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Immunometabolism in Arthropod Vectors: Redefining Interspecies Relationships

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Abstract

Metabolism influences biochemical networks and arthropod vectors are endowed with an immune system that affects microbial acquisition, persistence and transmission to humans and other animals. Here, we aim to persuade the scientific community to expand their interests in immunometabolism beyond mammalian hosts and towards arthropod vectors. Immunometabolism investigates the interplay of metabolism and immunology. We provide a conceptual framework for investigators from diverse disciplines and indicate that relationships between microbes, mammalian hosts and their hematophagous arthropods may result in cost-effective (mutualism) or energetically expensive (parasitism) interactions. We argue that disparate resource allocations between species may partially explain why some microbes act as pathogens when infecting humans and behave as mutualistic or commensal organisms when colonizing arthropod vectors.

Keywords

Arthropod Vectors; Immunometabolism; Microbes; Pathogens

Divergence from the conventional classification of host-microbial interactions

Vector-borne diseases occur in more than 120 countries and comprise millions of cases per year across the globe [1]. The bite of an infected arthropod vector (see **Glossary**) results in pathogen transmission to metazoan hosts [2] and recent changes in climate have introduced novel dynamics for these illnesses [3]. The arthropod is essential for microbial transmission while some vertebrate hosts often provide an environment for microbial amplification. Historically, the concept of pathogenicity has been rather inflexible in its attempt to describe the relationship between a microbe and its host [4]. Following the traditional definition, a microbe's pathogenicity is dependent on production of virulence factors, manipulation of the host cellular machinery and evasion of immune responses, whilst host fitness depends on

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pathogen resistance [5]. This relationship escalates in complexity with the addition of an arthropod vector. For instance, the Lyme disease spirochete *Borrelia burgdorferi* is pathogenic to humans [6]. However, *B. burgdorferi* has a mutualistic interaction with its vector, *Ixodes scapularis*. *B. burgdorferi* alters the expression of tick gut genes to promote successful larval molting [7]. Conversely, *B. burgdorferi* depends on a tick protein, Salp15, to protect it from antibody-mediated killing during arthropod transmission to mammals [8]. Similarly, *Anaplasma phagocytophilum*, the agent of Human Granulocytic Anaplasmosis, causes disease in animals [9], but enhances the tick's ability to withstand cold temperatures [10] and benefits from *I. scapularis* nutrients to support microbial infection [11–13]. Altogether, tripartite relationships in arthropod-borne illnesses are complex and necessary for disease propagation. Thus, the pathogenic potential of a microbe [14], not virulence, is reflective of interspecies relationships in vector-borne diseases.

Interspecies relationships are governed in part by the balance between metabolism and the immune system [15], a concept termed immunometabolism. Metabolite abundance varies across different species due to unique physiological demands (Figure 1). As an example, *Leishmania donovani*, the primary agent of leishmaniasis, uses a variety of carbon sources [16] and amino sugars when infecting mammalian macrophages [17]. Conversely, *L. donovani* mostly utilizes glucose or phosphoglycans as the primary carbon source within the sandfly [18, 19]. Adenosine triphosphate (ATP) is a primary source of energy and can be produced from two classical bioenergetic processes: glycolysis and oxidative phosphorylation. Both of these pathways are affected upon infection [20, 21] and microbial associations strongly correlate with the arthropod bioactive metabolite pool. Such metabolites allow obligate intracellular bacteria, which are otherwise pathogenic to humans, to maintain mutualistic interactions with a vector. These microbes shift their own metabolic state [22], indicating their reliance on metabolism for successful transmission within an arthropod vector [23].

The interaction of microbes with hematophagous vectors significantly contribute to their reproductive output and physiological development; thereby, impacting their lifecycle and evolutionary fitness. Endosymbionts inherited through transovarial transmission provide crucial metabolites for arthropods (Box 1) [24], whereas transstadial microbes assist in molting during larval development [25–27]. Furthermore, metabolites present in the blood act as a cue for adult females to lay eggs after feeding [28]. Finally, microbes that form the gut microbiota contribute to the development and fitness of arthropod vectors [29]. Evolution of these multifaceted relationships were likely driven by selective pressures placed on both the arthropod vector and the microbe. This co-existence contributes to vector competence.

In this *Review* article, we highlight studies in the literature, which lend evidence that the availability of nutrients to each species is an important factor dictating interspecies relationships (*i.e.*, parasitism, commensalism or mutualism). We suggest that contextual pathogenicity is a consequence of the metabolic disparity between microbes and arthropod vectors [4].

Immunometabolism in arthropods

The field of immunometabolism has made important contributions to the characterization of cell function and identification of biomarkers of disease [15, 30–33]. In mammals, disease may cause differential regulation of glycolysis and oxidative phosphorylation in immune cells altering metabolite levels [34]. Metabolites can then be used to indicate states of inflammation in sterile and infectious diseases [15, 30–32]. In cancer cells, glycolysis is preferred over oxidative phosphorylation for ATP production in the presence of oxygen, a phenomenon described as the Warburg effect [35, 36]. Furthermore, gene mutations and metabolomic approaches reveal that a single metabolite can alter cell-to-cell communication and fate. For example, succinate - a tricarboxylic acid (TCA) cycle intermediate, may act as an oncometabolite [37–39] and cause cells to adopt a pro-inflammatory phenotype through interleukin (IL)-1 β production [40]. Additionally, lactate accumulation in extracellular spaces also leads to inflammation and production of proinflammatory cytokines [34]. Conversely, itaconate, which regulates the enzymatic synthesis of succinate, generates an anti-inflammatory phenotype [34].

In *Drosophila*, metabolism regulates the Toll and the immune deficiency (IMD) pathways [41–43]. Endogenous metabolites, maintained by the intestinal epithelium, induce the immune response and return the system to homeostasis [44, 45]. As an example, microbial acetate activates the IMD pathway in enteroendocrine cells of the midgut which in turn increases expression of the peptide hormone tachykinin that regulates lipid metabolism and growth [46]. Evolutionarily conserved mechanisms of immunometabolism are also likely to occur in arthropod vectors. In the body louse, vitamins secreted from endosymbionts influence immunity and metabolism [47], while prodigiosin derived from the *Rhodnius prolixus* gut bacterium *Serratia marcescens* has trypanolytic activity [48]. Additionally, phenylalanine metabolism protects female mosquitoes from *Plasmodium* infection through melanization [49]. Bioactive macromolecules, such as proteins and peptides, influence hemocyte function [50], and microRNAs regulate amino acid metabolism, reproduction and parasite development in *Anopheles* mosquitoes [51]. Thus, metabolic reprogramming of the arthropod vector requires an intricate system of metabolites and regulators that affects immunity.

Hemocytes circulate systemically in the hemolymph or are localized in the head, thorax and abdomen of arthropods [52]. In the gut, hemocytes remain closely associated with the epithelium while the microbiota interacts with the peritrophic matrix. This arrangement prevents an undesired immune response against beneficial microbes [53]. In ticks, the spirochete *B. burgdorferi* alters the metabolic profile of the arthropod vector [54] and the rickettsial agent *A. phagocytophilum* shifts cellular metabolism towards glycolysis via the hypoxia inducible factor 1 α (HIF-1 α) [11]. Overall, how metabolites affect the immune response in arthropod vectors remain ill-defined. Within the near future, the integration of cutting-edge technological approaches with the recent affordability of functional read-outs in immunology will create greater opportunities to understand the plasticity of hemocytes in arthropod vectors (Figure 2).

Metabolic regulators in arthropod vectors

Rewiring of cellular metabolism may lead to disease tolerance upon microbial infection [55, 56]. The ability of the hematophagous vector to sustain shifts in metabolism is partially due to resource allocation and depends on nutrient availability, microenvironment conditions, tissue function and hormonal cues [57]. For instance, neuropeptides and other molecules manifest their effect on the insect fat body through significant metabolic changes [58, 59]. These molecules include the adipokinetic hormone, insulin-like peptides, ecdysone and the juvenile hormone that target the fat body. Juvenile hormone and 20-hydroxyecdysone (20E) also control hepatocyte nuclear factor 4 (*HNF4*) expression. HNF4 is a transcription factor in female *A. aegypti* mosquitoes that enhances the expression of genes associated with triacylglycerol catabolism and β -oxidation enzymes [60].

Metabolic regulators redirect cellular homeostasis to mount an immune response or synthesize transcription factors that induce co-operative behavior through downstream signaling. The phosphorylation state of the transcription factor myocyte enhancer factor 2 (Mef2) regulates both immunity and metabolism [61]. In healthy flies, Mef2 promotes glycogen and lipid biosynthesis, whereas in infected flies, Mef2 induces an immune response through antimicrobial peptides (AMPs) [61]. Flexible regulation of Mef2 may be considered detrimental during chronic immune activation, but beneficial during an infection. Dual metabolic regulators have yet to be identified in hematophagous arthropods.

Metabolic outcomes direct arthropod vector competence

Vector competence enables the acquisition, maintenance and transmission of microbes. Upon infection, the arthropod possesses two defense mechanisms: microbial resistance and tolerance [4, 62, 63]. Resistance limits microbial load, whereas tolerance reduces the negative impact of infections on vector fitness [4, 62, 63]. Indeed, these defense strategies lead to either of two outputs: resolution or persistent infections. Resolved infections are not transmissible. However, persistent infections can be subsequently transmitted to another species.

Metabolic outcomes likely play some role in both microbial resistance and tolerance. For instance, reactive oxygen species (ROS), the by-product of mitochondrial respiration, is necessary for arthropod defenses. In *Drosophila*, lipolysis affects ROS production in enterocytes, which is dependent on the target of rapamycin (TOR) kinase [64]. The metabolic switch from lipogenesis to lipolysis leads to activation of dual oxidase (DUOX), a member of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase family. NADPH oxidase ultimately produces microbicidal ROS [64]. In contrast, prolonged ROS generation after infection may cause arthropod death because ROS-mediated damage inhibits metabolite synthesis [65]. Therefore, ROS may be considered an example of a metabolic byproduct influencing arthropod defenses upon infection.

Current literature provides evidence that metabolism likely affects vector competence in several microbe-vector associations (Figure 3). For instance, fungal infection alters lipid composition in the fat body of engorged female *Rhipicephalus microplus* ticks [66].

Furthermore, *I. scapularis* tolerates intracellular microbes, such as the rickettsial agent *A. phagocytophilum*, through increased glycolytic enzymes [12, 13]. These examples of metabolic rewiring support the notion that metabolism partially drives mutualism and parasitism in arthropod vectors (Figure 4, Key Figure). Reasonably, we hypothesize that tolerance induces a pool of metabolites favorable for arthropod-borne microbial transmission to humans, whereas resistance induces a distinct metabolic signature conducive to pathogen elimination. As novel scientific approaches are continuously developed, their inclusion in studies related to vector-pathogen interactions will provide conceptual and mechanistic breakthroughs in the field.

Concluding Remarks

The traditional view in infectious disease research postulates that pathogens and their hosts are in a constant battle for survival. Pathogen survival depends on virulence, immune evasion, and its ability to be transmitted, whereas host endurance is contingent upon resistance to the pathogen [67]. However, complex tripartite relationships demonstrate that host endurance extends beyond pathogen elimination and microbes are under long-term selection to differentially respond to either the arthropod vector or the mammalian host in ways that promote their own fitness. Scientific evidence indicates that virulence is an evolutionarily “hazardous” strategy for a microbe to survive in nature [68, 69] and most “human pathogens” are harmless to arthropod vectors [69]. Therefore, persistent or chronic infections of “human pathogens” in arthropod vectors may result in augmentation of their overall fitness [70–73] or simply exist as neutral associations.

Thus, the “one size fits all” principle in infectious diseases may not be readily applicable to vector-borne illnesses. When microbes cycle between an arthropod vector and the human host, they establish a continuum of interactions, ranging from mutualistic to neutral to parasitic relationships. Importantly, metabolism appears to be an important factor in determining interspecies relationships. Historically, the scientific community has performed experimentation on a limited set of model species and investigators have chosen the relative merits of minimizing biological variation to reach mechanistic depth. Embracing a diverse set of organisms should reveal the breadth and diversity of interspecies relationships.

We anticipate this *Opinion* article will encourage entomologists, microbiologists and immunologists to be cognizant of the nuances when referring to microbial-vector or microbial-host interactions. Perhaps, we as scientists are looking backwards from an anthropocentric perspective and asking incomplete questions related to arthropod-borne diseases. The important query may not be why a microbe causes disease in humans. This question may be an oversimplification of the pathogenic potential of arthropod-borne microbes [14]. Rather, the broader enquiry may be how can we reconcile a given arthropod-borne microbial agent changing its symbiotic relationship from parasitism to commensalism or mutualism when cycling between two evolutionarily distant species?

We hypothesized that these types of relationships are somewhat a consequence of resource allocation (*See Outstanding Questions*). Microbes reorient their own metabolic network during the transition between species and supply metabolites to the arthropod vector. The

arthropod vector then reprograms its metabolism to decrease the energetic cost of an immune response when encountering a microbe. Consequently, some microbes support the vector with increased fitness by providing an optimal environment for long-term survival. This evolutionary approach favors microbial transmission to humans. Alternatively, humans, which are accidental hosts in most vector-borne diseases, repurpose their metabolism to mount an immune response and drive pathogen elimination. The identification of molecular biomarkers that discriminate between resistance and tolerance in vector-borne diseases will uncover important insights for vector-borne illnesses. The characterization of arthropod metabolic responses towards “true pathogens” when compared to microbes that do not cause harm in vectors but are considered “human pathogens” would be an intriguing area of research in the future.

Because vector-borne diseases are unique and many, a comprehensive effort from the scientific community will be needed to uncover conceptual and mechanistic breakthroughs in arthropod immunometabolism. Given the prominent role of metabolism and resource allocation in the vector, important questions are to be raised. *First*, which metabolites and genes are critical for mutualistic or parasitic phenotypic states in the arthropod and/or the mammalian host? *Second*, what are the metabolic correlates that ensure stability between species? *Third*, what is the optimal metabolic output for an environmental niche so that interspecies interactions are at equilibrium? *Fourth*, what are the mechanisms that return species interactions to homeostasis after microbial perturbations? As the vector-borne disease field progresses, we encourage more scientists to consider immunometabolism when they pursue research in vector-pathogen interactions. The future in research for vector-borne diseases is promising. However, interdisciplinary collaborations between microbiologists and immunologists with ecologists and evolutionary biologists and a wide range of experimental techniques will be needed to truly tackle the problem of vector-borne illnesses.

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Glossary

20-hydroxyecdysone (20E)

a molecule belonging to the family of phytoecdysteroids that regulates arthropod molting.

Adipokinetic hormone

a neuropeptide that mediates mobilization of energy substrates from the fat body into other organs of arthropods.

Arthropod vector

an invertebrate animal of the large phylum *Arthropoda* that transmits microbes to other organisms. A true biological vector is essential for a microbe's life cycle. This contrasts to a mechanical vector, which is more of a passive carrier that becomes contaminated and

transmits a microbe to another organism without being essential for the life cycle of a microbe.

Commensalism

relationship between two organisms in which one species benefits while the other neither benefits nor is harmed.

Contextual pathogenicity

a concept used in microbiology which considers biotic and abiotic factors to explain the effect of microbial virulence in one organism but avirulence in another.

Dual oxidase (DUOX)

dual oxidase enzyme that produces microbicidal reactive oxygen species.

Ecdysone

a steroidal prohormone in arthropods known to regulate molting, metamorphosis, reproduction, and diapause.

Endosymbionts

organisms that live intracellularly in another organisms. This relationship is most often, though not always, of a mutualistic nature.

Fat body

an insect organ analogous to the liver in mammals.

Hematophagous

an animal that feeds on blood; many hematophagous arthropods are vectors of disease and transmit pathogens to humans and livestock worldwide.

Hemocytes

blood cells of an invertebrate animal that regulate and perform immune functions.

Hemolymph

fluid occupying the body cavity of an invertebrate (hemocoel); blood equivalent in invertebrates.

Immune deficiency (IMD) pathway

Tumor necrosis factor-alpha (TNF α)-like immune pathway in arthropods that is triggered by Gram-negative bacteria to induce the secretion of antimicrobial peptides.

Immunometabolism

an emerging field of research studying the interdependence between the immune system and metabolic processes.

Insulin-like peptide

a peptide that mediates growth acting through the canonical insulin/IGF signaling pathway.

Juvenile hormone

a group of acyclic sesquiterpenoids that regulates development and reproduction in arthropods.

Melanization

non-specific immune response induced by injury in arthropods. This pathway is catalyzed by phenoloxidase and results in the deposition of melanin and the production of toxic molecules.

Mutualism

relationship that benefits each of the interacting species.

Parasitism

relationship where one organism causes harm to another species.

Peritrophic matrix

a semi-permeable non-cellular structure, rich in chitin, that lines the gut of many arthropods.

Tolerance

the ability to reduce the negative impact of infection on arthropod fitness without affecting pathogen density.

Toll pathway

an innate humoral pathway in arthropods that is triggered by Gram-positive bacteria and fungi and leads to the production and secretion of antimicrobial peptides.

Transovarial

transmission of a microbe from an organism to its offspring.

Transstadial

the passage of a microbe from one developmental stage to another.

Vector competence

the capacity of a vector to be infected, maintain, and transmit an infectious agent.

Warburg effect

altered cellular metabolism in the presence of oxygen that promotes glycolysis over oxidative phosphorylation and leads to lactate production.

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Outstanding Questions

- What metabolic signatures define interspecies relationships in arthropod vectors and humans? Will these molecular signatures be evolutionarily conserved?
- How do microbial-derived metabolites contribute to arthropod and host immunity?
- How do environmental cues and nutrients alter vector competence?
- Will it be possible to manipulate the metabolism of an arthropod vector so that a mutualistic microbe becomes parasitic? Or a parasitic microbe becomes mutualistic?
- Will it be feasible to modify the metabolism of humans so that a pathogen becomes a beneficial organism?
- Can synthetic metabolites be designed to manage vector-borne diseases?

Highlights

- Hematophagous arthropods transmit a wide variety of microbes that are mutualistic or commensal organisms to arthropods; yet, parasitic to humans.
- This disparate impact of a microbe in varying species suggests a role for partitioning of metabolites and resources in interspecies relationships.
- Immunometabolism, an emerging scientific field of research that investigates the interplay of metabolism with immunology, remains mostly unexplored in hematophagous arthropods.
- Upon encountering a microbe, nutrient allocation to tissues and organs may dictate whether interspecies relationships will be synergistic, neutral or antagonistic to an organism.

Box 1.**Microbes influence the metabolism of arthropod vectors**

Microbial metabolites have shown to directly or indirectly affect the arthropod vector. A single metabolite from the malaria parasite *P. falciparum*, (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP), enhances questing and feeding of mosquitoes [70]. Ticks and lice harbor *Rickettsia buchneri* and *Candidatus Riesia pediculicola*, respectively. These endosymbionts provide vitamins to the arthropod vector [74]. In tsetse flies, microbial interactions in the gut become important for physiological processes. For instance, *Wigglesworthia* secretes thiamine, which is scavenged by a transporter from *Sodalis* [75]. Thiamine is essential to prevent fat body degeneration [76–78]. Finally, *Serratia* and *Enterobacter* produce hemolysin that aid in erythrocyte lysis, facilitating egg development in mosquitoes [79, 80].

Figure 1. Metabolic preferences throughout the life cycle of an arthropod vector.

Arthropod vectors have distinct metabolic requirements to support their energy demands at different life stages [81]. Female vectors typically feed on blood where they acquire essential nutrients (*e.g.*, divalent metals and amino acids required for egg development). Metabolism then shifts towards lipid utilization that regulates egg hatching and maturation [73]. Larval development depends extensively on carbohydrate and lipid metabolism, which are mostly described in flies and obtained through the diet [82]. In the arthropod vector, a balanced carbohydrate and lipid metabolism influences its body size [83]. Pre-adult stages rely on protein metabolism to complete their maturation. The dotted line highlights the difference in transition from larvae to pre-adult stages. There are proteins (transporters or proteases) localized or enriched in a stage-specific manner, indicating a preferred type of metabolism for each developmental stage [73]. Components in the blood meal increase protease synthesis to facilitate protein digestion in the blood [84]. Mosquitoes and sandflies develop into pupa after the larval stage. Tick larvae develop into nymphs, and tsetse flies have three larval instars prior to pupal development. Triatomines (kissing bugs) have five nymphal stages before fully developing into grown adults. Each triatomine stage requires at least one blood meal to molt. ATGL; adipose triglyceride lipase, XDH; xanthine dehydrogenase.

Figure 2. Metabolic regulators during arthropod feeding.

Metabolism is a multi-dimensional process that can be managed primarily by lipids, proteins, microRNAs and micronutrients. Blood meal-dependent metabolic regulation includes hormones and peptides. These regulators enter the hemolymph circulation and target the fat body cells. Once into the fat body, these regulators bind to specific receptors forming a complex that translocates to the nucleus for downstream signaling. Inside the nucleus, regulators activate the expression of transcription factors. These transcription factors (e.g., *HNF4*, *HIF1 α* , *DUOX*) upregulate genes related to lipid, carbohydrate and amino acid metabolism. Microbes acquired through the bloodmeal interact with immune cells and manipulate the metabolism of arthropods. In mosquitoes, the metabolic profile is significantly altered through the diet in the presence of the malaria parasite *P. falciparum* [85].

Figure 3. Immunometabolism in microbial-vector interactions.

Tolerance allows the microbe to persist in the vector and, subsequently, be transmitted to the mammalian host. Resistance is the ability to limit microbial load by stimulating energetically costly immune responses (arthropod defenses). In general, arthropod defenses increase glycolysis and rapidly produce ATP. Glycolysis also produces large amounts of lactate from pyruvate, which downregulates oxidative phosphorylation. Conversely, enhanced oxidative phosphorylation and decreased glycolysis cause a less effective immune response leading to infection (arthropod susceptibility). Thus, a balanced metabolic activity dictates microbial survival and vector competence.

Figure 4, Key Figure. Metabolic reprogramming during microbial infection of arthropod vectors.

Pathogenic interactions (parasitism) cause degradation of proteins and nucleic acids in the arthropod vector. Intermediate metabolites direct metabolic regulators, such as transcription factors and hormones, to increase pathogenic immune responses. Enhanced glycolysis (blue) and downregulation of oxidative phosphorylation (gray) enhances pyruvate availability for conversion into lactate. Increased glycolytic intermediates (glucose-6-phosphate or G-6-P) feed into the pentose phosphate pathway (PPP) to provide ribose sugars for anabolic processes. Mutualism increases mitochondrial activity and drives the energy towards lipid catabolism. Lipids are broken down into fatty acids (blue), which reduce competition for energy and drives interspecies relationships towards mutualism. Red depicts parasitism and green depicts mutualism. Metabolic pathways depicted in gray arrows are less utilized during parasitism and mutualism, respectively. Conversely, metabolic pathways depicted in white arrows are increasingly utilized during these interspecies relationships. Dotted lines indicate intermediate metabolites not shown. This figure was created according to the principles and tenets of ecology and evolutionary biology and based on an empirical framework of metabolic supply and demand observed in mammals [15, 30–33, 86, 87]. Metabolic outcomes were then transposed to a conceptual outline in arthropod vector-microbial interactions.