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The analysis of the glucose-derived metabolites from *Shigella* and its host cells by ^{1}H-NMR for resolving the metabolic riddles during the infectious process

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Abstract

Shigella, one of the most important foodborne pathogens, cause bacillary dysentery in humans. During the process, bacterial invasion and the subsequent proliferation in the cytosol of intestinal epithelium are necessary for the progress of infection. Recently, the glucose has been reported as the major nutrient for facilitating its intracellular proliferation, and the excretion of acetate was the main metabolite during the metabolism. However, the extensive analysis of the intracellular glucose utilization still needs to be established.

^{1}H-NMR was used for analyzing ^{13}C-glucose-derived metabolites from the mid-log cultured *Shigella*, non-infected HeLa, and *Shigella*-infected HeLa cells. Then, the effects of the three major metabolites from our analysis, acetate, lactate, and formate on *Shigella* infection have been evaluated.

Our ^{1}H-NMR spectra showed that ^{13}C-EtOH, ^{13}C-acetate, and ^{13}C-formate were the main metabolites from the mid-log cultured *Shigella*. Also in the infection assay, these metabolites dominated the carbon flux from glucose together with ^{13}C-lactate generated by the HeLa cells. However, the ^{13}C-formate and ^{13}C-EtOH production were terminated when *Shigella* invaded into HeLa cells whereas ^{13}C-acetate production continued. We tested the ability of acetate, lactate, and formate to attenuate infection. A significant decrease in infection rate was obtained when HeLa cells were pretreated with formate. Contrarily, acetate pretreatment on HeLa cells resulted in an increased infection rate.

Our data firstly described that the main metabolites, acetate, EtOH and formate are potential good biomarkers for intracellular *Shigella* metabolism since HeLa cells essentially do not produce these. Observed changes in the ratio between these metabolites indicate that the fermentation pathway used by *Shigella* during intracellular proliferation compared to *ex vivo* conditions changed. Especially formate production was found to be sensitive to the environment

of the *Shigella* proliferation. While formate has been shown in literature to increase *Shigella* virulence we additionally observed that it also increases the ability of HeLa cells to withstand infection. Formate metabolism thus candidate for further investigations to understand it's complex role in pathogenesis. We think that detailed understanding of the intracellular lifestyle of bacterial pathogens is an alternative way for developing new therapeutic strategies adressing the increasing issue of antibiotics resistance of *Shigella* infection.