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# *Citrobacter rodentium* and *Escherichia coli* interactions with mucus producing epithelial cells

Akademinsk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, den 29 november, klockan 09:00

av Sinan Sharba

Fakultetsopponent:
Professor David Thornton, PhD
Division of Infection, Immunity & Respiratory Medicine, University of Manchester, United Kingdom

**I.** Maiti AK, Sharba S, Navabi N, Forsman H, Fernandez HR, Linden SK. **IL-4 protects the mitochondria against TNFα and IFNγ induced insult during clearance of infection with *Citrobacter rodentium* and *Escherichia coli*.** Scientific Reports **2015**; 5: 15434.

**II.** Maiti AK*, Sharba S*, Navabi N, Linden SK. **Colonic levels of vasoactive intestinal peptide decrease during infection and exogenous VIP protects epithelial mitochondria against the negative effects of IFNγ and TNFα induced during *Citrobacter rodentium* infection.** *PLoS One* **2018**; 13(9)**:**e0204567. * Equal contribution

**III.** Sharba S*, Navabi N*, Padra M, Persson JA, Quintana-Hayashi MP, Gustafsson JK, Szeponik L, Venkatakrishnan V, Sjöling Å, Nilsson S, Quiding-Järbrink M, Johansson MEV, Linden SK. **Interleukin 4 induces rapid mucin transport, increases mucus thickness and quality and decreases colitis and *Citrobacter rodentium* in contact with epithelial cells** *Virulence* **2019**; 10(1)**:** 97-117. * Equal contribution

**IV.** Sharba S, Venkatakrishnan V, Padra M, Winther M, Gabl M, Sundqvist M, Wang J, Forsman H, Lindén SK. **Formyl peptide receptor 2 orchestrates mucosal protection against *Citrobacter rodentium* infection.** *Virulence* **2019**; 10(1): 610-624.

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# *Citrobacter rodentium* and *Escherichia coli* interactions with mucus producing epithelial cells

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**Abstract**

The epithelial cells together with the mucus layer protect the host from noxious luminal substances and pathogenic invasion. Pathogens have evolved numerous strategies to circumvent these barriers and mount infection. *C. rodentium* is a murine model for the attaching and effacing intestinal *E. coli* (EPEC, EHEC) and share similar virulence strategies to infect their host.

We found that the colonic mucus layer is dynamically regulated by *C. rodentium* and the ensuing cytokine response. The cytokine profile investigated during the course of infection indicated a shift from pro- to an anti-inflammatory type of response at times of increased mucus layer thickness. The *in vitro* effect of signature cytokines of pro- and anti-inflammatory responses and the pathogens (EPEC, ETEC and *C. rodentium*) indicated that changes in mucin production and secretion are affected by the combined impact of these factors. The anti-inflammatory cytokine IL-4 alleviated mitochondrial dysfunction *in vitro* and accelerated mucin production and secretion, especially in the presence of EPEC, ETEC and *C. rodentium*. *In vivo* IL-4 treatment improved mitochondria and barrier functions and colitis symptoms. Similarly, VIP alleviated mitochondrial dysfunction during infection. The lack of Fpr2 lead to decreased barrier function and increased susceptibility to *C. rodentium* and EPEC infection. Harnessing the host's response to pathogens could improve the intestinal mucus barrier function by enhancing mucosal healing and shortening the duration of infection.

**Keywords**: A/E pathogens, cytokines, epithelium, mitochondria, mucus

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