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Helicobacter pylori-induced infection and its involvement in gastric cancer progression

Helicobacter pylori (Hp) is Gram-negative bacterium, which infects more than half of human population and can promote the development of severe diseases, such as atrophic gastritis, peptic ulcer, lymphoma of the mucosa-associated lymphoid tissue (MALT) or gastric adenocarcinoma. All these Hp-related pathological conditions are triggered by Hp-induced inflammation with the infiltration of innate immune cells in the gastric mucosa and the accumulation of pro-inflammatory factors (Moyat M and Velin D, 2014; Shi Y *et al.,* 2010). Hp infection is the strongest known risk factor for malignancies that arise within the stomach. Gastric cancer can metastasize in different ways and the epithelial mesenchymal transition (EMT) is the first cell transition for cancer spreading. During the EMT the expression of the tumor suppressor programmed cell death 4 (PDCD4) decreases, while there is an increased expression of the transcription factor TWIST1 which, in turn, down-regulates the expression of E-cadherin, a crucial protein for cell-to-cell adhesion *(Yu H et al., 2014)*. Although it has been suggested a role of Hp during EMT in gastric cancer *(Choi YJ et al., 2015)*, the molecular mechanisms and factors involved have not been elucidated yet. Similarly, although the contribution of tumor-associated macrophages (TAM) in the progression of several types of tumors is established, little is known about their role in the gastric cancer.

Therefore, we plan to evaluate the EMT pathways triggered by Hp infection addressing: i) the impact of Hp on the PDCD4/TWIST1 pathway in gastric cancer cells and ii) the role of Hp-infected macrophages on the EMT of gastric cancer cells. In particular, it would be assessed the expression of the genes mentioned above, but also the production of different pro-inflammatory molecules (VEGF, IL-10 and TGF-β) by Hp-activated macrophages, whose the role in EMT has been suggested *(Mak P et al., 2010; Choi YJ et al., 2015).*

In the past few years, it has been identified another important cellular component of the tumor microenvironment with immune suppressive ability: the myeloid-derived suppressor cells (MDSCs) *(Kumar V et al., 2016)*. MDSCs are a heterogeneous population of immature monocytes or granulocytes with different phenotypes and functional characteristics *(Gabrilovich DI and Nagaraj S, 2009)*. MDSCs are abundant in cancer patients and they can be recruited at the tumor site where they promote cancer progression *(Montero AJ et al., 2012)*. Moreover, MDSCs are also

involved in inflammation, autoimmunity, trauma, as well as bacterial infections *(Janols H et al., 2014; Gabrilovich DI and Nagaraj S, 2009)*. Whereas the role of MDSCs in the impairment of lymphocyte responses towards the tumor growth has been established *(Gabrilovich DI and Nagaraj S, 2009)*, there is only limited information about their involvement in acute and chronic bacteria-induced inflammation *(Obregón-Henao A et al., 2013; Heim CE et al., 2014)*. The aim of this part of the project is the identification and characterization of MDSCs in Hp-induced gastritis, a condition that in certain subjects may evolve in cancer. We plan also to assess if Hp promotes the activation of the immunosuppressive activity of MDSCs. Based on evidence reported in literature *(Solito S et al., 2014)*, we adopted a panel of different antibodies to identify specific subsets of MDSC by applying multicolor flow cytometry to the peripheral blood samples of Hp-chronic gastritis patients. Our preliminary data indicate that in blood collected from patients with Hp-induced chronic gastritis there is an increase of the granulocytic subtype of MDSCs (Lin^- $HLADR^-$ $CD33^+$ $CD11b^+$) with respect to healthy subjects.

The data obtained will contribute to elucidate the mechanisms and factors through which Hp facilitates the development of gastric cancer and its spreading.