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Review

Grandeur Alliances: Symbiont Metabolic Integration and Obligate Arthropod Hematophagy

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Several arthropod taxa live exclusively on vertebrate blood. This food source lacks essential metabolites required for the maintenance of metabolic homeostasis, and as such, these arthropods have formed symbioses with nutrient-supplementing microbes that facilitate their host's 'hematophagous' feeding ecology. Herein we highlight metabolic contributions of bacterial symbionts that reside within tsetse flies, bed bugs, lice, reduviid bugs, and ticks, with specific emphasis on B vitamin and cofactor biosynthesis. Importantly, these arthropods can transmit pathogens of medical and veterinary relevance and/or cause infestations that induce psychological and dermatological distress. Microbial metabolites, and the biochemical pathways that generate them, can serve as specific targets of novel control mechanisms aimed at disrupting the metabolism of hematophagous arthropods, thus combatting pest invasion and vector-borne pathogen transmission.

Microbiota Play Significant Roles in Host Biology

Microbial symbiosis, once regarded as an ecological anomaly, is now recognized as a major driver of metazoan evolution. Microbial symbionts impact all aspects of their host's biology, including growth [1,2], behavior (reviewed in [3,4]), immunological priming [5–7], and ecological plasticity such as thermal tolerance [8], resistance against natural enemies [9–11], detoxification of pesticides [12,13], and body coloration [14]. These crucial functions provide fascinating examples of how microbial symbionts facilitate the phenotypic complexity exhibited by their animal hosts [15,16]. Alliances with bacteria, regarded as repositories of high metabolic diversity [17], also drive host ecological expansion by enabling the occupation of specialized and often resource-restricted niches. For example, bacterial symbionts provide nutrients and catabolize recalcitrant biomass [18–21], thus allowing their hosts to thrive on highly restricted, nutrient-poor diets.

In this review we highlight examples of how evolution-driven host–symbiont metabolic integration has enabled two obligate hematophagous insects, the tsetse fly (*Glossina* spp.) and the bed bug (*Cimex* spp.), to flourish on nutritionally restricted vertebrate blood. Additionally, we briefly discuss the nutrient-providing roles of lice, reduviid bugs, and tick microbiota, which serve to illustrate the parallels in endosymbiont evolution and metabolism (Table 1). Notably, analogous patterns of evolution have also occurred in the rich array of microbial partnerships of insects feeding on other types of restricted diet, such as phloem and xylem sap (reviewed in [19]). The geographic distribution of these and other blood-feeding arthropods is spreading at a historically alarming rate due to various factors including environmental changes, pesticide resistance, globalization, and the increase in urban landscapes [22–26]. These insects, as well as other blood-feeding arthropods, pose significant public health challenges because of the pathogens they transmit,

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Table 1. Bacterial Symbionts of Obligate Hematophagous Arthropods Involved in Metabolic Homeostasis

Arthropod Host	Symbiont	Symbiont Location	Nutrient Provided	Means of Transmission
Tsetse flies (Insecta: Diptera)	*Wigglesworthia*	Bacteriocytes at anterior midgut	Folate (B9) Pyridoxine (B6) Thiamine (B1)	Vertical, milk-gland route
	Sodalis	Wide tissue tropism intra- and extracellular	Unknown	Vertical, milk-gland route
Bed bugs (Insecta: Hemiptera)	*Wolbachia* (*w*Cle)	Bacteriocytes adjacent to gonads	Biotin (B7) Riboflavin (B2)	Vertical, ovarian
	Unidentified gammaproteobacterium	Adjacent to w*Cle*, Malpighian tubules, ovary	Unknown	Unknown
Lice (Insecta: Phthiraptera)	*Candidatus* Riesia pediculicola	Bacteriocytes, stomach discs	Pantothenic acid (B5)[a]	Vertical, ovarian
Reduviid bugs (Insecta: Hemiptera)	*Rhodococcus*	Hindgut Extracellular	Biotin (B7)[a] Cobalamin (B12)[a] Niacin (B3)[a] Pantothenate (B5)[a] Pyridoxine (B6)[a] Riboflavin (B2)[a] Tetrahydrofolate (B9)[a] Thiamine (B1)[a]	Mixed, coprophagy
Ticks (Arachnida: Parasitiformes)	*Coxiella*	Wide tissue tropism	Biotin (B7)[a] Folic acid (B9)[a] Pyridoxine (B6)[a] Riboflavin (B2)[a] Thiamine phosphate (B1)[a]	Vertical, ovarian
	Rickettsia	Ovaries	Folate (B9)[a]	Vertical, ovarian
	Francisella	Hemolymph	Unknown	Vertical, ovarian

[a]Putatively assigned, based on symbiont genome capabilities.

the dermatological pathologies caused by bites (including allergic reactions and potential secondary infections with skin-associated pathogens), and the detrimental psychological ramifications associated with infections and/or infestations. Thus, understanding the molecular mechanisms that underlie microbiota-facilitated hematophagy is of vital importance, as detailed knowledge of these interactions can lead to the development of novel targets and control mechanisms for disrupting pest biology and pathogen transmission.

Tsetse Fly

Tsetse flies (Diptera: Glossinidae), localized exclusively to sub-Saharan Africa, are of medical significance as the cyclical and obligate vector of African trypanosomes (*Trypanosoma* spp.). These flagellate protozoa are the causative agents of human and animal African trypanosomiases, which are neglected diseases that result in significant morbidity and mortality across much of Africa [27–29]. In addition to potentially harboring trypanosomes, tsetse flies are associated with a consistent and restricted (i.e., low taxonomic richness) intestinal microbiota [30]. The simplicity of the microbiota, in stark contrast to those of many other animals, is likely to arise from two unique facets of the tsetse's biology. First, both male and female tsetse flies feed exclusively on sterile vertebrate blood. Second, tsetse flies employ a unique mode of reproduction known as adenotrophic viviparity during which all of embryogenesis, and most of larval development, occurs within the sterile maternal uterus [31]. These biological traits significantly curtail the fly's exposure to microbes during most life stages.

The tsetse fly's enteric microbiota primarily comprises two Gammaproteobacteria, the ancient obligate mutualist *Wigglesworthia* spp. [32] and the more recently acquired commensal *Sodalis*