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Review

Challenge in the new era: Translational medicine in gastrointestinal endoscopy and early cancer

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Abstract

Translational medicine is a new medical model that has emerged over the past 20 years and is dedicated to bridging the gap between basic and clinical research. At the same time, the diagnosis and treatment of digestive diseases, especially gastrointestinal endoscopy, have been rapidly developed. The emergence of new techniques for gastrointestinal endoscopy has changed the therapeutic spectrum of some diseases and brought huge benefits to patients. Targeted therapy has positively affected the individualized and precise treatment of patients with advanced gastrointestinal cancer. The construction of a standardized biobank provides a strong guarantee for clinicians to conduct translational medical research. Translational medicine has brought good development opportunities, but it also faces challenges. The training of translational medicine researchers and the transformation of educational models require sufficient attention for further development.

Keywords: Translational medicine; Endoscopy; Targeted therapy; Biobank

Introduction

The Lancet first proposed the concept of "translational medicine" in 1996 as "the marriage between new discoveries in basic science and clinical practice". Meanwhile, the Lancet also suggested the translation from basic scientific research results into practical clinical patient benefits poses a tremendous challenge.[1] The establishment of translational medicine aims to eliminate the barriers between basic research and clinical medicine, bridge the gap between basic

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researchers and clinicians, and ultimately improve the level of clinical diagnosis and treatment and benefit patients ("from bench to bedside").[2] Compared with traditional research, translational medicine also includes investments in training, research, and infrastructure to help researchers conduct clinical research. In the past half century, molecular biology has developed rapidly, but barriers between basic research and clinical practice have also emerged.[3] Although a large number of basic molecular biology research results and articles have been published, only a small number of results have been further verified in the clinical stage, and very few research results have actually been applied to the clinic.

The main criteria by which a basic science researcher is judged is by publications in top journals and the acquirement of the National Natural Science Foundation. On the other hand, clinicians who actually treat the patients are shackled by the onerous daily medical tasks. Based on the above contradiction, academic experts have redefined translational medicine as "bench to bedside" and "bedside to bench" (B-to-B).[4] The American National Institutes of Health (NIH) committed to establishing 60 Clinical and Translational Science Centers (CTSCs) with an annual investment of $500, 000, 000. Replacement of The Clinical Research Centers (GCRCs) by CTSCs is hoped to reshape the culture and bridge the valley between basic research and clinical medicine. In addition, researchers also suggested other models for translational medicine: "evidence-based implementation and sustainability", which emphasizes the importance of the application in translational medicine. The NIH formulated the new translational medicine model into 5 procedures as follows: epidemiological investigation, etiological investigation, intervention design, clinical research stage, and popularization and application.[5,6]

In recent years, gastrointestinal endoscopy has developed rapidly, and gastrointestinal endoscopy has evolved from a simple gastrointestinal tract diagnostic method to painless minimally invasive treatment and extraluminal organs diagnostic procedure. This is due to the collaboration of digestive surgeons with experts in other fields and translational medicine. Contrarily, China's gastrointestinal tumor burden has become increasingly heavy with esophageal cancer, stomach cancer, and colorectal cancer accounting for nearly one-third of the incidence of all cancer in China.[7] Esophageal cancer and gastric cancer account for nearly half of their global cancer incidence.[8] In recent years, experts in the digestive field have gradually shifted their focus on early digestive tract cancer screening and treatment. With the exception of endoscopy, there are only a few methods available for early gastrointestinal cancer screening, resulting in low detection rates and poor prognosis. The discovery of serological markers has greatly improved our understanding and management of many types of cancer.[9] However, there are currently very few biomarkers available for early detection and treatment of gastrointestinal cancer. Clinical validation and promotion of gastrointestinal tract cancer biomarkers are urgently needed.

Gastrointestinal endoscopy and translational medicine

In its 200 years of development history, gastrointestinal endoscopy has gone through the following 4 stages: rigid endoscopy, semi-flexible endoscopy, fibrous endoscopy, and electronic endoscopy and ultrasonic endoscopy. In terms of endoscopic diagnosis and treatment, new technologies such as chromoendoscopy, narrowband imaging, magnifying endoscopy and endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and endoscopic retrograde cholangiopancreatography (ERCP) are constantly emerging. The emergence of endoscopic ultrasonography (EUS) and natural orifice transluminal endoscopic surgery (NOTES) was a breakthrough from the previous gastrointestinal endoscopy blind area in the biliary and pancreatic system and other nearby organs. The history of gastrointestinal endoscopy is the embodiment of translational medicine in the field of gastroenterology. A series of new digestive endoscopic techniques are used in clinical practice which enabled digestive physicians to make great strides in areas that were previously inaccessible, and ultimately, these advances benefited patients.

Artificial intelligence (AI) helps early diagnosis of gastrointestinal cancer

Although gastroenterologists have become increasingly aware of early cancer screening in recent years, data show that the diagnosis rate of early gastric cancer is only 10% in China, far lower than that of early gastric cancer diagnosis rates in Japan (70%) and Korea (50%).[10] The main reasons for this phenomenon include China's huge population base, shortage of endoscopic physicians, lack of advanced equipment, and the inadequacy of early diagnosis skills and experience by endoscopic physicians. In addition, the

extremely unbalanced medical development level among regions also hinders the improvement of the early cancer detection rate in China. Based on the above reasons, researchers have become dedicated to exploring new ways to assist endoscopists to improve early cancer detection rate. The emergence of artificial intelligence (AI) and its successful application in medical imaging and pathology provide a new way to solve this problem.[11,12] Convolutional neural networks (CNN) constructed several deep learning models for image feature recognition in the training set of early cancer. Finally, through the output of a convolutional layer, AI could realize the frame selection for suspicious lesions. A number of studies have shown that the sensitivity and specificity of the AI system for the identification of early gastric cancer and colorectal adenomatous polyps are higher than those of high-grade and low-grade endoscopic physicians.[13–18] Furthermore, this was shown beyond just for simple images. In a prospective randomized controlled study in Sichuan Provincial People's Hospital of China, Wang et al demonstrated that real-time automatic detection system increases colonoscopic polyp and adenoma detection rates. AI assisted colonoscopy improved adenoma detection rates (ADR) from 20.3% to 29.1%, and the mean number of adenomas per patient from 0.31 to 0.53.[19] For the surveillance of gastrointestinal precancerous disease, Maeda et al[20] applied AI assisted endocytoscopy (a new type of magnifying endoscopy enable endoscopic physicians to make the histological diagnosis[21]) to detect histologic inflammation associated with ulcerative colitis. This fully automatic diagnosis system achieved 76% sensitivity, 97% specificity, and 91% accuracy. In addition, Itoh et al[22] reported that the CNN model trained by endoscopic images of patients with helicobacter pylori infection can effectively identify the helicobacter pylori infection in the upper digestive tract, with a sensitivity and specificity both 86.7%. The implementation of AI in gastrointestinal tract early cancer screening powerfully decreased the omission diagnostic rate and improved the detection efficiency, especially for low-grade digestive endoscopic physician.

Application of 3-dimensional (3D) imaging in flexible endoscopy

The detection of polyps is of great significance for colorectal cancer prevention, but the protective value of this procedure is weakened by missed lesions. Polyps that are of flat elevated shape, have a diameter less than 5 mm, and are the same color as the background mucosa are difficult to detect with conventional 2-dimensional colonoscopy. Despite their small size, these polyps may be tubular or even serrated adenoma in histopathology. At present, 3D imaging technology has been widely used in the field of laparoscopic therapy.[23] The application of dual-lens 3D endoscope in soft endoscope is limited by the space occupation of optical equipment and soft structure. While the emergence of single-lens 3D devices well solved this problem. 3D imaging systems form both left and right eye images by a computer algorithm and image processing, thereby creating a binocular parallax image to realize stereoscopic vision and providing spatial vision for more accurate visualization of lesions. In addition to the 3D image real-time conversion system, the photometric stereo endoscopy (PSE) system could achieve the compatibility between 3D imaging and the flexible endoscopy with the synchronous switching of multiple light sources PSE algorithm to calculate the surface orientation.[24] Since a 3D colonoscopy could provide better depth vision, incorporating 3D imaging may be useful for the placement of snare in polypectomies, and decrease complications such as bleeding and perforation.[25] As flat elevated shape, a diameter less than 5 mm, and being the same color as the background mucosa are the main reasons polyps not being detected. Shinichiro Sakata et al[26] studied the polyp detection efficiency of 3D assisted colonoscopy through a randomized, complete, across-subjects study with simulated situation. The 3D group achieved a 25.1% increase in detection rate than 2D group. A randomized controlled study based on capsule endoscopic 3D video reconstruction showed 3D significantly improved the ability of novices in identifying small bowel tumor.[27] More multicenter prospective cohort studies should be performed to further verify the efficiency of the adenoma detection rate by 3D colonoscopy. 3D imaging of the surgery field in gastrointestinal endoscopy, such as ESD and ERCP, and incorporating AI has broad application prospects too.

Capsule endoscopy: fill the deficiency of traditional endoscopy

For a long time, the small intestine has been a restricted area with regards to gastrointestinal endoscopy. As a result, a number of obscure gastrointestinal bleeding (OGIB) issues rely on intervention angiography or surgical probe to confirm the diagnosis. The advent of capsule endoscopy largely solved the technical barriers. In terms OGIB diagnosis, several studies

reported that capsule endoscopy had similar overall diagnostic rates as double-balloon enteroscopy.[28,29] Furthermore, the need for a comfortable endoscopy, capsule endoscopy has directed the development of esophageal capsule endoscopy,[30,31] colon capsule endoscopy,[32,33] and magnetics stomach capsule endoscopy.[34,35] This is of particular benefit to patients with severe cardiovascular disease who cannot tolerate ordinary gastrointestinal endoscopy and general anesthesia.

Over-the-scope-clipsystem (OTSC): escort for endoscopic treatment

The OTSC anastomosis clip, made of a nickel-titanium alloy with elastic memory, is a new kind metal clip applied to gastrointestinal hemostasis and perforation.[36] It is equipped with the double-arm pliers and an anchor hook, which makes the positioning more precise.[37] Compared with traditional titanium clips, OTSC anastomosis clip can achieve full-thickness closure within 30 mm while achieving blood flow through the gap between the teeth without causing tissue necrosis. For acute non-variceal upper gastrointestinal bleeding (ANVGIB), the current guidelines advocate that drug therapy combined with endoscopic hemostasis is the first choice. However, in some cases, endoscopic hemostasis is ineffective. In these cases, only surgical treatment and interventional vascular embolization were possible in the past. Studies declared that OTSC hemostasis has a similar success rate to surgical treatment for refractory ulcer bleeding, and significantly reduces hospital stays, operating time, and patient costs.[38] Digestive tract perforation has been a serious complication of endoscopic treatment, which limited the development of gastrointestinal endoscopy. Previous animal studies have shown that OTSC is superior to conventional endoscopic treatment for the ability to close iatrogenic perforations.[39] Another study reported that OTSC anastomosis was successful in all cases of digestive tract perforation treatment or prevention, without the need for further intervention.[40] In a retrospective study comparing perforation repair after endoscopic full-thickness resection (EFTR), Xu et al[41] reported that OTSC treatment has the equal efficacy with nylon-titanium clip suture (king closure). Both groups achieved a 100% success rate with no late bleeding, perforation, and infection complications. The proportion of self-drop after OTSC treatment is low, and the indications for endoscopic OTSC removal need further investigation.

Early diagnosis and precise treatment of gastrointestinal tumors

The incidence of malignant tumors is increasing year by year and the main treatments are surgery, chemotherapy, radiotherapy, and other comprehensive treatments. A large number of tumor patients are already in the middle and late stages of disease at diagnosis. At this point, the treatment effect is uncertain and the toxicity and adverse effects are more severe. With the advancement of biotechnology, researchers have been exploring the pathogenesis of tumors, especially at the molecular level, and discovered a series of valuable serological markers and therapeutic drugs for specific targets. Standardized gradient screening of gastrointestinal tumors and precise treatment is attracting more and more attention.

Esophagus

The poor prognosis of esophageal squamous cell carcinoma (ESCC) and the low rate of early detection highlight the limitations of biomarker studies. In order to predict recurrence, prognosis, and sensitivity to treatment, there is an urgent need to identify biomarkers for ESCC. The ability to promote early diagnosis and treatment of ESCC will help guide endoscopic, surgical, and adjuvant therapies based on individual risk. Clinical testing of the predictive efficacy of serum markers is an important part of translational medicine. Liu et al[42] found that the combined diagnosis with CA724, CEA, CA199, and AFP for esophageal cancer reached 93.85% sensitivity and 83.71% specificity. Another study[43] demonstrated that the combined diagnosis with CYFRA21-1, CEA, and NSE for older esophageal cancer reached 84% sensitivity and 86% specificity. Regarding miRNA in the diagnosis of early ESCC, Takeshita et al[44] showed the area under curve (AUC) of serum miR-1246 is 0.754, and the sensitivity and specificity were 71.3% and 73.9%, respectively. Preoperative neoadjuvant chemotherapy can improve tumor staging and as such, bring opportunities for radical surgical resection. Raltitrexed is a thymosin synthetase inhibitor that is actively taken up by cells *in vivo* to inhibit thymic synthetase action, thereby inhibiting cellular DNA synthesis. Compared with the traditional treatment regimen, raltitrexed combined with cisplatin adjuvant chemotherapy has achieved a higher overall response rate (ORR) and significantly reduced levels of tumor markers CEA and SCC.[45] Cetuximab belongs to the immunoglobulin G1

monoclonal antibody family and can specifically inhibit endogenously expressing epidermal growth factor receptor (EGFR), thereby exerting an anti-tumor effect. Liu et al[46] studied the efficacy of cetuximab combined with postoperative chemotherapy in the treatment of advanced esophageal cancer. The results showed that the cetuximab group achieved a higher ORR than the conventional group (65.0% vs. 42.5%), significantly reduced SCC and CEA levels and improved the quality of life. As another EGFR inhibitor, Erlotinib-targeted therapy combined with radiotherapy was found to be more effective than radiotherapy alone group (88% vs. 64%) and achieved higher 2 year survival after treatment (93.18% vs. 75.00%).[47] However, a phase II/III randomized controlled trial of concurrent chemoradiotherapy combined with cetuximab in the treatment of esophageal cancer showed that cetuximab treatment reduced median overall survival (mOS) and increased incidence of non-hematologic adverse events.[48] The investigators concluded that this may be related to the superposition of adverse reactions after combined use.

Stomach

Early gastric cancer has no obvious specific symptoms and tumors are often diagnosed in advanced stages when patients have obvious symptoms. If early gastric cancer is treated promptly and effectively, its 5 year survival rate can reach more than 90%, while the 5 year survival rate of advanced gastric cancer is only 30–40%.[49] At present, the diagnosis rate of early gastric cancer in China is only 10%. Therefore, early diagnosis and treatment and gastric cancer screening still have a long way to go. By analyzing the serological markers (CEA, CA199, CA724, and CA242) and lymph node metastasis of 584 patients with gastric cancer, Bai et al reported the combined sensitivity reached 96.3%, the specificity was 69.8%, and the AUC was 0.899. In addition, the researchers used the Fisher discriminant function to establish a predictive model, which has a predicted coincidence rate of 76.6% for lymph node metastasis.[50] In addition to existing conventional serological markers, researchers are also exploring other types of tumor biomarkers and studying their clinical translation value. Long noncoding RNA (lncRNA) is a physiologically characterized RNA with a length of more than 200 nucleotides. As a hot research topic in recent years, lncRNA has been confirmed to be involved in angiogenesis, cell proliferation, apoptosis, and migration.[51] Through testing 39 candidate lncRNAs in 110 gastric cancer patients and control populations by RT-qPCR, Dong et al[52] filtrated the following 3 potential diagnostic marker for gastric cancer: CUDR, LSINCT-5, and PTENP1. The AUC value for the 3 serum lncRNA combinations is 0.920. They demonstrated the risk model based on 3 serum lncRNAs that could distinguish gastric cancer patients from health people effectively. Advanced gastric cancer has a short survival time and no definite treatment method, especially for Her2-negative patients. Ramucirumab is a targeted drug for the treatment of advanced gastric cancer or gastric esophageal junction adenocarcinoma that fails chemotherapy. As one humanized monoclonal antibody, it can specifically block vascular endothelial growth factor receptor 2 (VEGFR2) and downstream angiogenesis-related pathways. In a global III phase randomized control trial study consisting of 645 Her-2 negative advanced gastric cancer patients, the results found that the combination of ramucirumab and first-line chemotherapy can postpone disease progression or death.[53] In another phase III clinical trial evaluating the efficacy and safety of bevacizumab combined with capecitabine and cisplatin in the treatment of advanced gastric cancer, the results showed that the combined treatment group improved the ORR (46.0% vs. 37.4%) and prolonged median progression-free survival (mPFS, 6.7 Month vs. 5.3 months).[54]

Colorectum

In recent years, due to the popularity of colonoscopies and the improvement of people's health awareness, the incidence of colorectal cancer in China has declined. However, due to the uneven distribution of medical resources and the rate of missed polyps, colorectal cancer is still an important medical burden in China. Negm et al[55] detected and screened 6 representative colorectal cancer autoantibodies (alpha-fetal protein (AFP), p53, K-Ras, NY-CO-16, RAF1, and Annexin) by protein chip technology. The combined testing of these 6 autoantibodies achieved 75% sensitivity for colorectal cancer prediction. In a randomized phase III clinical trial of cetuximab plus FOLFIRI (folinic acid + fluorouracil + irinotecan) for the treatment of metastatic colorectal cancer, cetuximab increased overall survival by 8.2 months compared with FOLFIRI treatment alone.[56] In another phase III clinical trial for metastatic colorectal cancer, cetuximab plus FOLFIRI achieved 3.7 months higher overall survival than bevacizumab. However, the PFS and ORR were not significantly different and thus demonstrated the therapeutic effect is equivalent

between the 2 target drugs as a first line plan. In FIRE3 subgroup analysis with regards to KRAS mutant advanced colorectal cancer patients, the bevacizumab group achieved better PFS (58.1% vs 38.2%), mPFS (12.2 months vs 6.1 months), and OS (20.6 months vs 16.4 months) than cetuximab. This suggests that bevacizumab is more suitable for advanced colorectal cancer patients with RAS mutations.[57]

The bridge of gap: biobank

In the development history of modern medicine, numerous cell-based in vitro experiments, animal-based *in vivo* experimental results, and papers published clarified the etiology and pathogenesis of most diseases more clearly. However, the credibility deficiency of the research, as it based on cells and animal models, has been the insurmountable gap between basic research and clinical practice. Researchers have been pondering how to construct one reusable, scaled, and standardized clinical resource to solve this problem. The emergence of the "biobank" concept effectively solved this problem and has successfully built a bridge between basic research and clinical research.

High quality biobank

The biobank contains both plentiful basic research information and clinical research information. The efficient operation of the biobank relies on standardized and normalized sample collection, storage, and a management system. The establishment of the biobank of digestive diseases should be strictly in accordance with the guidelines.[58] The biobank should be equipped with advanced sample collection, information registration, sample storage and an automated temperature control system hardware, and professional management software. The digestive biobank mainly contains blood samples, excretions, and various surgical resection tissues. The sample should have complete clinical data, such as biochemical examination, blood routine, imaging data, pathological results, and detailed medical records. Cohort samples should have corresponding follow-up information, such as disease outcomes and survival status. After the sample is shipped out, the user is asked to feedback the sample usage, including the sample quality and the specific experimental data generated. The feedback data can be used for future research, avoiding sample reuse. The standardized biobank should perform regular random sampling to ensure the correctness and completeness of the sample information.

Biobank assist digestive translational medicine

Basic research results need a large number of clinical samples to verify their translational potential. In this context, the biobank has become a sharp weapon in medical research. Digestive physicians can start with real-world clinical problems, using samples from the biobank for high-throughput sequencing of genomes, methylation sequencing, and chip-seq (chromatin immunoprecipitation sequence) to find risk factors for a disease in a genetic background. Irritable bowel disease (IBD) is a digestive tract disease with an etiology that is not completely clear. It is affected by many factors such as genetics, environment, and immunity.[59,60] Digestive disease researchers can find and verify the risk genes of IBD through the analysis of massive samples in the biobank and design a risk prediction model for the clinical onset of IBD to guide the clinical diagnosis, prevention, and treatment. In recent years, there have been many reports that demonstrate the clearance of helicobacter pylori can cause an increase in the incidence of IBD, which may be related to the long-term "immune escape" caused by chronic helicobacter pylori infection. The number of regulatory T cells (Tregs) in the body after helicobacter pylori clearance may reduce and affect the immune balance of the body.[61] Therefore, there is still some controversy as to whether or not asymptomatic helicobacter pylori infection should be eradicated, especially younger populations. The risk gene detection of IBD on this type of patient can help identify people with a higher risk and realize the individualized and precise treatment of IBD. Serrated adenoma (SA) is a new type of colorectal adenoma with both serrated structures of hyperplastic polyps and cell dysplasia. It is considered to be another colorectal precancerous lesion independent of traditional adenomas.[62,63] Early studies have suggested that the serrated pathology is associated with inhibition of apoptosis. Moreover, reports show gene epigenetic modification, microsatellite instability (MSl) play an important role in the development of serrated adenoma.[64] In colorectal cancer with SA, the hypermethylation of the mismatch repair gene *hMLH1* and *MGMT* promoter region is closely related to the occurrence of MSI and plays an extremely important role in this pathway.[65] Through genome and transcript sequencing and microarray detection of SA samples, identifying high-risk groups and enforcing more stringent colonoscopy screening is of great significance for early treatment and reduction of cancer rate.

Exosome research and clinical translation

Exosomes are an important subgroup of extracellular vesicles (EVs) and are considered to be vesicles secreted by cells with a phospholipid bilayer structure and contained valuable biological information (such as microRNAs and secreted proteins). Valadi et al[66] verified that cells can exchange genetic materials with each other through exosomes. In addition, researchers have suggested that exosomes play an important regulatory role in the microenvironment of tumor.[67] Based on the above research, exosomes in blood and body fluids can provide physiological status information of the body in real time, and have broad application prospects in the field of liquid biopsy. Circulating miRNAs could be derived from cancer cells, fibroblasts, apoptotic cells, and even necrotic cells, and are highly heterogeneous. Small extracellular vesicle (sEV) membranes can effectively protect internal miRNAs from RNase, making sEVs-derived miRNAs more reliable than circulating miRNAs in body fluids such as blood. Li et al performed exosomal extraction of blood from colorectal cancer patients and normal controls from the Beijing Friendship Hospital, and the next generation sequencing (NGS) method was used to map miRNA expression spectrum in sEV of patients with early colorectal cancer.[68] The study found 60 differentially expressing miRNAs (DEM) that overlapped with the The Cancer Genome Atlas (TCGA) database, and each DEM from sEV had a similar sensitivity and specificity with TCGA. Target genes corresponding to these 60 DEMs are involved in the formation of cytoskeleton, cell migration, ATP binding, biosynthesis, and other cancer-related pathways. The researchers further screened 4 colorectal cancer candidate miRNA markers: let-7b-3p, miR-150−3p, miR-145−3p, and miR-139−3p and tested 134 samples in biobank for diagnostic verification. Logistic regression model analysis showed that the combined AUC of let-7b-3p, miR-145−3p, and miR-139−3p was as high as 0.927 and significantly higher than plasma miRNA. In addition, Kamerkar et al[69] demonstrated that fibroblast-derived exosomes could carry specific siRNA or shRNA which could degrade the oncogene $KRAS^{G120}$. Moreover, they found exosomes treatment inhibited tumors in a variety of pancreatic cancer mouse models and significantly improve their overall survival.

Prospective

Translational medicine aims to promote the transformation of medical science research concepts, emphasizing multidisciplinary cross-research and cooperation, abandoning the research mode that only focuses on results and ignores practical value. With the increasing investment and attention of the government and medical institutions in translational medicine, translational medicine in gastroenterology has ushered in a new development opportunity. As the golden key to bridge the gap between basic research and clinical research, the construction of biobanks provides an important weapon for clinicians. How to find new screening molecular indicators to guide targeted drug therapy and prognosis analysis is the next hot research area. Clinicians should start with clinical practical problems, follow the "B to B″ research mode to engage in translational medical research, and ultimately provide individualized, optimized treatment options for patients.

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Conflict of interest

None.

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