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Letters to the Editor

Towards the integrative analysis of tick microbiome

Dear Editor,

A recent paper by Duron et al. (2018) outlined the importance of the tick microbiome in tick physiology, highlighting the contribution of bacteria of the genus *Francisella* in the synthesis of vitamin B, which is deficient in the tick blood meal and essential for ticks. The study demonstrated that *Francisella* bacteria are passed by the maternal lineage to the offspring and, by complementing a nutritional deficiency of tick diet, seems to be fundamental for tick survival. Elimination of *Francisella* in the maternal lineage and therefore impairment of transmission from mother to offspring produced anomalies in tick development. Another symbiont, *Coxiella*, is also thought to be a nutritional symbiont of ticks (Duron et al., 2015) because its genome was found to contain vitamin B biosynthesis pathways (Gottlieb et al., 2015). These studies drive to a change of paradigm: *'most bacteria found in tick microbiome are fundamental for tick biological processes, and only from an "anthropocentric" point of view they were considered as pathogens'*. Important conceptual leaps have derived from abandoning the *'only-pathogens'* paradigm when studying tick-associated microorganisms. Remarkably, it is now recognized that, at least for some bacterial genera, shifts between pathogenic and non-pathogenic forms are a common evolutionary process with ecological and epidemiological implications (Bonnet et al., 2017).

Recent studies allow also glimpsing positive and negative associations among bacteria that impact the transmission and circulation of some agents. For example, Narasimhan et al. (2014) elegantly demonstrated that the composition of *Ixodes scapularis* gut microbiome influences *Borrelia burgdorferi* colonization of tick gut. A tick gut microbiome composed by a high abundance of *Rickettsia*, *Thioclava*, and *Delftia*, and a low abundance of *Aquabacterium*, *Brevibacterium*, and *Novosphingobium* did not favour *B. burgdorferi* colonization of the tick gut. Another study showed that tick colonization by *Anaplasma phagocytophilum* perturbs the tick gut microbiome by decreasing the relative abundance of bacteria involved in biofilm formation which in turn damage the tick peritrophic matrix potentially affecting *B. burgdorferi* colonization (Abraham et al., 2017).

This change of paradigm challenges current methodologies of tick-associated microorganism detection, reporting and deriving ecological relationships. This integrative microbiology should ideally combine high-throughput detection of pathogens and next generation sequencing for microbiome characterization, but still poses technical and analytical bottlenecks (Cabezas-Cruz et al., 2018). However, a key element is the capture of the effects that the bacterial metapopulation has on the tick physiological processes. It is not enough to know the microorganisms associated with ticks, but it is also necessary to understand how they interact among them and with the molecular processes that allow ticks to regulate the bacterial diversity associated with them. It is now recognized that the microbiome of ticks is the result of complex relationships between ticks, their host(s) and the environment. For instance, the microbiome of ticks changes according to their developmental stage. In particular, the moult to successive life stages in the tick's life cycle is associated with a decrease in the bacterial diversity. However, the molecular mechanisms involved in the selection of retained bacteria and the resulting phylogenetic diversity are yet to be discovered. Furthermore, the tick microbiome, even in the same species, is highly dependent on the ecological context (probably explaining an effect of the blood-meal and thus of available hosts). Individual specimens collected within the same site might carry a different bacterial composition. We just have begun to scratch the surface of the complexity of the bacterial communities colonizing different tick organs. Probably the comparison of annotated proteomes of the involved bacteria would provide a crucial overview of the potential significance of these associations and the bacterial contribution to tick physiology.

We believe that it is necessary not to restrict microbiome studies to a mere taxonomic reporting of bacterial taxa. Listing and providing prevalence data of bacteria (genera or higher taxonomic ranges) has been an important step towards understanding the microbial complexity associated with ticks. Further ecological insights, however, are necessary to be derived by quantifying the associations between bacteria found in ticks. We proposed recently the use of graph theory to define the microbiome of ticks, an approach that could be applied to any bacterial metapopulation (Estrada-Peña et al., 2018). Graph theory has deep roots in social sciences and has been successfully used to explain the relationships of interacting organisms at several taxonomic levels. Networks are mathematically tractable entities that can be used to pinpoint the links between coexisting bacteria, computing the so-called centrality indexes. These indexes allow the identification of the most prominent taxonomical entities in the resulting network of bacteria in individual ticks. Interestingly, the approach indicated that phylogenetically close bacteria tend not to coexist in individual ticks (Estrada-Peña et al., 2018). This can be due to competition between closely related bacteria for the same tick resource. Another explanation can be that physiological requirements of the ticks are fulfilled by a given combination of bacteria and phylogenetic close bacteria providing similar resources are excluded by the ticks. Ideally, enough data derived from field studies would provide insights about a yet hypothetical core microbiome. Methods exist to evaluate *in silico* the outcome on the complete network of the removal of selected bacteria, and how the removal of presumed prominent bacteria would affect the cohesiveness of the network, which is nothing less than a metapopulation. We also proposed to provide measures of the bacterial phylogenetic diversity detected in ticks, which illustrates the genetic diversity of the recorded bacteria, instead of binomial names or "taxonomic diversity" of bacteria that exceedingly lacks information.

There is a potentially fertile field of research regarding the tick microbiome. Once methodological issues are solved it is necessary to capture both the trophic relationships among the recorded bacteria and

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how they complement the physiology of the carrier ticks. Methods exist to step over the listing of bacterial taxa and to provide coherent phylogenetic information on the physiological relationships over which ticks and bacteria interact. While laboratory-controlled experiments can shed light on the finely tuned molecular messages between ticks and bacteria, field surveys could eventually provide an essential framework on which disentangle the phenological relationships between ticks and its microbiome.

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