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The tick gut microbiome - critical gatekeepers

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B. burgdorferi colonization and transmission involve interactions between the tick gut and the spirochete and are orchestrated spatially and temporally by molecular changes in the spirochete and the tick gut. While several studies have defined global changes in *B. burgdorferi* genes during spirochete colonization of the tick and transmission to the host, little is known of *I. scapularis* gut genes. The realization that the tick gut is also co-habited by diverse indigenous microbiota brings a new correlate to tick-spirochete interactions in the context of colonization and transmission. We show that PIXR, a secreted tick gut protein, inhibits bacterial biofilm formation and maintains tick gut bacterial homeostasis. The

tick gut bacterial composition shapes the metabolite milieu of the gut, as seen by changes in the gut metabolome upon PIXR abrogation. The gut metabolome may influence the spirochete entering the tick gut by providing: (i) molecular cues that present the spatial context critical for *B. burgdorferi* to prepare for colonization and (ii) a nutrient milieu essential for spirochete survival. This study underscores the functional significance of the three-way interactions between the tick, its microbiome and the spirochete and offers a new insight into how the tick vector modulates *B. burgdorferi* colonization.

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