PROGETTO

Supervisore:: _____CARLA TAVEGGIA_____

Titolo/*Title*: Molecular Mechanisms regulating perineural invasion in pancreatic adenocarcinoma_____

Curriculum: _____NEN_____

Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento: ___https://research.hsr.it/en/institutes/institute-of-experimental-neurology/axo-glia-interaction.html_

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

Direct cross communications between cancer cells and peripheral nerves actively influence the tumor microenvironment as well as tumor progression and metastasis[1,2]. However, the events controlling how nerves and cancer cells influence each other are complex[3], and likely regulated by the tumor microenviroment and by the type of nerve fibers innervating the tumor[4,5]. Regardless of the mechanism, the communication between tumor cells and nerves regulates cancer initiation, invasion and metastasis, often through the release of neurotransmitters[6].

Rationale and hypothesis

The centrality of nerves in cancer is particularly compelling in perineural invasion (PNI), which constitutes an alternative route for cancer cell dissemination in addition to lymphatic and hematogenous spreading and is characterized by nerve hypertrophy [7]. PNI has its higher incidence in pancreatic adenocarcinoma (PDAC), in which it is present in almost 80%-100% of tumors [8,9]. PDAC is the fourth leading cause of cancer-related death, with a 5-year overall survival (OS) of only 5% in all affected patients and of 25% in those undergoing surgery [10]. In PDAC, PNI is a recognized risk factor of poor survival after surgery and correlates with pain, additionally impacting the quality of life of patients [9,11,12]. Thus, characterizing the molecular events at the basis of PNI in PDAC is urgent as it could lead to the development of new therapies that might effectively limit disease progression.

In PDAC, Schwann cells (SCs), the glial cells of the peripheral nervous system (PNS), colonize the tumors before cancer invasion [13] and actively degrade the extracellular matrix and instruct cancer cell by directly contacting them [3,14]. Moreover they can indirectly

modulate the tumor microenvironment by acting onto angiogenesis and the inflammatory milieu[15].

Objectives and specific aims

A PhD project is available to investigate the role of PNI in PDAC, by looking at the interactions between cancer cells and nerve/glial cells of the PNS. Our previous studies indicate that the mechanisms regulating PNI in PDAC strongly resembles those activated to induce nerve repair upon injury. Further, we have identified a molecular target involved in PNI formation and development, using ad hoc designed in vitro system with neuron/glial cells and PDAC organoids. The candidate will be asked to evaluate the role of the nerve repair program in PNI in PDAC by using orthotopic transplantation of organoids in which the expression of target molecules have been ablated by crispr/cas9 technologies. In addition, to better characterize all events at the basis of PNI, the candidate will exploit a newly developed animal model, already available in the Institute that develops PDAC and PNI and analyze the role of the nerve repair program in vivo in tumor formation by spatial transcriptomic analyses.

Expected outcome

The results of these studies might pave the way to identify new therapeutic strategies to counteract PNI formation in PDAC.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi)

We expect the student to become skillful with complex in vitro culture systems, generation and maintenance of pancreatic organoids and in vivo analyses. Thus, he/she will acquire expertise in mouse genetics and in morphological analyses of the nervous system and of the pancreas.
Further, he/she will become proficient in cell biology, mainly primary cultures and in the biochemical/functional characterization of nerve-glial cells-tumor cells interaction in tumor formation and spreading.

Bibliografia (max. 15)

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