SUMMARY

The gastric epithelium experiences intermittent hypoxia due to various physiological and pathological conditions. Hypoxia and hypoxia-reoxygenation (H-R) are also integral components of the solid tumor microenvironment (TME). However, the impact of hypoxia and H-R of gastric epithelial cells (GECs) on *Helicobacter pylori*-mediated gastric cancer (GC) has never been investigated. Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) facilitate *H. pylori* adhesion onto GECs. The experiments performed in this thesis evaluated the effect of hypoxia and H-R on CEACAM6-mediated *H. pylori* binding, infection, reactive oxygen species (ROS) generation and GEC proliferation. Hypoxia-inducible factor 1 (HIF1α), a subunit of the transcription factor HIF1 that is stabilised during hypoxia, and CEACAM6 levels were assessed in various GECs. ROS were measured in GECs. Bioinformatics analyses were performed to identify the most prominent stomach adenocarcinoma (STAD)-associated NADPH oxidase (NOX) followed by validation by overexpression/suppression studies and western blotting. GC biopsies were examined by immunofluorescence microscopy. Hypoxia-exposed, reoxygenated or control cells were compared for ROS generation and *H. pylori* infection. MTT assay determined cell proliferation. It was also noted hypoxia and HIF1-mediated upregulation of CEACAM6 in GECs. CEACAM6 significantly promoted ROS generation by inducing NOX4 in hypoxic GECs. HIF1α, CEACAM6 and NOX4 upregulation was detected in gastritis and GC tissues. *H. pylori* infection significantly increased in hypoxia-exposed GECs as compared to normoxic GECs. Infection of hypoxia-reoxygenated GECs also resulted in significantly increased CEACAM6 and NOX4-mediated ROS generation as compared to normoxic GECs. In addition, adhesion of *H. pylori*, cytotoxin-associated gene A (CagA) translocation and GEC proliferation were significantly enhanced in hypoxia-reoxygenated GECs. Collectively, the findings of this thesis establish that, hypoxia and H-R of GECs facilitate *H. pylori* infection and infection-mediated

GEC proliferation. The hypoxic core of tumor tissue sends out various signaling cues to attract circulating macrophages. Tumor-associated macrophages (TAMs) are key players in the schematics of the TME. Immunofluorescence imaging revealed a higher infiltration of M2 (Arginase+) macrophages in cancer tissues and a reduction in M1 (iNOS+) macrophage infiltration. Furthermore, it was also confirmed that hypoxia-mediated CEACAM6 upregulation led to enhanced migration and proliferation in GECs. Exposure of macrophages to the supernatant from CEACAM6-expressing GECs led to the suppression of the M1 phenotype and polarization towards the M2 phenotype. In conclusion, this thesis asserts the importance of CEACAM6 in hypoxia-driven GC progression. Moreover, CEACAM6 emerged as a promising target in the treatment of GC.