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No evidence of a role for mitochondrial complex I in *Helicobacter pylori* pathogenesis

Running title: Complex I activity does not alter gastritis

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ABSTRACT

Background: Complex I is the first enzyme complex in the mitochondrial respiratory chain, responsible for generating a large fraction of energy during oxidative phosphorylation. Recently, it has been identified that complex I deficiency can result in increased inflammation due to the generation of reactive oxygen species by innate immune cells. As a reduction in complex I activity has been demonstrated in human stomachs with atrophic gastritis, we investigated whether complex I deficiency could influence *Helicobacter pylori* pathogenesis.

Materials and Methods: *Ndufs6^{gt/gt}* mice have a partial complex I deficiency. Complex I activity was quantified in the stomachs and immune cells of *Ndufs6^{gt/gt}* mice by spectrophotometric assays. *Ndufs6^{gt/gt}* mice were infected with *H. pylori* and bacterial colonisation assessed by colony-forming assay, gastritis assessed histologically and *H. pylori*-specific humoral response quantified by ELISA.

Results: The immune cells and stomachs of *Ndufs6^{gt/gt}* mice were found to have significantly decreased complex I activity, validating the model for assessing the effects of complex I deficiency in *H. pylori* infection. However, there was no observable effect of complex I deficiency on either *H. pylori* colonisation, the resulting gastritis or the humoral response.

Conclusions: Although complex I activity is described to suppress innate immune responses and is decreased during atrophic gastritis in humans, our data suggest it does not affect *H. pylori* pathogenesis.

INTRODUCTION

Helicobacter pylori is a significant pathogen that colonizes the human stomach, typically from childhood, and which over decades, drives a chronic inflammatory response (gastritis) that, in some individuals, results in peptic ulcer disease and gastric cancers (1, 2). The magnitude of the inflammatory response mounted against *H. pylori* is believed to be a key determinant of whether individuals develop disease, with those individuals capable of limiting inflammation to a level that does not result in excessive tissue damage remaining asymptomatic for life. Many

proinflammatory cytokines and metabolites, including IL-1 β , IL-8 and reactive oxygen species (ROS), contribute to the pathology following infection (3-5).

Mitochondria have emerging roles in regulating the inflammatory response to infection. These include critical roles in initiating cell death, modulation of antiviral signalling, and of known relevance to *H. pylori* infection, the production of ROS which contributes to bactericidal activity and also ultimately triggers several distinct immune mechanisms (6, 7). Additionally, mitochondrial components released during infection or inflammation can activate the NLRP3 inflammasome (8, 9), a key inflammatory complex that is involved in the production of IL-1 β in response to *H. pylori* (10, 11). Although mitochondria are linked with many inflammatory pathways, and mitochondrial ROS has been linked to the increased proliferation of gastric cancer cell lines *in vitro* (12), studies demonstrating the role of mitochondria in the immune response to bacterial infections are currently lacking.

Mitochondrial complex I is the first enzyme complex in the respiratory chain, responsible for generating a large fraction of energy during oxidative phosphorylation (OXPHOS), and also the primary source of mitochondrial ROS in pathological scenarios (13). Defects in complex I are primarily associated with several inherited neurological diseases including Leigh syndrome, where disease onset is often triggered by an infection (14-16), as well as in Alzheimer's and Parkinson's disease (17). However, key roles for complex I activity were recently demonstrated in suppressing innate immunity. For example, *Ndufs4*^{-/-} mice, which have a severe deficiency in complex I, display basal systemic innate inflammation (18). In isolated immune cells from these mice, proinflammatory gene expression is driven by increased mitochondrial ROS production (18). In addition, treatment of mice with complex I inhibitors (i.e. metformin or rotenone) prior to pulmonary LPS exposure reduced the production of proinflammatory cytokines and subsequent inflammation, with similar effects observed in isolated neutrophils (19). A role for complex I may also be present in gut inflammation. Mice that had the C57BL/6 nuclear genome but inherited mitochondria from different inbred strains develop different severities of chemically-induced colitis that inversely correlate with the innate OXPHOS capacity of inherited mitochondria (20).

In humans, atrophic gastritis is associated with reductions in both maximal OXPHOS and decreased complex I activity (21). Given these associations and growing evidence for a role for mitochondria and complex I activity in modifying the

inflammatory response to infection, we theorized that the activity of complex I could be a key regulatory mechanism that controls inflammation following *H. pylori* infection.

MATERIALS AND METHODS

Mice

Specific pathogen-free 7-9 week old female C57BL/6 wildtype and *Ndufs6*^{gt/gt} mice (22) were bred and housed in the Disease Model Unit, Murdoch Childrens Research Institute, The Royal Children's Hospital, Melbourne, Australia. Experiments were performed with ethical approval from the Murdoch Childrens Research Institute Animal Ethics Committee.

Complex I activity assays

Supernatants (post-600 g) from homogenates of whole stomach or red blood cell-depleted splenocytes were prepared. Activities of complex I (rotenone-sensitive oxidation of NADH with coenzyme Q₁ as electron acceptor) and citrate synthase were measured spectrophotometrically over time, as described previously (23), except that assays were performed at 25°C for mouse tissues. Complex I activity was expressed relative to citrate synthase activity to correct for any variation in mitochondrial content between samples.

***Helicobacter pylori* culture**

H. pylori strain SS1 (24) was grown on horse blood agar plates (Blood Agar Base No. 2 (Oxoid, Basingstoke, UK), 5% horse blood (Australian Ethical Biologicals, Coburg, Australia) and 2.5 µg/mL Amphotericin B (Sigma, Castle Hill, Australia) in an anaerobic jar with a microaerophilic gas generating kit (Oxoid) for 2 days at 37°C. For infection of mice, bacteria were subcultured into brain heart infusion broth (BHI; Oxoid) containing 2.5 µg/mL Amphotericin B and 5% horse serum (Sigma) and grown in microaerophilic conditions for 24 hours at 180 rpm, 37°C. Mice were infected with a single oro-gastric dose of 10⁷ *H. pylori* (estimated by light microscopy) suspended in 100 µL BHI.

Colony-forming assay

Half stomachs (divided longitudinally) were homogenised in BHI and serial dilutions cultured on Glaxo selective supplement plates (as horse blood agar except with 3.75 µg/mL Amphotericin B, 12 µg/mL vancomycin hydrochloride, 0.4 µg/mL

polymyxin B sulphate, 24 µg/mL bacitracin and 13 µg/mL nalidixic acid) for 5 days in conditions as above. Colonies were counted and colony-forming units per stomach calculated (25).

Assessment of gastritis

Longitudinally halved stomachs were fixed in 10% neutral buffered formalin, embedded in paraffin, 5 µm sections cut and stained with H&E. Infections were assessed histologically as previously described (26): (1) cellular infiltration where 0, none; 1, mild multifocal; 2, mild widespread or moderate multifocal; 3, mild widespread and moderate multifocal; 4, moderate widespread or severe multifocal; 5, moderate widespread and severe multifocal; 6, severe widespread; (2) functional atrophy (loss of parietal cells) and (3) “mucus metaplasia” (development of large, clear, mucus producing cells) where 0, absent; 1, mild; 2, moderate; 3, severe.

Antibody ELISA

Sera were collected by cardiac puncture and anti-*Helicobacter* antibody levels determined by standard direct enzyme-linked immunosorbent assay (ELISA). Maxisorp immunoplates (Nunc, Roskilde, Denmark) were coated overnight with 50 µL of *H. pylori* SS1 sonicate lysate (100 µg/mL) in bicarbonate buffer, pH 9.6. Wells were blocked with 1% bovine serum albumin (BSA) in PBS (blocker) for 1 hour at room temperature (RT). Sera were serially diluted 1:10 in PBS–BSA, and 50 µL was added to duplicate wells, before incubation at RT for 1 hour. After washing, 50 µL of horseradish peroxidase conjugated goat anti-mouse IgG (Pierce, Rockford, IL, USA; diluted 1:5000 in PBS–BSA) was added per well and incubated at RT for 1 hour. Colour was developed by addition of 3,3',5,5'-tetramethylbenzidine (TMB) (Invitrogen, Camarillo, CA, USA), and the reaction was stopped by adding 50 µL of 2 mol/L sulfuric acid. Absorbance was read at 450 nm and end point titres calculated.

Statistics

Histological scores were assessed by Mann-Whitney U-test and all other data were log-transformed then compared by analysis of variance (ANOVA) with Dunnett's post hoc analysis (SPSS statistics version 21, IBM, Armonk, NY, USA).

RESULTS

Decreased complex I activity in stomachs and immune cells from *Ndufs6*^{gt/gt} mice

Although previous studies have demonstrated a clear role for complex I in inflammation using *Ndufs4*^{-/-} mice (18), NDUF54 deficiency results in neurological symptoms that necessitate euthanasia from 6+ weeks of age (27), making them unsuitable for investigating *Helicobacter* pathogenesis, which typically requires two months of infection to cause gastritis. We therefore examined the *Ndufs6*^{gt/gt} mouse, which has variable loss of complex I activity ranging from ~90% loss in heart to ~25% in brain (22). Female *Ndufs6*^{gt/gt} mice do not develop clinical symptoms until past 6 months of age (22), and were thus suitable for assessing gastritis development following *H. pylori* infection. Initially, we tested complex I activity in the stomach, the primary site of *H. pylori* infection, and red blood cell-depleted splenocytes, a representative leukocyte population, as the magnitude of complex I deficiency in these specific cells and tissue had not previously been characterised. *Ndufs6*^{gt/gt} stomachs and splenocytes had significantly decreased complex I activity corresponding to an average of 40% and 33% that of wildtype respectively (Figure 1). This confirmed the *Ndufs6*^{gt/gt} mouse as a valid model to examine the effects of decreased complex I activity on the severity of *H. pylori* gastritis.

Decreased complex I activity does not affect the severity of *H. pylori* gastritis in mice

Wildtype and *Ndufs6*^{gt/gt} mice were infected with *H. pylori* SS1 for two months before assessment. At this time point, there was no evidence of differential bacterial burden (Figure 2).

The development of a humoral response was assessed by measuring *H. pylori*-specific serum IgA and IgG (Figure 3). While infected mice had significantly higher *H. pylori*-specific IgG titres as expected, there was no difference between wildtype or *Ndufs6*^{gt/gt} mice, demonstrating no role of complex I deficiency in influencing the systemic humoral response to *H. pylori*.

Assessment of inflammation by quantification of stomach weights and histopathology revealed that both groups developed a significant cellular infiltrate with atrophic gastritis when infected with *H. pylori*, with no observable difference between wildtype and *Ndufs6*^{gt/gt} mice (Figure 4). These data demonstrate that complex I deficiency has no effect on *H. pylori* burden or the associated gastritis.

DISCUSSION

Regulatory mechanisms that control excessive inflammation are of great importance in preventing diseases that result from *H. pylori* infection. It is becoming clear that mitochondria are key regulators of innate immune responses, with potential roles in many infections (28). Although mitochondrial complex I was recently described to suppress innate immune activation (18), here we were unable to identify an effect of decreased complex I activity on *H. pylori* pathogenesis.

In this study we investigated the possibility that decreased complex I activity during atrophic gastritis modulated the host inflammatory response to *H. pylori* infection, a hypothesis that arose from previous studies that demonstrated decreased complex I activity during atrophic gastritis in humans and that complex I activity suppresses aspects of the innate immune response in mice (18, 21). However, we found that there was no correlation between decreased complex I activity and inflammation, the development of anti-*H. pylori* specific antibodies or bacterial colonisation. These data therefore do not support a role for complex I activity in *H. pylori* pathogenesis.

One discrepancy between our study and Jin et al (who demonstrated that complex I modulates the innate immune response) (18) was that we used *Ndufs6*^{gt/gt} mice, which overall display a less severe complex I deficiency than *Ndufs4*^{-/-} mice. As such, we cannot rule out that a more severe complex I deficiency may influence *H. pylori* pathogenesis. However, if a severe deficiency is required to demonstrate an effect, it is unclear what relevance this would have to human disease as *H. pylori* infection causes disease over decades and patients with severe complex I deficiencies generally succumb to early life mortality.

Our study raises the possibility that decreased complex I activity in the gastric mucosa may simply be a consequence rather than a modulator of the inflammatory response. Various immune cells, including macrophages and dendritic cells, when activated by proinflammatory stimuli, switch to glycolysis from oxidative phosphorylation as a primary means of generating energy (29). Therefore, downregulation of oxidative phosphorylation might result from recognition of *H. pylori* and subsequent activation of inflammatory signalling. These alterations, although clearly important in some situations, such as sepsis (30), appear unimportant for *H. pylori* inflammation, at least in mice.

One limitation of our study is that we only investigated the effects of complex I deficiency in female mice, due to our previous observations that male mice develop

very little inflammation in response to *H. pylori* infection (31). Recently, Dankowski et al reported a male-specific association between a polymorphism in the *MTND4* gene, which encodes a different subunit of mitochondrial complex I, with ulcerative colitis (32). This raises the possibility that defective complex I activity may only influence certain diseases in males. In order to further confirm our findings, future studies could include infecting male complex I-deficient mice with *Helicobacter felis* which, unlike *H. pylori*, is capable of inducing approximately equivalent inflammation in male versus female mice (33).

In conclusion, we have evaluated *H. pylori* pathogenesis in complex I deficient mice and have found no evidence to suggest that decreased complex I activity modulated bacterial colonisation or the immune response to infection.

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FIGURE LEGENDS

Figure 1: Stomachs and splenocytes from *Ndufs6*^{gt/gt} mice have decreased complex I activity. Stomach tissue or red blood cell-depleted splenocytes from wildtype (WT) and *Ndufs6*^{gt/gt} mice were assessed for complex I activity and the results normalised to citrate synthase activity. *Ndufs6*^{gt/gt} stomachs and spleens had significantly decreased complex I activity corresponding to an average of 40% and 33% compared to WT respectively (***, p<0.001; ANOVA). Graphs present samples from individual animals (points) and the median (bar).

Figure 2: Mitochondrial complex I deficiency does not affect *H. pylori* burden. Wildtype (WT; n=8) and *Ndufs6*^{gt/gt} mice (n=9) were infected with *H. pylori*. Two months after infection bacterial colonisation was assessed in individual animals by colony-forming assay on half stomachs. There was no significant difference in

colony-forming units between WT and *Ndufs6^{gt/gt}* mice (ANOVA). Graph presents individual animals (points) and the median (bar).

Figure 3: Mitochondrial complex I deficiency does not affect serum antibody titres after *H. pylori* infection. Wildtype (WT; n=8) and *Ndufs6^{gt/gt}* mice (n=9) were infected with *H. pylori*. Two months after infection sera was collected and anti-*H. pylori* IgA and IgG humoral responses assessed by ELISA. Infection with *H. pylori* resulted in significantly higher IgG endpoint titres (**p<0.01; ***p<0.001; ANOVA). However, there were no significant differences between WT and *Ndufs6^{gt/gt}* mice. Box-plots present the median (horizontal bar), interquartile range (box) and 10th and 90th percentiles (bars).

Figure 4: Mitochondrial complex I deficiency does not affect gastritis development after *H. pylori* infection. Wildtype (WT; n=8) and *Ndufs6^{gt/gt}* mice (n=9) were infected with *H. pylori*. Two months after infection (A) stomachs were weighed and (B) gastritis was assessed histologically from blinded H&E stained sections. *H. pylori* infection resulted in significantly increased cellular infiltrate and atrophy (*p>0.05; **p>0.01; ANOVA cf respective uninfected group). However, there were no significant differences between WT and *Ndufs6^{gt/gt}* mice. (A) Box-plot presents the median (horizontal bar), interquartile range (box) and 10th and 90th percentiles (bars); (B) Graph presents individual animals (points) and the median (bar).

Figure 1

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Figure 2

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Figure 3

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Figure 4

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