THESIS TOPIC

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Thesis title:
Interaction between T cells and the enteric nervous system in colorectal cancer

Unit / team: TENS-INSERM 1235

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Socio-economic and scientific context (approximately 10 lines):
Colorectal cancer (CRC) is the third most common cancers in the world. Despite recent progress in CRC survival as a result of improved screening and treatments, it is still the second most deadly form of cancer. Further understanding of the remodeling of the tumor microenvironment during CRC and its impact on tumor development is essential to improve CRC prognosis. Among key constituents of the tumor microenvironment gaining increased interest in digestive cancers is the enteric nervous system (ENS). The ENS is composed of neurons and glial cells located all along the gastrointestinal tract, involved in gut motility and epithelial barrier homeostasis. Colorectal tumor development is associated with a remodeling of the ENS. Different studies including ours have shown that tumor-associated ENS promotes tumor development by inducing tumor cells migration and proliferation through direct interaction. Beside directly interacting with epithelial cells, enteric neurons and glial cells modulate the functions of immune cells, including macrophages and innate lymphoid cells, and play thus an important role in mucosal immunosurveillance. We recently uncover a role for the ENS in modulating conventional T cells survival and activation state. Despite the importance of T cells infiltrate for CRC prognosis and treatment, the role of the ENS in modulating T cells-mediated colorectal cancer immunosurveillance remains unknown.

Working hypothesis and aims (approximately 8 lines):
Our hypothesis is that the ENS can impact CRC progression by modulating the tumor immune environment, and especially T cells mediated cancer immunosurveillance.

Our aims are 1) to characterize the interaction between T cells and the ENS in intestinal plexus around tumors and at distant sites in both CRC patients and animal models 2) to decipher the impact of the ENS on T cells anti-tumoral functions both in vitro and in preclinical models of CRC.

Main milestones of the thesis (approximately 12 lines):

Task 1. Characterization of T cells-ENS interaction in colorectal cancer (year 1 and 2)
This part aims at characterizing the interaction between T cells and ENS (enteric neurons and glial cells) in a tumoral context. T cells (CD3), glial cells (S100b) and neurons (Hu, Tuj) will be stained on fixed tissues from CRC patients (from our already existing biobank) and from mice models of CRC (AOM treated mice). The myenteric plexus will be analysed and spatial proximity or potential contacts between T cells and enteric neurons or glial cells will be quantified.

Task 2. Impact of T cells-ENS interaction on T cells functions (year 1 and 2)
Primary culture of ENS and T cells will be used to study the functional impact of ENS-T cells interaction on T cells functions, including IFNγ production, cytotoxic activity and the expression of immune checkpoint molecules.

Task 3. Impact of the ENS on tumor immune infiltrate in vivo (year 2 and 3)
In this part we will study the functional impact of T cells-ENS interaction for tumor progression. This part will be done in parallel of another project from the laboratory, which aims at characterizing the ENS remodeling in a tumoral context. This project will use sequencing approaches in order to identify candidate neuromediators involved in tumor progression. We will thus block the identified neuromediators (by pharmacological or genetic tools) in mice models of CRC and study the consequence on tumor growth and on tumor immune infiltrate at different time points.
### Scientific and technical skills required by the candidate (2 lines):

The candidate must have an experience in cell culture, including primary cultures, and immunofluorescence staining. Solid knowledge in immunology and/or tumor immunology will be a plus.

### 3 publications from the team related to the topic (last 5 years):


### National and international collaborations:

- Shaynoor Dramsi (Institut Pasteur, Paris)
- Mathias Chamaillard (Institut Pasteur, Lille)
- Laurence Zitvogel (IGR, Villejuif)