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Evaluation of Fucosylated Receptors for Cholera Toxin in the Human Small Intestine

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Ragnar Sandberg, Medicinaregatan 7A, Göteborg, Fredagen den 15 November, klockan 09.00

av Jakob Cervin

Fakultetsopponent:
Professor **Bruce Turnbull**
School of Chemistry,
University of Leeds

Avhandlingen baseras på följande delarbeten

I. Cervin J, Wands AM, Casselbrant A, Wu H, Krishnamurthy S, Cvjetkovic A, et al.;
GM1 ganglioside-independent intoxication by Cholera toxin
PLoS Pathog 2018 14(2): e1006862. https://doi.org/10.1371/journal.ppat.1006862II

II. Amberlyn M. Wands, Jakob Cervin, He Huang, Ye Zhang, Gyusaang Youn, Chad A. Brautigam, Maria Matson Dzebo, Per Björklund, Ville Wallenius, Danielle K. Bright, Clay S. Bennett, Pernilla Wittung-Stafshede, Nicole S. Sampson, Ulf Yrlid, and Jennifer J. Kohler;
Fucosylated Molecules Competitively Interfere with Cholera Toxin Binding to Host Cells
ACS Infectious Diseases 2018 4 (5), 758-770 DOI: 10.1021/acsinfecdis.7b00085III

III. B Jakob Cervin, Andrew Boucher, Gyusaang Youn, Xiaoxi Yo, Surita R. Bhatia, Per Björklund3, Ville Wallenius, Michael Lebens, Lynda Mottram, Nicole S. Sampson and Ulf Yrlid;
Fucose-galactose polymers inhibit cholera toxin binding to fucosylated structures and galactose-dependet intoxication of human enteroids
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Evaluation of Fucosylated Receptors for Cholera Toxin in the Human Small Intestine

Jakob Cervin

Avdelning för Mikrobiologi och Immunologi, Institutionen för Biomedicin, Sahlgrenska akademin, Göteborgs universitet, Sverige.

ABSTRACT

Cholera toxin (CT) produced by Vibrio cholerae is the causative agent for the diarrheal disease cholera. Cholera is yearly afflicting millions and is estimated to kill over 100 000 people every year. In this thesis I aimed to better understand the role of noncanonical CT receptors, e.g. receptors other than the glycolipid GM1. Epidemiological studies have found a link between cholera severity and blood group indicating that histo-blood group antigens (HBGAs) could play a role as receptors for CT. The work presented in this thesis shows that CT readily binds to the HBGA Lewis X on cells and on some cells CTB binding correlates with the level of Lewis X. Furthermore, we show that other fucosylated glycans such as Lewis Y, A/BLewis Y and 2′-fucosyllactose (found in human breast milk) readily inhibit CT binding to cell lines and primary cells from human small intestine. In contrast, sialylated or non-fucosylated glycans did not show any inhibitory effect on CT binding to human cell lines indicating a fucose-dependent binding. This was further confirmed in blocking studies using long synthetic polymers displaying glucose, fucose, galactose or a mix of the latter two. Functional evaluation identified that the fucose-binding lectin AAL completely blocked the effect of CT, but so could the galactose-binding lectin PNA. The galactose-fucose polymers yielded a partial inhibition of CT intoxication of human small intestinal enteroids whereas GM1 glycan completely blocked the effect of CT. Hence, fucosylated glycans are involved in attachment of CT to the intestinal wall. However, if this binding assists or counteracts subsequent internalization by other receptors carrying terminal galactoses remains to be determined. Importantly, these receptors can be other glycans than GM1 as this thesis show GM1-independent CT-mediated intoxication.

Keywords: Cholera toxin, Lewis, HBGA, HMO, fucose, GM1

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