, Imd, and JNK. Tang et al., (2019) showed that while Eiger can enhance Toll-mediated responses, it actually reduces the Imd-Relish arm, and while the full melanization response to G-negative bacteria requires Eiger/JNK, there is no effect of Eiger on the melanization response to G-positive bacteria. Similarly, Schneider et al. (2007) showed that *eiger* mutants produced more Imd-stimulated AMPs. Although metabolic effects were not analyzed in these works, modulating the Toll-Imd-JNK immune response most likely also affects Toll-Imd-JNK metabolic responses, suggesting a fine-tuning according to the type of infection. Parasitoid wasp infections differ in many aspects from the immune response induced by bacterial challenges and this is also probably reflected in metabolic modulation. JNK does not seem to be strongly activated by wasp attack (Schlenke et al., 2007). While co-activation of Toll and EGFR signaling in the lymph gland is important for the response to parasitoid wasp infection (Louradour et al., 2017), Toll is not required in the fat body for an effective immune response against parasitoid wasps (Schmid et al., 2014) although it is activated there (Schlenke et al., 2007). JAK-STAT is not strongly activated in the fat body by parasitoid infection and it is not required for an effective response (Yang and Hultmark, 2016). While Toll and JNK activation might not play a strong role, the release of Ado as well as Upd2 and Upd3 from hemocytes and Upd-activation of JAK-STAT signaling in muscles might have the most important roles during this type of infection. However, bacterial infection also leads to Ado and Upd3 release, being important during the immune response to this type of infection (Agaisse et al., 2003; Bajgar and Dolezal, 2018), suggesting that these signals are not specific to a response to parasitoids. There are not many studies primarily focusing on the metabolic role in the immune response and each usually focuses on one or a few specific types of infection as viral, bacterial (and often only a particular strain) or parasitoid. To get a clearer picture, it will be necessary to analyze particular signaling cascades or processes and compare their importance across different types of infection, as shown for example by (Troha et al., 2018).

7. Keeping the response within limits and turning it off

The effect of infection on the global suppression of storage, growth, and other non-immune processes is now well established. Enhancing

the Ado effect, associated with a more extensive impact on energy stores, can even lead to a more efficient phagocytosis (Bajgar and Dolezal, 2018). The suppression of insulin signaling at various levels during the immune response is also well documented, however its actual importance for the effectivity of the acute immune response still remains to be tested. What has actually been shown is the adverse effects of the prolonged suppression of insulin signaling during chronic infections (Dionne et al., 2006).

The immune reaction, although life-saving for the host in its task in killing the pathogen, is also more or less harmful to the host, and thus keeping the response within a certain range and its eventual down regulation are necessary (Schneider, 2007). Sometimes, the immune response itself is more harmful to the host than the pathogen. The host cannot be prepared for every possible pathogen. Sometimes, the host just cannot get rid of the pathogen since it does not possess an effective immune response against that particular infection. Disease tolerance is now being recognized as an integral part of the defense mechanisms – it is a host strategy that reduces the negative impact of infection on host fitness without affecting the pathogen load (Schneider and Ayres, 2008). This includes limiting the tissue damage caused by the host's own immune response, but it most likely also includes limiting the metabolic effects of the activated immune response. Energy stores are limited and the energy supply for the immune system may also be exploited by the pathogen. For example, Howick and Lazzaro (2018) found that SNPs associated with disease tolerance were enriched in the genes involved, among others, in the regulation of the metabolism.

Although lowering insulin signaling is a common response and probably important for an effective immune response as discussed above, in the case of chronic, intracellular pathogen infections, which cannot be effectively removed by the host, the suppression of insulin becomes eventually harmful to the host. For example in case of mycobacterial infection, compensating for the negative regulation of insulin signaling during infection by the hypomorphic *foxo* mutation reduces the negative impacts of infection, such as wasting, and improves the survival of the flies, without changing bacteria numbers (Dionne et al., 2006). This is an example of a chronically provoked immune response and reducing the long-term impact on the metabolism may actually help to increase disease tolerance, even though initially lowering insulin might be important for effective resistance. Another such example is the dual effect of Eiger. Eiger is important for resistance against extracellular pathogens but becomes harmful in the case of intracellular infection where removing Eiger actually improves survival (Schneider et al., 2007). One possible explanation is the extensive effect of Eiger on metabolism, which does not help the host to fight the intracellular infection and only does unnecessarily harm to the host. Removing Eiger in such a scenario may increase disease tolerance.

What are the molecular mechanisms limiting the impact of the immune response on metabolism? Is it a disappearance of the original immune stimulatory (pro-inflammatory) signals? The disappearance would eventually unblock insulin signaling. For example, Toll activation suppresses insulin signaling in the fat body (DiAngelo et al., 2009) and it is logical that, with no pathogen around to activate Toll, insulin will no longer be suppressed. An active autoregulatory loop is mediated by the Toll-activated WntD expression, which in turn blocks Toll activation by binding to the Frizzled 4 receptor (Gordon et al., 2005; Lamiable et al., 2016). Zaidman-Rémy et al. (2006) beautifully demonstrated a negative feedback loop downregulating Imd signaling by peptidoglycan degradation by amidase PGRP-LB, which is activated by Imd itself. PGRPs together with Pirk represent very important regulators of Imd (Paredes et al., 2011).

In the case of immunometabolic regulatory loops, one such regulating mechanism was uncovered in the case of the Ado-induced metabolic switch. ADGF-A is the fly adenosine deaminase, which removes extracellular Ado from circulation by converting it to inosine (Dolezal et al., 2005). ADGF-A is strongly expressed in fully differentiated lamellocytes, encapsulating parasitoid wasp eggs (Novakova and Dolezal, 2011), suggesting that Ado, initially important in inducing the metabolic switch, is degraded once the egg is in the process of being successfully encapsulated. Removing one copy of the *ADGF-A* gene or knocking it down specifically in hemocytes lowers glycogen stores during bacterial infection of the adult flies (Bajgar and Dolezal, 2018) demonstrating that ADGF-A limits the use of energy reserves. Rising *ADGF-A* expression in hemocytes beautifully coincides with the hyperglycemic peak upon *S. pneumoniae* infection; upon knocking-down *ADGF-A*, hyperglycemia continues beyond this peak at the expense of glycogen stores. This has interesting consequences. Enhancing energy supply to hemocytes, by downgrading ADGF-A and thus enhancing Ado effects on metabolism, increases their phagocytic activity and reduces thus the *S. pneumoniae* load. However, in the case of intracellular *L. monocytogenes* infection, which a fly cannot clear, the chronic lowering of glycogen stores is associated with an increased intracellular pathogen load. One possible explanation is that enhancing the Ado effects and the release of energy does not help to kill intracellular bacteria and instead leads to feeding it. Summarizing these effects, privileged immune cells first release Ado upon their activation to suppress the systemic metabolism so that the energy is available in higher quantities to the immune system. Later, the same immune cells limit their own privilege (or selfishness) by releasing the regulator of Ado levels, the ADGF-A adenosine deaminase. ADGF-A limits the actions of Ado, preventing its excessive effects on the systemic metabolism and thus preventing a larger loss of energy reserves, and maybe also the unnecessary feeding of the pathogen.

The regulation of metabolism during the immune response is crucial. It ensures adequate energy for an effective response (resistance) but it must also be kept under tight check because it interferes with other physiological traits. Energy is not unlimited and it may also be exploited by the pathogen. If the energy release is not properly regulated, it may, in the end, decrease fitness via a lowering of disease tolerance. Understanding the regulation of immunometabolism is thus important for both resistance and tolerance mechanisms.

8. Concluding remarks

Molecular immunometabolic interactions have become an intensively studied subject in recent years and although studies on insects have been somewhat lagging behind the studies on mammalian systems, recent research is now uncovering the parallels between insects and mammals both in metabolic reprogramming of the activated immune cells and in the regulation of systemic metabolism during the immune response. Insect-based studies of the metabolic reprogramming of immune cells are still rather scarce. Technological advances such as cell sorting and metabolomics (Cox et al., 2017) may soon change this. There are many well established infection models *in vivo* using insects as models, which might be combined with these technological advances in the future to study the metabolism of immune cells *in vivo*. Insects, being relatively simple compared to mice, and especially *Drosophila* with the excellent genetic tools available to work with them, already serve as great models to study inter-organ communication (Droujinine and Perrimon, 2016) and thus can also be used to study the regulation of systemic metabolism and inter-organ communication during the immune response. There are many interesting results linked to immunometabolic interactions already available, but the studies were often focused either on the immune or metabolic function of the molecule under study, but not both. No less interesting is the dietary influence of immunometabolism and the relationship to microflora and gut immunity, which can be expected to affect metabolic regulations during immune response to a large extent. Although this review did not cover these topics, studies are now emerging even in these areas and have been recently covered in (Galenza and Foley, 2019).

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