UMEÅ UNIVERSITET

# Effects of bacterial genotoxins on immune modulation, chronic inflammation and cancer development

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## Abstract

The intestinal microbiome of Inflammatory Bowel Disease and colorectal cancer patients is enriched in genotoxin-producing bacteria, which cause DNA damage in the host cells. Genotoxins have recently been identified as a novel family of effectors produced by pathogenic and commensal bacteria. At present, only three types of bacterial genotoxins have been identified: colibactin, produced by some *Escherichia coli* strains; cytolethal distending toxins, produced by several Gram-negative pathogens; and the typhoid toxin, produced by *Salmonella enterica* serovar Typhi.

Exposure to high toxin doses activates the classical DNA damage response, which will block proliferation and eventually will induce death in mammalian cells. However, exposure to low toxin doses has shown to promote classical signs of carcinogenesis *in vitro*, such as cell survival and acquisition of genomic instability. Despite an extensive characterization of their mode of action *in vitro*, we have a poor understanding of genotoxins´ role in chronic infection and, considering the genotoxic potential, of their carcinogenic capacity. We focused specifically on *Salmonella* Typhi, since it is the only genotoxin-producing bacterium that induces a chronic infection associated with increased risk of tumor development in humans.

The results presented in this thesis show that these unusual bacterial effectors are not classical toxins, but rather act as immunomodulators, highlighting a complex and tissue specific crosstalk between two very conserved stress responses: the immune response and the DNA damage response. Our data indicate that the impact of genotoxin-producing bacteria on the modulation of the host mucosal response is still poorly characterized and suggest that the host-microbe interaction and the tissue microenvironment are the key players in determining the outcome of the infection and the toxin carcinogenic potential.

**Keywords**
bacterial genotoxins; DDR; immune response; immunomodulation; microenviroment; senescence; typhoid toxin

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