The importance of IL-33 in the monitoring of the gastric epithelial barrier function and the regulation of inflammatory processes induced by local bacterial pathogens as well as diet and pharmacological agents.

Gastrointestinal epithelial cells build a selectively permeable barrier that separates the external environment from the internal organs. This barrier has a protective role against harmful particles and pathogens, while allowing efficient transport of nutrients. Gastric epithelium is cylindrical and forms a compact layer covered with a mucus. Mucins present in mucus bind pathogens via sugar molecules and inhibit their adhesion to epithelial cells thus preventing the development of specific infections. Proteins such as occludin, claudin and adhesive proteins play an important role in maintaining the integrity of the epithelial barrier due to binding adjacent cells. These proteins determine the tightness of the epithelial barrier and also regulate cell division as well as cell differentiation. Proper function of the gastric epithelial barrier is required to maintaince a balance between cell division and cell death. Excessive proliferation may increase the risk of dangerous mutations and the development of gastric tumors. In contrast, the weakened cell regeneration can result in an inhibition of wound healing. Growth of epithelial cells is controlled by many factors secreted locally or on endocrine way. Prostaglandins have the protective effect by reducing the concentration of gastric acid and regulating mucus secretion as well as blood flow.

Until 1983 it was believed that stomach is free from microbes due to acidic pH. However, now we know that some microbes can survive or even propagate in such environment. *Helicobacter pylori* bacteria are well adopted to acidic environment of the stomach. They successfully colonize the gastric epithelium. Adhesion of these bacteria to the gastric epithelium plays the main role in the development of infection. The surface adhesins are involved in this process including sialic acid binding adhesin – SabA, blood group antigen binding adhesin – BabA and outer membrane inflammatory adhesin – OipA. These molecules are recognized by receptors of epithelial cells.

Damage of epithelial cells by soluble *H. pylori* factors or molecules derived from degraded bacterial cells can initiate the development of an inflammatory response, which involves an accumulation of immune cells. Neutrophils are coming first. They are attracted by soluble molecules so called cytokines, including interleukin (IL) -8. Neutrophils are innate immune cells which are characterized by a strong ability to engulf and destroy infectious agents. Although neutrophils produce reactive oxygen species (ROS), they are not effective in digestion of *H. pylori* bacteria enclosed within the phagosome. However, ROS are released to the gastric environment, where they destroy surrounding tissues. Also pro-inflammatory cytokines secreted in excess can destroy the tight junctions of epithelial cells.

Gastric mucosa is exposed to diet compounds and pharmacological agents. Non-steroidal anti-inflammatory drugs, which include acetylsalicylic acid (ASA), known as aspirin, are widely used for treatment of pain, fever and inflammation. Patients with coronary heart disease receive low-dose aspirin treatment in order to inhibit blood clothing. Aspirin irritates gastric epithelial cells, increasing the risk of erosions and gastric ulcers. Probably aspirin inhibits the process of wound healing. Since *H. pylori* infections are very common and cause stomach ulcers it is possible that intake of aspirin may increase epithelial cell damage. In addition, damage caused by aspirin may enhance the risk of *H. pylori* infections. The stability of gastric epithelial barrier may be disrupted by food compounds especially lipid such as cholesterol, which can initiate an inflammatory response in the gastrointestinal tract. The gastric epithelium may contain lipid islands, which include low-density lipoprotein (LDL) in oxidized form. An increased concentration of cholesterol is associated with eleveted levels of conventional pro-inflammatory cytokines such as TNF-alpha and IL-6. It should also be mentioned that dietary lipids can locally increase inflammation and contribute to the development of malignancy. It can be assumed that the gastric epithelial damage caused by *H. pylori* may be depened by drugs and dietary lipids. Damaged epithelial cells secrete molecules called DAMPs (damage-associated molecular patterns), which act as alarming signals informing the immune system about the disruption of homeostasis. DAMPs include: heat shock proteins (Hsp), fibronectin, double-stranded and mitochondrial DNA, ATP, high-mobility group protein B1 (HMGB-1), IL-1α and IL-33. The level of IL-33 significantly increases in response to the epithelial barrier damage and due to an infection. This cytokine is produced primarily by epithelial cells and vascular endothelium. It acts like a traditional cytokine or as regulator of transcription. It is suggested that during *H. pylor*i infection, its production can be inhibited. IL-33 mediates the response of T helper lymphocytes of Th2-type. Due to this the diminished concentration of IL-33 may play important role in an induction of Th1-type immune response during *H. pylori* infection.

The current knowledge of the processes in the gastric epithelium initiated with aspirin and diet lipids, with the local *H. pylori* co-infection is insufficient. Therefore, in this project we would like to investigate the effects of *H. pylori* colonizing the gastric epithelium in humans and oxidized fraction of low-density lipoprotein (7-ketocholesterol) as well as ASA on the stability of gastric epithelial cells using *in vitro* cellular models. We plan to evaluate epithelial cell functions on the basis of their adherence, the expression of tight junction proteins, epithelial tightness, resistance measurement, the flow of ions, the cell cycle, signs of necrosis and apoptosis. We will assess whether dysfunction of epithelial cells increases the secretion of IL-33 and a panel of proinflammatory cytokines as well as an expression of ICAM-1 (intercellular adhesion molecule 1) integrin, which promotes infiltration of immune cells. IL-33 is probably responsible for mobilization and activation of granulocytes. Therefore, we would like to examine, using a dual cell culture system containing epithelial cells and granulocytes isolated from peripheral blood of healthy individuals, whether granulocytes can infiltrate epithelial cells in milieu of *H. pylori* antigens, dietary lipids, ASA and IL-33. On the basis of myeloperoxidase produced by neutrophils, we want to estimate the degree of granulocyte activation. We want to know how IL-33 influences the ability of granulocytes and macrophages to engulf and eliminate *H. pylori*. These studies haven't been undertaken yet and would lead to the explanation how selected *H. pylori* antigens influence gastric epithelial cells alone and in the presence of dietary lipids or aspirin. We will discover whether the effects initiated by an infectious agent may be aggravated by drugs and dietary lipids. Whether mobilization of the immune cells such as granulocytes, which play a crucial role in the development of inflammatory response during *H. pylori* infection depends on IL-33. We will explain know whether IL-33 increases or inhibits bactericidal activity of granulocytes and macrophages against *H. pylori*. These study will help to understand the chronic nature of *H. pylori* infections and will explein possible relationships between local inflammatory response within the gastric epithelium and systemic inflammatory response. This aspect is particularly interesting because many data, suggest that chronic *H. pylori* infection may contribute to the development of coronary heart disease. An independent risk factor for this disease is the oxidized low density lipoprotein. This is why we are focusing on the role of dietary lipids in the maintenance of inflammatory response. It should also be noted that both *H. pylori* and food lipids are related to the development of cancer.