

Carcinogenesis and gastric haemorrhage - genetic modulation of the risk to address prevention

ABSTRACT

The habilitation thesis entitled "Carcinogenesis and gastric haemorrhage - genetic modulation of the risk to address prevention" synthesizes the relevant contributions that my activity as a researcher, clinician and educator has brought in the approached fields. The first part of the thesis presents the original results I carried out after obtaining my PhD degree and the results published or presented at scientific events. The second part of the thesis describes the strategies, directions and personal goals for my career development as a researcher, doctor and university teacher.

Original research represents our contribution in understanding the interaction of clinical, environmental and genetic factors modulating the risk for neoplasia and haemorrhagic digestive disease in order to improve the prevention strategies. The first chapter synthesized the observations regarding the interaction of clinical and environmental factors in the pathology of the upper digestive tract. We observed that not active inflammatory gastritis like in western population is the most important influenced risk factor for ulcer on endoscopy in aspirin consumers, but concomitant use of other gastrototoxic drugs, like in Asian population, even that patients were treated with proton pump inhibitors, the most accepted preventing strategy for bleeding. We confirmed the low predictive role of active infection with *H. pylori* or symptoms in endoscopic or histologic lesions occurrence in large series of patients with compensated diabetes, or biliary reflux, in both resected or non-operated stomach, rising the problem of general efficacy of current prevention strategies in patients with different ethnic and genetic background.

In the second chapter I synthesized our results regarding the genetic modulation of inflammatory and precancerous gastric lesions in their progression on carcinogenesis cascade. We studied some genetic polymorphism influencing inflammatory responses in gastric mucosa and cancer progression, as well as the metabolism of carcinogens, drugs, or reactive oxygen species. Among all single nucleotide polymorphism we studied we found that: 1) the variant C allele and variant homozygous CC genotype of *AGT* A-20C, gene polymorphism influencing gastric inflammation, in patients treated with aspirin is associated with reactive gastropathy and bleeding ulcers; 2) the variant genotype of *GPX1* Pro198Leu (Pro/Leu or Leu/Leu) and *MnSOD* Ala16Val variant genotype (Val / Val or Val / Ala) were associated with an increased risk for reactive gastropathy, but not with inflammatory or premalignant histologic gastric lesions. 3) the *TGF-β1* + 869T>C gene polymorphism is associated with a decreased risk for corporeal localization of premalignant lesions in immunohistochemically *H. pylori* negative patients. Our own results and the extensive review of literature allowed us to underline that in order to develop efficient preventive strategies, larger studies using multivariable models to test the modifying effect of *H. pylori* infection on the relationship between gene variants and premalignant lesions, and to test the interaction between environmental factors (diet, smoking, medication) and gene variants should be conducted. I coordinated studies regarding autoimmune gastritis, gastric polyps, effect of chronic consumption of proton pump inhibitors or duodenal lymphocytosis in the research teams including students. Based on these achievements as young researchers, some of my students were accepted or finalized their PhD programme. The majority of the studies we performed and published were supported from the research grants I won as a project manager in the internal competition of University in collaboration with Prof. Dr. Claudia Bănescu from Genetic Discipline and Centre for Advanced Medical and Pharmaceutical Research (CCAMF) of GE Palade UMPHST Targu Mures. My scientific activity has resulted in the publication of 22 scientific papers indexed ISI (2 on Q1 and 5 on Q2 as main author), with 89 citations generating a Hirsh index of 6.

In the third chapter I underlined the landmarks of my career. After my graduation in 1997 at University of Medicine and Pharmacy Targu Mures, I fulfilled the Master in "Management of social and health services". I obtained the PhD degree with thesis "Gastrointestinal complications of antiplatelet and anticoagulant medication" in 2010, the training stages in Germany and Holland as a member of international research grant for gastric cancer helping me to fulfil the research. I became Teaching Assistant (2001), Assistant

Professor (2005) Senior Lecturer (2015) and Associate Professor (2019) in Medical Semiology Discipline of Faculty of Medicine in the same University I graduated. I am the Head of Internal Medicine III Discipline, teaching Medical Semiology for more than 20 years, being a member in the Board of M4 Department - Clinical Science. I am senior consultant gastroenterologist (2013) and internal medicine (2006), performing inpatients and outpatient medical activity, after regular training rotation as resident and specialist in university hospitals in Bucharest, Cluj-Napoca and Targu Mures. I am coordinator of Internal Medicine Residency from 2019 and a member of Research Ethic Comity of GE Palade UMPHST of Targu Mures. I performed activity in PhD evaluation thesis comity, I delivered post-graduating courses, organised scientific meetings and I was investigator in international clinical studies.

The second part of the thesis reflect the objectives and strategies I set to develop my career. I intend to use my experience as a clinician and researcher, to further coordinate multidisciplinary teams to submit projects in national and international calls, to improve infrastructure and techniques for both clinical practice and medical research. I will focus my activity on the controversial or unresolved issues in the context of the latest advances in the field of research, with a focus on the predictive factors and biomarkers for carcinogenesis and gastrointestinal bleeding. I will continue and extend the integrated approach of environmental and genetic factors influencing the neoplastic and non-neoplastic pathology of the digestive system in the perspective of personalized medicine, for an early diagnosis and appropriate treatment. I will continue to design, perform and disseminate the results of our projects involving young researchers. I intend to continue in some formal settings to improve my teaching and coordination skills obtained through research, teaching and medical activity. I will further apply the principles of integrated model for patient care, the innovation and ethic in the research activity and I will use all knowledge most effectively in the healing art. I intend to fulfil the passion for teaching and training activities of young specialists and researchers, mentoring