Transcriptional regulation of the nickel and iron metabolism in *Helicobacter pylori*.
Florian D. Ernst (Defence: 15.12.2005)

Up to half of the world's population is infected with *Helicobacter pylori*, a bacterium which colonizes the mucus layer of the human stomach. *H. pylori* is a neutralophilic bacterium that survives in the acidic conditions occuring in the mucus layer with the help of the enzyme urease. Urease is a nickel-cofactored enzyme that converts urea into ammonia and carbon dioxide, thereby keeping the intracellular and periplasmic pH at neutral.

Metal ions play an important role in metabolism of all living cells, by functioning as cofactors of enzymes and participation in redox reactions. However, metal ions like nickel or iron can also be dangerous for bacteria, as they can react with oxygen in order to create reactive oxygen species that in turn can destroy macromolecules of the cell. Therefore, the bacterial metal metabolism has to be tightly regulated. In *H. pylori* only two metal-regulatory proteins are known, the ferric uptake regulator Fur, and the nickel responsive regulator NikR.

Fur is a regulatory protein that can sense and bind intracellular Fe^{2+} ions, and subsequently represses its target genes in high-iron conditions by binding to specific sequences in its target promoters (Fur-boxes). Unlike all other Fur homologs known so far, *H. pylori* Fur can also bind to Fur-boxes in an iron free form (apo-Fur). At first a complete Fur regulon was identify and characterize with the help of microarray analysis. A set of 32 genes was found to be Fur-dependently regulated, of which 16 genes are classical iron- and Fur-dependently repressed and 16 genes were found to be iron-induced and apo-Fur-dependently expressed. One of the newly identified genes is the iron-containing superoxide dismutase gene *sodB*, which is important in the defense of *H. pylori* against toxic reactive oxygen species, like those produced by the immune system. Using gelshift and DNase footprint assays it was demonstrated that the *sodB* gene is directly regulated by apo-Fur in *H. pylori*. This regulation constitutes a novel mechanism for regulation of expression of Fe-containing superoxide dismutases in prokaryotes.

It is furthermore demonstrated that the nickel-dependent regulator NikR of *H. pylori* functions both as repressor and inducer of gene transcription. It is involved in the regulation of nickel metabolism by direct nickel-dependent repression of the nickel uptake system *nixA* by binding to the promoter region of the *nixA* gene. NikR is also involved in the acid resistance by nickel-dependent induction of the urease gene *ureA* by binding to a region upstream of the *ureA* promoter. Whether NikR of *H. pylori* functions as repressor and activator of gene transcription seems therefore to dependent on the position of the NikR binding site. Furthermore, NikR was previously demonstrated to indirectly mediate the iron metabolism of *H. pylori* via regulation of Fur. However, next to this indirect route, NikR is also able to regulate the iron-uptake genes *frpB3* and *fecA3* by direct nickel-dependent binding to the promoter region of these genes.

The use of overlapping and crossresponding regulons by *H. pylori* may allow the finetuning of the multifactorial response to unique environmental stresses encountered in the gastric mucosa and thus aids the lifelong colonization of the gastric mucosa by *H. pylori*.

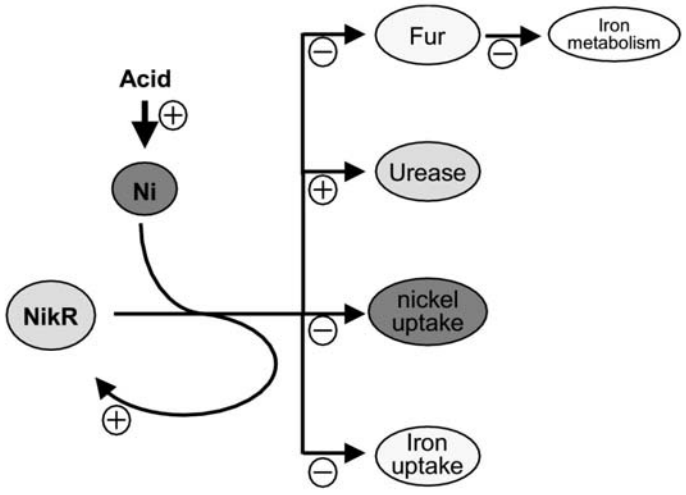

Fig. 1. NikR- and Fur-dependent regulation in *Helicobacter pylori*.