Article

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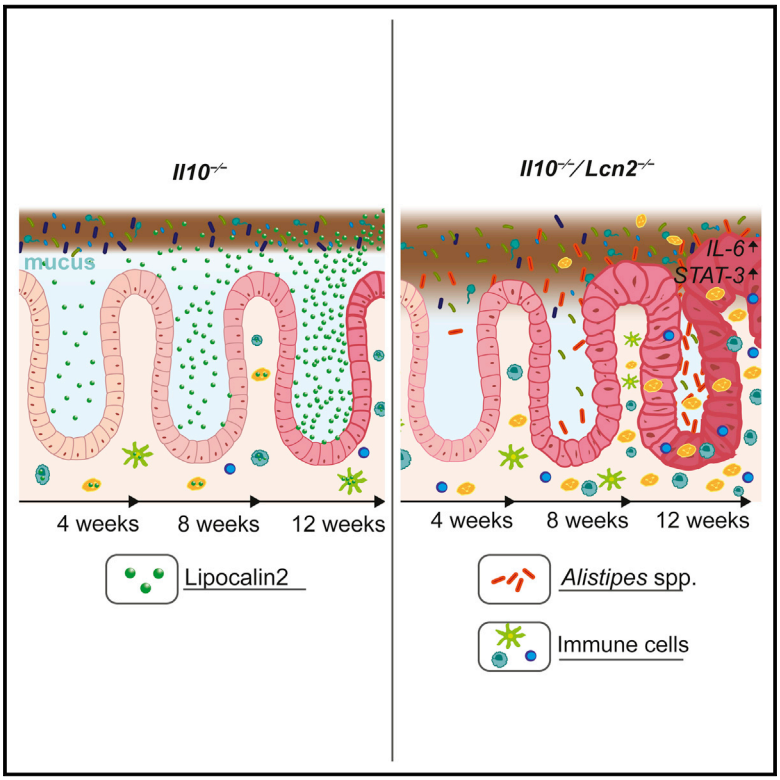
Lipocalin 2 Protects from Inflammation and Tumorigenesis Associated with Gut Microbiota Alterations

Graphical Abstract



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In Brief

Lipocalin-2 is a host defense protein that is upregulated during inflammation. Moschen et al. demonstrate that Lipocalin-2 protects from intestinal inflammation and spontaneous tumor formation in experimental colitis through its impact on microbial composition, specifically *Alistipes* spp., which induces colitis and tumors when transferred to *Il10*$^{-/-}$ mice.

Highlights

- Antimicrobial peptide Lipocalin-2 (Lcn2) is strongly induced in *Il10*$^{-/-}$ colitic mice
- Lcn2 deficiency exacerbates *Il10*$^{-/-}$ colitis and causes spontaneous right-sided tumors
- Inflammation and tumorigenesis are due to altered gut microbiota and are transmissible
- *Alistipes* spp. is sufficient to induce colitis and site-specific tumors in *Il10*$^{-/-}$ mice

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Lipocalin 2 Protects from Inflammation and Tumorigenesis Associated with Gut Microbiota Alterations

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SUMMARY

High mucosal and fecal concentrations of the antimicrobial siderophore-binding peptide Lipocalin-2 (Lcn2) are observed in inflammatory bowel disease. However, Lcn2 function in chronic intestinal inflammation remains unclear. Here, we demonstrate that Lcn2 protects from early-onset colitis and spontaneous emergence of right-sided colonic tumors resulting from IL-10 deficiency. Exacerbated inflammation in *Lcn2*$^{-/-}$/*Il10*$^{-/-}$ mice is driven by IL-6, which also controls tumorigenesis. *Lcn2*$^{-/-}$/*Il10*$^{-/-}$ mice exhibit profound alterations in gut microbial composition, which contributes to inflammation and tumorigenesis, as demonstrated by the transmissibility of the phenotype and protection conferred by antibiotics. Specifically, facultative pathogenic *Alistipes* spp. utilize enterobactin as iron source, bloom in *Lcn2*$^{-/-}$/*Il10*$^{-/-}$ mice, and are sufficient to induce colitis and right-sided tumors when transferred into *Il10*$^{-/-}$ mice. Our results demonstrate that Lcn2 protects against intestinal inflammation and tumorigenesis associated with alterations in the microbiota.

INTRODUCTION

The mammalian intestinal tract harbors the highest density of microbial organisms in the body (Ley et al., 2006). The host-microbe relationship is based on a mutualism that is essential for host nutrient acquisition, immune development, and pathogen defense (Lozupone et al., 2012). This intimate juxtaposition necessitates a sophisticated spatial compartmentalization between commensal bacteria and the mucosal immune system, and the knowledge of host factors that regulate the host-commensal relationship and drive gut microbial community structures is of great clinical and scientific interest.

Lipocalin 2 (Lcn2), also known as 24p3 or neutrophil gelatinase-associated lipocalin (Ngal), is a member of the lipocalin superfamily (Skerra, 2000). Lipocalins share a three-dimensional β-barrel structure that forms a central binding grove capable of accommodating ligands of different chemotypes, sizes, and shapes (Akerstrom et al., 2000; Chakraborty et al., 2012). Lcn2 has been implicated in several biologic processes, such as acute phase response, kidney morphogenesis, tissue involution, erythropoiesis, iron metabolism, and immune functions (Liu et al., 2013).

Lcn2 is produced by various cell types including myeloid and epithelial cells and is strongly upregulated upon IL-1β, IL-22, Toll-like receptor (TLR) ligation, and ischemia-reperfusion injury (Behnsen et al., 2014; Chakraborty et al., 2012). It acts as an antimicrobial defense mediator by binding a subset of bacterial siderophores, thereby preventing bacterial iron acquisition and growth of siderophore-dependent strains (Goetz et al., 2002). Accordingly, Lcn2-deficient animals are prone to infection and sepsis from enterobactin-dependent bacteria (Flo et al., 2004). By interacting with its surface receptor 24p3R, Lcn2 is capable of modulating intracellular iron concentrations (Devireddy et al., 2005).