PROJECT

Supervisor:	Prof. Silvio Danese MD, PhD
Title:	Risk of covert submucosal invasion cancer in Large Non-Pedunculated Colorectal Polyps: molecular and metagenomics characterization and correlation with histopathological findings
Curriculum:	Clinical and Experimental Medicine
Link to the personal page of the University or relevant hospital site website:	https://www.hsr.it/dottori/silvio-danese

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Colorectal cancer (CRC) ranks among the most prevalent malignancies globally, with 1.9 million new cases diagnosed annually and 900,000 deaths.

CRC typically develops through the adenoma-carcinoma sequence, with submucosal invasive cancer (SMIC) marking the critical transition to invasive disease with metastatic potential. Advanced endoscopic techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) enable minimally invasive removal of Large Non-Pedunculated Colorectal Polyps (LNPCPs) with superficial invasion, avoiding surgery. However, optimal management hinges on accurate pre-resection SMIC risk assessment. Current practice relies on morphological and endoscopic features achieving only 70-90% pre-resection diagnostic accuracy. Particularly challenging are lesions with "covert cancers" that lack obvious endoscopic malignancy features yet harbor deep submucosal invasion (>1000μm).

Recent evidence demonstrated the gut microbiota's role in CRC pathogenesis. It influences carcinogenesis through genotoxic toxin production, chronic inflammation induction, and immune response modulation. Studies confirm distinct microbial signatures across CRC stages, with enrichment of pro-inflammatory species in tumor tissues and correlation with tumor aggressiveness and worse prognosis. Despite these advances, we lack an understanding of how gut microbiota specifically influences submucosal invasion and which molecular mechanisms drive this process.

Rationale and hypothesis

LNPCPs harboring covert cancer likely exhibit unique molecular and microbial profiles distinct from overt cancers. Identifying these signatures will reveal pathophysiological mechanisms driving submucosal invasion and enhance pre-resection SMIC prediction beyond current endoscopic assessment limitations.

Objectives and specific aims

1. Investigate the association between molecular characteristics (transcriptomic and meta-transcriptomic) of LNPCPs without features of overt cancer and histological findings, including SMIC, with subsequent validation of identified molecular markers through immunohistochemical analysis of biopsy samples.

2. Characterize mucosal and faecal microbiota across LNPCPs with/without SMIC, and explore the potential for an integrated predictive model combining endoscopic, transcriptomic, and microbiota data for pre-resection SMIC risk assessment.

3. Evaluate potential in vitro therapeutic interventions based on microbiota modulation.

Expected outcomes

• Identify molecular signatures distinguishing LNPCPs with covert/overt cancer;

• Characterize microbiota associated with SMIC;

• Develop insights into microbiota-host interactions driving the invasion process;

• Discover potential therapeutic targets for preventing progression to invasive disease.

Skills that the student should acquire (max. 600 characters including spaces):

• Proficiency in LNPCPs optical assessment;

• Competency in advanced endoscopic resection (EMR, ESD);

• Familiarity with multi-omics data analysis techniques;

• Ability to integrate host and microbiota data;

• Skills in developing and validating predictive models for risk stratification;

• Proficiency in statistical analysis, scientific writing and communication skills;

• Interdisciplinary collaboration between gastroenterology, pathology, and biology.

References (max. 15)

(1) Bray, F.; Laversanne, M.; Sung, H. et al. Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2024, 74(3), 229–263.

(2) Leslie, A.; Carey, F. A.; Pratt, N. R. et al. The Colorectal Adenoma–Carcinoma Sequence. British Journal of Surgery 2002, 89 (7), 845–860.

(3) Ikematsu, H.; Yoda, Y.; Matsuda, T. et al. Long-Term Outcomes After Resection for Submucosal Invasive Colorectal Cancers. Gastroenterology 2013, 144 (3), 551–559.

(4) Jacques, J.; Schaefer, M.; Wallenhorst, T. et al. Endoscopic En Bloc Versus Piecemeal Resection of Large Nonpedunculated Colonic Adenomas: A Randomized Comparative Trial. Ann Intern Med 2024, 177 (1), 29–38.

(5) Pimentel-Nunes, P.; Libânio, D.; Bastiaansen, B. A. J. et al. Endoscopic Submucosal Dissection for Superficial Gastrointestinal Lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2022. Endoscopy 2022, 54 (06), 591–622. https://doi.org/10.1055/a-1811-7025.

(6) Fuccio, L.; Repici, A.; Hassan, C. et al. Why Attempt En Bloc Resection of Non-Pedunculated Colorectal Adenomas? A Systematic Review of the Prevalence of Superficial Submucosal Invasive Cancer after Endoscopic Submucosal Dissection. Gut 2018, 67 (8), 1464–1474.

(7) Burgess, N. G.; Hourigan, L. F.; Zanati, S. A. et al. Risk Stratification for Covert Invasive Cancer Among Patients Referred for Colonic Endoscopic Mucosal Resection: A Large Multicenter Cohort. Gastroenterology 2017, 153 (3), 732-742.e1.

(8) Kudo, S.; Tamura, S.; Nakajima, T. et al. Diagnosis of Colorectal Tumorous Lesions by Magnifying Endoscopy. Gastrointestinal Endoscopy 1996, 44 (1), 8–14.

(9) Sano, Y.; Tanaka, S.; Kudo, S.; et al. Narrow-band Imaging (NBI) Magnifying Endoscopic Classification of Colorectal Tumors Proposed by the Japan NBI Expert Team. Digestive Endoscopy 2016, 28 (5), 526–533.

(10) Pai, R. K.; Chen, Y.; Jakubowski, M.A. et al. Colorectal Carcinomas with Submucosal Invasion (pT1): Analysis of Histopathological and Molecular Factors Predicting Lymph Node Metastasis. Modern Pathology 2017, 30 (1), 113–122.

(11) Schmitt, M.; Greten, F. R. The Inflammatory Pathogenesis of Colorectal Cancer. Nat Rev Immunol 2021, 21 (10), 653–667.

(12) Li, Q.; Geng, S.; Luo, H. et al. Signaling Pathways Involved in Colorectal Cancer: Pathogenesis and Targeted Therapy. Sig Transduct Target Ther 2024, 9 (1), 266.

(13) Montalban-Arques, A.; Scharl, M. Intestinal Microbiota and Colorectal Carcinoma: Implications for Pathogenesis, Diagnosis, and Therapy. EBioMedicine 2019, 48, 648–655.

(14) Dougherty, M. W.; Jobin, C. Intestinal Bacteria and Colorectal Cancer: Etiology and Treatment. Gut Microbes 2023, 15 (1), 2185028.

(15) Bennedsen, A. L. B.; Furbo, S.; Bjarnsholt, T. et al. The Gut Microbiota Can Orchestrate the Signaling Pathways in Colorectal Cancer. APMIS 2022, 130 (3), 121–139.