UNIVERSITÀ DEGLI STUDI DI MILANO

D-MEM PhD-UNIMI | Doctorate program Milan EXPERIMENTAL MEDICINE

Adipo-NETwork: inside the crosstalk between adipose cells and gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

General overview and rationale of the study

A growing body of evidence suggests that adipose cells, such as mature adipocytes and adipose-derived mesenchymal stem cells, sustain the development and progression of several solid tumors both at the systemic level and locally, as a part of the tumor microenvironment (1, 2). In gastroenteropancreatic neuroendocrine tumors (GEP-NETs) a significant association between obesity-related disorders and tumor onset/aggressiveness has been recently described (3, 4). However, the potential crosstalk between GEP-NETs and adipose tissue is still unknown and no data are available about the characterization of adipose cells in the tumor microenvironment of these neoplasms.

In several tumors, adipose and tumor cells establish a bidirectional communication, which is mediated by the secretion of hormones, growth factors and cytokines, as well as of exosomes containing bioactive molecules. Indeed, cancer cells induce a massive secretion of inflammatory adipokines and growth factors in adipose cells, able to sustain reciprocally cell proliferation. Tumor cells can also stimulate adipocytes to secrete fatty acids, which in turn support tumor metabolism. In this frame, several pharmacological agents have been recently developed to target lipid metabolism in cancer cells for therapeutic purposes (5, 6). This pharmacological strategy could be promising for GEP-NETs, in which alterations in lipid synthesis/metabolism have been detected (7).

Different platforms combining in vitro co-cultures and in vivo experiments in zebrafish are currently available to study the crosstalk between adipose and cancer cells (8). In the last years, we have developed an innovative preclinical model to study tumor-induced angiogenesis and invasiveness through the xenotransplantation of NET cells in zebrafish embryos (9). We took advantage of the *Tg(fli1a:EGFP)*^{y1} line which expresses enhanced green fluorescent protein (EGFP) in endothelial cells under the control of the fli1a promoter, thus labelling all blood vessels and providing a live visual marker for vascular development due to the optical transparency of zebrafish embryos. This quick transplantable platform resulted particularly suitable for cancer drug testing. Interestingly, we have collected preliminary data on GEP-NET immortalized cell lines and patient-derived adipose cells implanted in zebrafish embryos, demonstrating their attitude to stimulate angiogenesis and migrate far from the injection site within only two days post-injection (dpi). These data represent a promising starting point to study the crosstalk between adipose cells and GEP-NETs.

Aims

- To study the reciprocal influence of GEP-NETs and adipose cells on 1) cell viability, cell cycle, apoptosis, migration, secreted factors and adipose tissue-derived exosomes, through an in vitro co-culture model; 2) proangiogenic and invasive potential of both cell populations, using an in vivo zebrafish platform.
- To study the anti-tumor activity of new drugs targeting lipid metabolism in GEP-NETs, taking advantage of previously reported in vitro and in vivo models.

References

1. Chu DT et al. The Effects of Adipocytes on the Regulation of Breast Cancer in the Tumor Microenvironment: An Update. Cells. 2019;8(8):857.
2. Di Franco S et al. Adipose stem cell niche reprograms the colorectal cancer stem cell metastatic machinery. Nat Commun. 2021;12(1):5006.
3. Barrea L et al. Cardio-Metabolic Indices and Metabolic Syndrome as Predictors of Clinical Severity of Gastroenteropancreatic Neuroendocrine Tumors. Front Endocrinol (Lausanne). 2021;12:649496.
4. Santos AP et al. Visceral Obesity and Metabolic Syndrome Are Associated with Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors. Cancers (Basel). 2018;10(9):293.
5. Drury J et al. Inhibition of Fatty Acid Synthase Upregulates Expression of CD36 to Sustain Proliferation of Colorectal Cancer Cells. Front Oncol. 2020;10:1185.
6. Cheng S et al. Fatty acid oxidation inhibitor etomoxir suppresses tumor progression and induces cell cycle arrest via PPARγ-mediated pathway in bladder cancer. Clin Sci (Lond). 2019;133(15):1745-1758.
7. Vernieri C et al. Impact of Metformin on Systemic Metabolism and Survival of Patients With Advanced Pancreatic Neuroendocrine Tumors. Front Oncol. 2019;9:902.
8. Koual M et al. Aggressiveness and Metastatic Potential of Breast Cancer Cells Co-Cultured with Preadipocytes and Exposed to an Environmental Pollutant Dioxin: An in Vitro and in Vivo Zebrafish Study. Environ Health Perspect. 2021;129(3):37002.
9. Vitale G et al. Zebrafish as an innovative model for neuroendocrine tumors. Endocr Relat Cancer. 2014;21(1):R67-83.

Tutor

Prof. Giovanni Vitale

Contacts

email: giovanni.vitale@unimi.it Phone: +39 02.61911.2023

Laboratory/Department

Laboratory of Geriatric and Oncologic Neuroendocrinology Research, Istituto Auxologico Italiano.
Department of Medical Biotechnology and Translational Medicine, University of Milan.
https://www.auxologico.it/laboratori-ricerca/laboratorio-sperimentale-ricerche-neuroendocrinologia-geriatrica-oncologica

Most relevant publications for the project

1. Gaudenzi G, Albertelli M, Dicitore A, Würth R, Gatto F, Barbieri F, Cotelli F, Florio T, Ferone D, Persani L, Vitale G. Patient-derived xenograft in zebrafish embryos: a new platform for translational research in neuroendocrine tumors. Endocrine. 2017 Aug;57(2):214-219

2. Fenizia C, Bottino C, Corbetta S, Fittipaldi R, Floris P, Gaudenzi G, Carra S, Cotelli F, Vitale G, Caretti G. SMYD3 promotes the epithelial-mesenchymal transition in breast cancer. Nucleic Acids Res. 2019 Feb 20;47(3):1278-1293.

3. Vitale G, Carra S, Ferraù F, Guadagno E, Faggiano A, Colao A; NIKE. Gastroenteropancreatic neuroendocrine neoplasms and inflammation: A complex cross-talk with relevant clinical implications. Crit Rev Oncol Hematol. 2020 Feb;146:102840.

4. Gaudenzi G, Carra S, Dicitore A, Cantone MC, Persani L, Vitale G. Fishing for neuroendocrine tumors. Endocr Relat Cancer. 2020 Jun;27(6):R163-R176.

5. Carra S, Gaudenzi G, Dicitore A, Saronni D, Cantone MC, Plebani A, Ghilardi A, Borghi MO, Hofland LJ, Persani L, Vitale G. Vandetanib versus Cabozantinib in Medullary Thyroid Carcinoma: A Focus on Anti-Angiogenic Effects in Zebrafish Model. Int J Mol Sci. 2021 Mar 16;22(6):3031. doi: 10.3390/ijms22063031.

Most recent publications

1. Cantone MC, Dicitore A, Vitale G. Somatostatin-Dopamine Chimeric Molecules in Neuroendocrine Neoplasms. J Clin Med. 2021 Feb 1;10(3):501. doi: 10.3390/jcm10030501.

2. Vitale G, Cozzolino A, Malandrino P, Minotta R, Puliani G, Saronni D, Faggiano A, Colao A. Role of FGF System in Neuroendocrine Neoplasms: Potential Therapeutic Applications. Front Endocrinol (Lausanne). 2021 Apr 14;12:665631. doi: 10.3389/fendo.2021.665631.

3. Dicitore A, Bacalini MG, Saronni D, Gaudenzi G, Cantone MC, Gelmini G, Grassi ES, Gentilini D, Borghi MO, Di Blasio AM, Persani L, Garagnani P, Franceschi C, Vitale G. Role of Epigenetic Therapy in the Modulation of Tumor Growth and Migration in Human Castration-Resistant Prostate Cancer Cells with Neuroendocrine Differentiation. Neuroendocrinology. 2022;112(6):580-594. doi: 10.1159/000518801.

4. Karabid NM, Wiedemann T, Gulde S, Mohr H, Segaran RC, Geppert J, Rohm M, Vitale G, Gaudenzi G, Dicitore A, Ankerst DP, Chen Y, Braren R, Kaissis G, Schilling F, Schillmaier M, Eisenhofer G, Herzig S, Roncaroli F, Honegger JB, Pellegata NS. Angpt2/Tie2 autostimulatory loop controls tumorigenesis. EMBO Mol Med. 2022 May 9;14(5):e14364. doi: 10.15252/emmm.202114364.

5. Vitale G, Caraglia M, Jung V, Kamradt J, Gentilini D, Di Martino MT, Dicitore A, Abate M, Tagliaferri P, Itro A, Ferro M, Balsamo R, De Sio M, Facchini G, Persani L, Schmitt K, Saar M, Stöckle M, Unteregger G, Zappavigna S. Molecular Characterization of Cancer Associated Fibroblasts in Prostate Cancer. Cancers (Basel). 2022 Jun 14;14(12):2943. doi: 10.3390/cancers14122943.

UNIVERSITÀ DEGLI STUDI DI MILANO

D-MEM PhD-UNIMI | Doctorate program Milan EXPERIMENTAL MEDICINE

Graphical Abstract