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Клінічні аспекти трансляційних досліджень онкогенезу шлунка й розробки нових методів лікування

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У цьому короткому повідомленні представлено дисертацію на отримання ступеня доктора філософії на тему трансляційних досліджень із використанням передових методів міждисциплінарної інтеграції між базовими й клінічними дослідженнями та між сухими (обчислювальними) і практичними (експериментальними та клінічними) дослідженнями. Результати показали можливий причинно-наслідковий зв'язок між невральною іннервацією і онкогенезом раку шлунка через передавання сигналів Wnt і метаболічне репрограмування в мікросередовищі пухлини. Відповідно, потенціал для лікування раку шлунка показали селективна ваготомія, ботулінічний нейротоксин типу A (ін'єкційне введення в ділянки пухлини), RAD001 (також відомий як еверолімус), CPI-613 (девімістат) та івермектин. Оцінювання показало, що цей трансляційний дослідницький підхід гарантує ефективний розвиток нових знань із фундаментальних медичних наук, а також що визначення ролі вагусної іннервації та можливості її модуляції під час онкогенезу шлунка становить цінний внесок у сфери дослідження гастроентерології й раку. Можливі ролі ангіогенезу проти нейрогенезу й нервової регуляції травної системи варто вивчати в подальших дослідженнях.

Ключові слова: гастроентерологія, онкологія, трансляційне дослідження, аденокарцинома шлунка, онкогенез, метаболічне репрограмування.

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Clinical aspects in translational research on gastric tumorigenesis and development of new treatments

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This brief communication presented a dissertation of PhD thesis on translational research using state-of-the-art methods of multi-disciplinary integrations between basic and clinical research and between dry- (computational) and wet- (experimental and clinical) investigations. The findings showed possible causal association between neural innervation and tumorigenesis of gastric cancer via Wnt signaling and metabolic reprogramming within the tumor microenvironment. Accordingly, selective vagotomy, Botulinum neurotoxin type A (injection into the tumor areas), RAD001 (also known as Everolimus), CPI-613 (devimistat) and ivermectin were found to be potential for treatment of gastric cancer. The assessment showed that this translational research approach guaranteed the efficient development of novel knowledge in fundamental medical sciences, and that the identification of the role of vagal innervation and the possibilities of its modulation during gastric tumorigenesis represented valuable contributions to the fields of gastroenterology and cancer research. Possible roles of angiogenesis vs neurogenesis and brain-gut axis would be worth exploring in further research.

Keywords: Gastroenterology, oncology, translational research, gastric adenocarcinoma, tumorigenesis, vagotomy, metabolic reprogramming.

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Introduction

Translational research can be defined as "a bidirectional process that involves multidisciplinary integration among basic, clinical, practice, population, and policy-based research". The overall goal of translational research is to close the "bench-to-bedside gap" by speeding up scientific discovery for patients and community benefit. The essential loop of translational research should compose both clinical aspects, such as questions and needs in the bedside and patients' outcome, and laboratory research including study hypotheses, aims, experimental designs, interpretation of findings and introduction to clinical trials and practice. In historical perspectives, gastric adenocarcinoma (GA) has been an excellent example of translational research. GA is a heterogeneous disease, both genetically and phenotypically which progresses via different pathways of tumorigenesis. There are still knowledge gaps between "bedside" and "bench-side", particularly regarding the roles of neural innervation and metabolic reprograming in GA tumorigenesis and progression. Thus, research strategy of this series of studies that included three publications and one manuscript in the PhD thesis was to investigate the vagal innervation and metabolic reprograming of GA, providing clinical and experimental evidence for developing new treatments [1-4].

Potential contributions to knowledge

This series of studies included four cohorts of 180 patients, eight datasets of 763 patients and 948 mice (GA models and controls) and 4 cell lines of human GA. Clinical cohort studies, clinical trial phase IIa, preclinical trials, *in vivo*, *in vitro* and *in silico* experiments were performed. Transcriptomics and metabolomics in combination with multiple bioinformatics and computational drug-target interaction prediction and drug repurposing were applied. The results showed that vagotomy reduced the risk of gastric stump cancer after distal gastrectomy and there was a possible causal association between vagal innervation and GA tumorigenesis in which certain signaling pathways, particularly hyperactivity of Wnt signaling, were involved. There was correlation between human GA and mouse GA model in terms of signaling pathways in general and metabolic gene expression profile in particular. Clinically-used surgery and drugs were found to be potential for treatment of GA, particularly including selective vagotomy, injection of Botulinum neurotoxin A into the tumor areas, and drugs such as RAD001 (also known as Everolimus), CPI-613 (devimistat) and ivermectin. In addition, a biomarker network of gastric intestinal metaplasia (GIM) for GA tumorigenesis was established. Thus, this series of studies provided new evidence in understanding the molecular mechanisms of association between the tumorigenesis and neural innervation and in identifying molecular biomarkers and networks for developing new treatments for GA and GIM. In particular, vagal innervation contributed to gastric tumorigenesis via M3 receptor-mediated Wnt signaling in the stem cells and denervation might represent a feasible strategy for the control of GA. Vagotomy and metabolic inhibitors reversed the metabolic reprogramming in GA and intratumoral injection of Botulinum neurotoxin A with systemic administration of everolimus and CPI-613 could be a potential therapy for GA. Ivermectin might be a promising drug candidate for treatment of GA. Taken together, the results of this series of studies and other relevant studies have made contribution to bridge the knowledge gaps between "bedside" and "bench-side" particularly regarding "cancer-nerve crosstalk" in general [5-11].

Furthermore, this translational research might represent a state-of-the-art methodology including multidisciplinary integrations between basic and clinical research and between dry- (computational) and wet- (experimental and clinical) investigations (Fig. 1).

Assessment of contributions

The series of studies included in this thesis demonstrated a broad scope, incorporating both clinical and preclinical research based on significant high numbers of patients involved and mice used. This comprehensive approach was commendable for gaining new insights into gastric cancer and understanding Correa's pathway, from gastritis, atrophy, intestinal metaplasia, dysplasia, to ultimately malignant neoplasms. It perfectly demonstrated that the translational research approach guarantees the efficient development of novel knowledge in fundamental medical sciences.

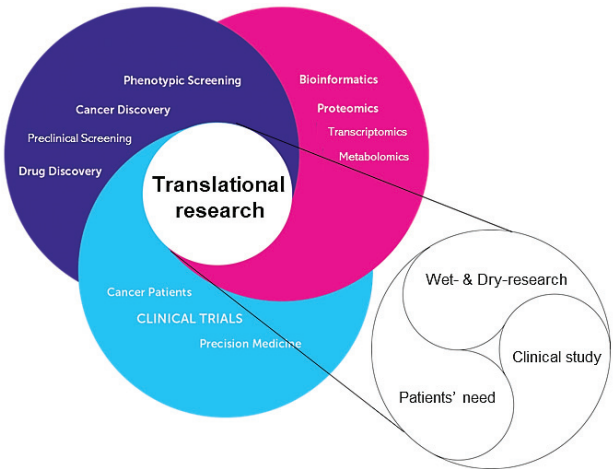

Figure 1. Methodology and methods of translational research presented in this series of studies. Note: Translational research starts from clinical observations and patient medical needs. "Bedside-to-Bench through wet- and dry-laboratory" research promotes the search for new evidence and interventions, which can be accelerated in "Bench-to-Bedside" research by clinical study to impact research activities. Colored circles show various methods used in this series of studies and potential impacts for the future, i.e., precision medicine

This research was one of the pioneering works in understanding mechanisms-of-action by vagotomy, pharmacological inhibition, muscarinic antagonists and M_3 receptor knockout in connection with gastric cancer. It also discussed the link or cycle between preclinical and clinical trials. Furthermore, it discussed how metabolic reprogramming played a role in gastric tumorigenesis and potential underlying mechanism behind vagotomy-induced tumor prevention. Accordingly, drug repurposing through translational approach was discussed. The thesis also discussed how biomarkers will be helpful in clinical management and suggested the molecular network instead of individual biomarkers for prediction, early diagnosis, potential prevention and treatment.

Research methodologies were based on diverse research approaches, including wet-lab experiments *in vivo*, *in vitro*, and dry-lab studies *in silico* (computational modelling), and human clinical trials. This diversity enhanced the credibility of the findings and their applicability to clinical practice, bridging the gap between scientific discoveries and their practical implementation in clinical settings. The identification of the role of vagal innervation and the possibilities of its modulation during gastric tumorigenesis proposed as therapeutic strategies represented valuable contributions to the fields of gastroenterology and cancer research. Identification of a novel "molecular network" as a potential biomarker of progression from gastric intestinal metaplasia to gastric adenocarcinomas will help improve knowledge in gastric carcinogenesis. This is necessary for the effective clinical management of gastric cancer, including screening, differential diagnosis, prognosis determination, and prediction of treatment response. This thesis will serve as a good example of how to facilitate the transition of findings from basic sciences into effective treatments and interventions. It will accelerate the advancement of medical innovations and benefits oncology patients by offering new personalized treatment options.

The thesis was a multiple center research and experimental investigations at levels of molecular signaling, cell biology, physiology and pharmacology, and patients to establish a connection between experimental research data obtained *in vivo*, and *in vitro*, as well as lab data about gene expression profiling and *in silico* modelling and patient cohorts. It presented exceptional examples for introduction of contemporary healthcare innovation. Of note, combination of retrospective and perspective approaches in multi-center cohorts and the form of presentation with focusing on the clinical aspects were appreciated.

However, there were some limitations in the thesis. For instance, the number of the patients enrolled in the clinical trial would be ideally higher than ones enrolled. The roles of angiogenesis *vs* neurogenesis [12] and brain-gut axis [13] in gastric tumorigenesis would be worth discussing for further research.

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