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Regulation of Innate Immunity for Host-Bacteria Symbiosis

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One of the fundamental questions relevant to all metazoans is how commensal microbiota can be maintained despite the robust anti-microbial properties of the digestive tract. At present, host factors required to maintain commensal-gut homeostasis are largely unknown. Here, we show that the intestinal homeobox gene *Caudal* (*Cad*) is indispensable for immune homeostasis in preserving the indigenous commensal community and host health. In a commensal-rich gut environment where the NF-κB activation is constitutive albeit at a low level, *Cad* maintains the minimum antimicrobial potential by repressing NF-κB-dependent antimicrobial peptide (AMP) genes. *Cad-RNAi* flies with severely reduced *Cad* expression showed a constitutive gut-specific AMP overexpression, which in turn acts as a novel selection pressure altering the commensal community. In these flies, the dominance of a novel gut pathogenic commensal microbe, *Gluconobacter* sp. strain *EW707*, eventually leads to high gut apoptosis, resulting in host mortality. Importantly, the restoration of the basal AMP level, healthy microbiota community structure and normal host survival in the *Cad-RNAi* flies can be achieved by genetic reintroduction of *Cad*. Thus, Cad is an essential determinant that regulates a delicate immune homeostasis for healthy commensal-gut interaction. This study presents a potential model wherein the linkage between host genetic deficiency and gut commensal community structure can be utilized to dissect molecular mechanisms of chronic inflammatory diseases frequently found in the commensal-contacting epithelia.