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Coordinatore: Chiar.mo Prof. *Antonietta Leone*

Regolazione epigenetica dell'espressione del fattore peptidico gastrointestinale TFF1

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Dottorando
Dott.ssa
Piera Ferro

Tutore
Chiar.ma Prof.ssa
Alessandra Tosco

ABSTRACT

TFF1 is a protein expressed in the gastrointestinal tract, belonging to the trefoil folding factor family, characterized by a conserved “trefoil domain” containing six cysteine residues that form a cloverleaf disulfide structure. TFF1 is able to bind copper *in vitro*, favoring its homodimerization. TFF1 plays a key role in the correct formation of the mucous layer, promotes the epithelial restitution after injury and protects the integrity of the epithelial barrier. Its expression is regulated by epigenetic mechanisms such as histone modifications and DNA methylation. Altered gene expression in different pathologies is often associated with an altered DNA methylation pattern of TFF1 promoter, while histone modifications are essential in activating TFF1 transcription mediated by estrogen stimulation. Furthermore, TFF1 secreted in the gastric mucus layer may act as docking site for *H. pylori* adhesion on mucosal surface and it was demonstrated that the infection induces aberrant methylation correlated with gastric cancer risk.

This project is aimed at investigating the role of the epigenetic control on the TFF1 gene promoter, particularly DNA methylation. The conditions of high resolution melting method were optimized in order to evaluate the differential state of methylation of several CGs on the promoter region of tff1 in different experimental conditions. The study was mainly focused on the involvement of TFF1 in neoplastic processes and inflammatory diseases, as gastric cancer and *H. pylori* infection, in order to gain insight into the pathogenic mechanisms and provide useful tools to interfere and slowing down the disease progression.

Moreover, further attention is dedicated to the ongoing study regarding the effects of copper on transcriptional regulation of TFF1 and epigenetic modifications. It was demonstrated that TFF1 expression is regulated by copper and that the transcription factor Sp1 is involved in this metal-mediated regulation of transcription. Copper is not able to affect TFF1 promoter methylation in copper overload conditions. This was demonstrated with a method of High Resolution Melting which was assessed on TFF1 promoter and validated. Deep analysis on TFF1 promoter methylation status let us find out a minimum region responsible for TFF1 expression regulation by DNA methylation.

Concernig *H. pylori*, we focused on the early step of the infection to study the role of TFF1 using two cell models with different features and TFF1 expression: we lighted up alterations of TFFs, inflammatory cyitokines and EMT markers, that were differentially induced or repressed in the two different cell lines. Furthermore an altered methylation of TFF1 and genes involved in Wnt pathway emerged.