



**Karolinska  
Institutet**

**Institutionen för Mikrobiologi, Tumör och Cellbiologi (MTC)**

**Inflammation and host-microbe signaling in the  
development and progression of colorectal carcinoma**

**AKADEMISK AVHANDLING**

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## Abstract

Gut microbiota play an integral role in the postnatal development and maturation of the intestinal epithelium as well as the innate and adaptive immune system. Gut microbes communicate to the host via pattern recognition receptors (PRRs) which regulate intestinal homeostasis during health and disease. My thesis has elucidated the role of gut microflora and PRR-mediated signaling during inflammation, infection and tumor development. I have examined the relevant contributions of host-microbe crosstalk in the regulation of intestinal tumorigenesis (Paper I and II) and innate immune responses to enteric pathogens (Paper III), as well as the transcriptional regulation of gene expression during inflammation and cancer development (Paper IV).

In Paper I, the role of microbiota-derived signals in promoting tumor growth in APC<sup>Min/+</sup> mice, a mouse model of colorectal cancer (CRC) was examined. Our data showed that germ-free APC<sup>Min/+</sup> mice have a reduced tumor load compared to that observed in APC<sup>Min/+</sup> mice harboring gut microbiota. Further in-depth characterization studies suggested a role for c-Jun/JNK and myeloid cell-dependent STAT3 activation pathways in the acceleration of tumor growth. Thus, gut microbiota can accelerate tumor growth.

In Paper II, the role of PRR-mediated signaling in intestinal tumorigenesis was studied. By introduction of a constitutively active Toll-like-receptor 4 transgene (CD4-TLR4) to the intestinal epithelium of APC<sup>Min/+</sup> mice, we found a marked reduction of intestinal tumor burden in CD4-TLR4-APC<sup>Min/+</sup> mice. This tumor suppression was likely due to the observed Cox-2 down-regulation and IFN $\beta$  induction which resulted in increased apoptosis of tumor cells. These results unravel a previously unrecognized role of TLR4 signaling in modulating the balance between proliferative and apoptotic signals.

In Paper III, the regulation of host innate immune responses during *Salmonella* Typhimurium induced colitis was studied. Our data demonstrated an aggravated colitis in infected mice lacking the innate immune regulator gene - PPAR $\gamma$  in the intestinal epithelium. This increased tissue damage correlated with the elevation of lipocalin-2 (Lcn2) expression, which promoted the stabilization of tissue degrading enzyme, matrix metalloproteinase 9 (MMP-9). Interestingly, Lcn2-deficient mice were markedly protected from *S. Typhimurium* induced colitis. These findings therefore illustrate how enteric pathogens can exploit the host's mucosal defense mechanisms to disrupt normal host-microbe homeostasis, in order to ensure colonization and survival in the host.

In Paper IV, I have examined the significance of histone modifications and chromatin-binding proteins in the transcriptional regulation of T lymphocytes. Our results demonstrate that the bromodomain-containing protein, BRD4, is important in regulating Pol II Ser2-mediated transcriptional elongation in human CD4<sup>+</sup> T cells.

In conclusion, my thesis work further underscores the significant impact of gut microbiota mediated signaling in the regulation of intestinal homeostasis and tumorigenesis.