Intestinal metaplasia (IM) is a pre-neoplastic lesion characterized by a phenotypic switch from the normal mucosa to an intestinal phenotype. IM typically appears in the context of chronic inflammation, in locations such as the gastric and the esophageal mucosa. In the stomach, IM is strongly associated to Helicobacter pylori (Hp) infection and subsequent inflammation and is triggered by “de novo” expression of the intestinal gene CDX2. We have been studying the mechanisms that regulate CDX2 expression in gastric cells. We showed that Hp and the BMP/SMAD4 pathway, which is overexpressed in IM foci, upregulate CDX2 expression in gastric cell lines. In addition, these factors down-regulate SOX2, which negatively regulates CDX2, contributing for CDX2 expression and consequent loss of gastric differentiation and gain of intestinal differentiation. Finally, we observed that CDX2 is autoregulated, possibly perpetuating intestinal differentiation after removal of the initial triggering event.