EP0039
ePoster Session
Interesting stories about virulence and pathogenesis

Deregulation of microRNAs in a mouse model of Helicobacter pylori-associated gastric lymphomagenesis

Pauline Floch*[1], Caroline Capdevielle[1], Cathy Staedel[2], Francis Megraud[3], Philippe Lehours[1]

[1]*University of Bordeaux, Inserm U1053, Bordeaux, France*

[2]*University of Bordeaux, Inserm U869, Bordeaux, France*

[3]*University of Bordeaux, Inserm U853, Bacteriology, Bordeaux, France*

Background: *Helicobacter pylori* (*H. pylori*) infection is considered an excellent model of chronic inflammation-induced tumor development. Our project focuses on gastric MALT lymphoma (GML) related to *H. pylori* infection, the most common extranodal digestive lymphomas but less studied than gastric carcinoma. Nevertheless, it is a severe disease which originates from a chronic inflammatory process initiated by *H. pylori*. Recently, microRNAs (miRNAs) have emerged as a new class of gene regulators and play a key role in inflammation and carcinogenesis acting as oncogenes or as tumor suppressors. The precise characterization of the role of miRNAs in the development of inflammation and their contribution in regulating responses of host cells to infection by *H. pylori* have been little explored. Our goal was to analyze the miRNAs specifically induced in a mouse model of GML previously described by the laboratory using BALB/c mice thymectomised at day 3 post-birth (d3Tx model) (Chrisment D *and al.*, Am J Pathol 2014) and to clarify their implication in GML pathogenesis.

Material/methods: Gastric and sera samples from d3Tx and non-thymectomised BALB/c mice were used. A global approach based on PCR array was first conducted on a limited number of gastric samples. Overexpression of 5 miRNAs was confirmed by RT-qPCR on a large number of samples in order to evaluate more precisely their specific dysregulation at lymphoma stage. miRNA expression was correlated with the gastric inflammatory scores previously described. miRNA expression in serum was also evaluated by RT-qPCR. *In situ* hybridization on paraffin gastric biopsies were carried out to verify the overexpression of one of these miRNAs and to identify the cells at the origin of this deregulation within the tumor.

Results: We identified five miRNAs (miR-21a, miR-135b, miR-142a, miR-150, miR-155) overexpressed in the stomachs of GML-developing d3Tx mice infected by *H. pylori*. The analysis of their putative targets using the Targetscan website and review of the literature, allowed us to propose possible targets of these miRNAs, and among them TP53INP1 an antiproliferative and proapoptotic protein, which is targeted by 4 of the 5 miRNAs upregulated in our model. We propose a scenario by which these miRNAs may be involved in cell survival and lymphocyte proliferation and act in synergy to promote the development of GML. miR-142a was also overexpressed in sera samples and therefore could serve as a diagnostic marker. ISH on gastric samples revealed a global upregulation of this miRNA at lymphoma stage.

Conclusions: Overexpression of these 5 miRNAs could play a critical role in the pathogenesis of GML and might have potential application as therapeutic targets and novel biomarkers for this disease. The analysis of these miRNAs in human biopsies or histological sections would validate their deregulation at GML stage and define potential new therapeutic targets.