ABSTRACT

One of the most common infections of a human organism is an infection of stomach induced by pathogenic bacteria *Helicobacter pylori (H. pylori)*. It is estimated that every second person is infected, with even higher prevalence in developing countries. As a quiet enemy, *H. pylori* can colonise a human stomach for decades without manifestation of infection-associated symptoms. However, chronic infection may cause severe damage to the stomach tissue, subsequently leading to the development of gastric diseases, including gastritis and ulcer disease. *H. pylori* infection is also a driving cause of gastric cancer, with 80% of gastric cancers being associated with chronic infection. *H. pylori* ensures its life-long persistence in a human host organism *via* the action of its virulence factors, which have a pleiotropic effect on multiple systems, mostly acting on the attenuation of a human immune system and the induction of atrophy of stomach tissue. The irreversible changes of stomach epithelium are induced by activation of an innate immune response in *H. pylori*-exposed epithelial cells through the stimulation of ALPK1/TIFA/NF-κB signalling pathway upon a recognition of β-ADP heptose, an intermediate product of bacterial lipopolysaccharide biosynthesis, and consequently leading to the formation of DNA double-strand breaks in host cells. We observed that *H. pylori*-induced DNA damage occurs in a manner dependent on an NF-κB-driven transcription, predominantly in cells undergoing DNA replication. In addition, we showed that DNA double-strand breaks are formed as a result of collisions between replication and transcription machineries driven by the accumulation of genotoxic RNA:DNA hybrids, referred to as R-loops, in the host genome. In conclusion, we showed that *H. pylori*-induced oncogenic transformation of stomach tissue might be initiated *via* the excessive formation of DNA double-strand breaks induced as a consequence of R-loop-mediated replication stress in a manner dependent on ALPK1/TIFA/NF-κB signalling pathway.

Keywords: *Helicobacter pylori*, R-loops, replication stress, DNA damage, gastric cancer