# Abstract

All animals live in permanent contact with bacteria and have evolved strategies to protect themselves from this constant threat. Innate immunity can be traced back a billion years ago to the emergence of the first multicellular organisms. It acts as a first line of defense against bacteria and is regulated by pattern recognition receptors (PRRs). PRRs lie at the interface between the internal milieu and microbes, they detect microbe-associated molecular patterns (MAMPs) and act through evolutionarily conserved signaling cascades to induce immune effectors. These pathways are particularly important in organs such as the gut, which harbors a microbial population that can be as large as the number of cells in the body. Intestinal immunity is therefore indispensable to keep bacterial populations in check, and impaired immunity is often associated with dysbiosis. However, defects in innate immune mechanisms are also associated with epithelial damage, chronic inflammation, maldigestion and malabsorption. Despite decades of research, how innate immunity shapes gut health and disease and the role of commensal bacteria in these regulations remain elusive. This highlights the complexity of these interactions and the importance of further investigation in this area.

Fundamental mechanisms regulating innate immunity were discovered in the invertebrate *Drosophila melanogaster*, before their existence was confirmed in mammals. Powerful genetic tools are available in *Drosophila*, while the basic mechanisms controlling innate immunity and metabolism are highly conserved in evolution. This makes *Drosophila* an ideal system to study the crosstalk between gut bacteria, the innate immune system and intestinal physiology.

In this study, we show that signaling downstream of PRRs suppresses fundamental functions of the gastrointestinal tract, including nutrient digestion, absorption and metabolism in *Drosophila*. These suppressions lead to the depletion of systemic metabolic stores. We show that PRRs act through non-canonical signaling to exert these functions, and we provide a partial dissection of the pathways that act downstream of PRRs to regulate gut function.

Finally, we show that these regulations play a defensive role by reducing intracellular bacterial loads locally and in peripheral organs. We propose that suppression of gut function reduces nutrient availability to starve intracellular bacteria and suppress their proliferation.

This research provides fundamental insights into the complex interplay between innate immunity and the function of the intestinal epithelium, and the physiological purpose of these regulations.