Direct binding of gangliosides to Helicobacter pylori vacuolating cytotoxin (VacA) neutralizes its toxin activity

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Abstract:

Gangliosides are target receptors for bacterial entry, yet those present in human milk exhibit a protective role against bacterial infection. Here, we show that treatment with ganglioside mixture at a concentration of 100 mu g/mL resulted in significant inhibition of the vacuole formation activity of Helicobacter pylori vacuolating cytotoxin (VacA) in gastric epithelial cancer AZ-521 cells. All gangliosides (GM1, GM2, GM3, GD1a, GD1b, GD3 and GT1b) examined showed good neutralizing capacity against VacA. A pull-down assay was performed using lyso-GM1 coupled to Sepharose as the tagged polysaccharide polymer to capture VacA from H. pylori culture supernatant. GM1-VacA complexes were successfully precipitated, suggesting that GM1 binds directly to VacA. The hydrodynamic binding of lyso-GM1 and VacA measured by fluorescence correlation spectroscopy had a K(d) value of 190 nM. VacA also bound to lyso-GM1 at pH 2 corresponding to the physiological pH of human stomach. Collectively, these results showed that direct binding of H. pylori VacA to free gangliosides neutralizes the toxin activity of VacA. These findings offer an alternative insight into the role of gangliosides in VacA toxicity and the pathogenesis of H. pylori.

Keywords:
fluorescence correlation spectroscopy; ganglioside; GM1; Helicobacter pylori; VacA

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