



The Small Bowel Cancer Incidence Enigma

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Abstract

Although the small bowel is a vast organ with a highly proliferative epithelium, the incidence of small bowel cancers is surprisingly low. Many factors could be involved in this unexpected cancer incidence, including difficult access to the exploration of the small bowel mucosa, which might lead to missed diagnoses of non-obstructive and non-bleeding small tumours. Moreover, possible factors that influence the low incidence include more efficient machinery of DNA replication and DNA repair enzymes, peculiarities in microbiota components, competence of the immune system, and the speed of intestinal transit. Importantly, the answer for the enigmatic risk of driver mutations caused by replication errors may be hidden in the small bowel, which is an obscure part of digestive tract that is usually inaccessible by endoscopic or colonoscopic conventional investigations. These observations warrant the necessity of an urgent exploration of small bowel features, including the evaluation of DNA replication controls and expression of DNA repair genes, in order to shed light on these obscure events.

Keywords Small bowel cancer · Low incidence · DNA repair · Enigma

Cancer Risk

The identification of patients at higher risk of cancer is one of the challenges of cancer control [1–3].

Recently, in an extremely elegant paper Tomasetti and Vogelstein [4] proposed a schematic classification of cancer causes. This innovative interpretation of cancer origin addi-

tionally provided a plausible explanation for a large amount of anterior cancer sites related to “unknown causes”.

Accordingly, the causes of driver mutations that lead to cancer are as follows: hereditary, environmental, and replicative [4].

In some cases, cancers from hereditary and environmental causes can be prevented. Nevertheless, replicative cancers, which occur by chance during the replication of stem cells, are currently not preventable [4].

Since the contribution of replicative errors to the total number of driver mutations that are able to trigger the carcinogenesis process is highly relevant (66%), this group of causes remains a challenge to be faced [4].

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Stem Cell Replicative Errors

The stem cell origin of cancer has been extensively debated and gained strength after many robust confirmatory experiments. Due to their high longevity, plasticity and resistance to injuries, these cells can accumulate the necessary driver mutations that lead to cancer and are currently considered the origin of cancer, independent of a cancer being caused by hereditary, replicative or environmental causes [5, 6].

All cells, including stem cells, carry a considerable chance of errors (10^{-8} to 10^{-10} mutations per base pair per cell division) during the replicative process [7, 8]. Nevertheless, most of these errors will be corrected or, if not, they usually do not have any importance in cell homeostasis. If there are non-correct harmful errors, the cell is regularly discharged [9, 10].

However, non-corrected errors during the replication of stem cells that result in driver mutations are the most frequent causes of a great number of cancer types [11, 12].

The replicative errors also contribute to the other two causes of cancer, namely, environmental and hereditary [13, 14]. Thus, the importance of these events and the gap of knowledge regarding possible mechanisms implicated in the risk rates need to be aggressively addressed.

Small Bowel: The Replicative Cause Hypothesis Weakness

To support the hypothesis that stem cell replication error is a frequent cause of cancers, an extensive investigation of cancer incidences and their relationship to the number of stem cell replication was conducted, and the results strengthened this assumption [7, 15, 16]. Nevertheless, there is an “Achilles heel” in this work, i.e., the small bowel.

The small bowel has an extremely proliferative epithelium, harbouring a great number of stem cells along many metres of gut [17]. Intriguingly, small bowel epithelial cancers are very rare [18]. Additionally, the small bowel is the principal site of nutrient absorption, and thus it is extremely exposed to environmental carcinogens, as well as endogenous risk factors and bile components; however, the organ almost never presents with cancer [19, 20].

On the other hand, the large bowel is one of the most common sites of cancer although it is much shorter than the small intestine [21, 22]. Moreover, familial adenomatous polyposis leads to several polyps and cancer onset in the colon but not the small bowel [23, 24]. Meanwhile, in an experimental *Apc*^{Min+} mouse model with knockout of APC gene, which resembles the human genetic alteration, there was much more provocation of small bowel polyps and tumours compared to the colon [25].

The reasons for these inconsistencies remain allusive. Among the exploratory explanations, possible factors that influence the human cancer incidence include more efficient machinery of DNA replication and DNA repair enzymes, peculiarities in microbiota components, competence of the immune system, and the speed of intestinal transit [26, 27].

The Intestinal Metaplasia and Gastric Cancer Risk

Gastric cancer (GC) remains one of the most lethal cancers worldwide [28]. More than half of GC driver mutations are caused by environmental causes, but over than 40% of them are due to replicative errors [4].

According to the Lauren classification, gastric adenocarcinomas are epithelial cancers with two main histological subtypes, namely, the intestinal and diffuse types [29].

Regarding the intestinal type, the following cascade of cellular events was proposed by Correa and Piazeolo [30]: *Helicobacter pylori* causes chronic gastritis, followed by the development of gastric atrophy, complete intestinal metaplasia, incomplete intestinal metaplasia, dysplasia and finally, cancer.

The sequential events proposed by Correa have some weaknesses, since most of these pre-malignant lesions will never evolve to cancer; also, some cancers might develop without passing through every stage of the proposed cascade [31, 32].

Incomplete intestinal metaplasia is widely recognized as a risk factor for cancer, while complete intestinal metaplasia is referred to as a low-risk lesion [33, 34].

Incomplete intestinal metaplasia resembles the large bowel phenotype, whereas complete intestinal metaplasia is similar to the small bowel phenotype. This similarity mimics what is seen regarding small bowel and colon cancer incidences. Assuming small bowel-like morphology, the expected risk of cancer for complete intestinal metaplasia is likely to be very low. On the other hand, incomplete intestinal metaplasia brings a high risk of cancer, resembling the high incidence of colon cancer [35].

Following the sequential events proposed by Correa's cascade, the hypothesis of a progressively growing risk for cancer loses consistency, since atrophy brings a higher risk than complete intestinal metaplasia [36].

A possible explanation for this discrepancy is the dichotomization of potential events after atrophy. If the route of complete metaplasia is the case, then the cancer risk is low; however, if the following event is incomplete metaplasia, then the risk of cancer is higher [33, 34]. Additionally, an interchangeable possibility between these two routes might be considered.

These observations warrant the necessity of an urgent exploration of small bowel features, including the evaluation of DNA replication controls and expression of DNA repair genes, in order to shed light on these obscure events.

The answer for the enigmatic risk of driver mutations caused by replication errors may be hidden in the small bowel, which is an obscure part of digestive tract that is usually inaccessible by endoscopic or colonoscopic conventional investigations.

Strategies to Unravel Features of Small Bowel Protection

Among possible strategies to try to aid the understanding of supposed small bowel protection against the occurrence of epithelial cancers, we suggest a double approach that includes human and animal investigations.

Regarding human investigation, taking into consideration that access to the small bowel mucosa is tricky and that the extension of the epithelium is very long, obtaining representative samples of the small intestine is a challenge.

Nevertheless, there are some opportunities available to take samples during enteroscopy, surgery, and post-mortem.

The main reason for performing enteroscopy is to investigate occult bleeding and other enteric diseases. Frequently, these investigations are negative for both, and biopsies might be taken for research purposes [37, 38].

Surgeries for both benign and malignant diseases of other abdominal organs, or even trauma of the small intestine, usually require resection of segments of the small bowel during reconstruction of the digestive tract for technical and tactical reasons [39–41]. These samples seem to be the best samples for research investigation, since they do not affect the gut, and include the wall, mesentery and possibly the lymph nodes.

Post-mortem samples can be as large and multiple as desired but lack the possibility of precise functional analysis.

Thus, a combination of such sources of samples may be considered, according to the specific research goals.

Regarding the experimental approach, the *Apc*^{Min+} mouse model brings both the desired samples and interventions without limitations. Moreover, according to the hypothesis that cancer incidence is linked to stem cell division, these animals present many more polyps and cancers in the small bowel than the colon, which is different from human findings [25]. Additionally, a therapeutic approach to reduce cancer risk or even treat tumours in these models yields different results between small and large bowel tumours. These peculiarities bring optimism regarding the acquisition of useful information from such investigations.

What to Look for?

Since replication errors in stem cells are supposed to be one of the main focuses of investigation [4, 7], at least three aspects need to be addressed, namely, the stem cell, the replication function, and errors of the DNA repair enzymes, since the last could bypass the process by correcting errors or discharging the affected cells [9, 12]. Additionally, the local immune competence could abort the development of cancer at the beginning, resulting in a very low index of diagnosed cancers. This hypothesis should also be investigated [26, 27].

Regarding the stem cells, the position, number, and pattern of gene expression should be checked and compared to colon and gastric stem cells in order to identify differences implicated in small bowel protection.

The complete machinery of DNA replication and DNA repair should also be examined and compared to others digestive sites.

Another point of great interest is related to the microbiome. The influence of the microbiome on human homeostasis and diseases such as cancer is increasing exponentially [42–44]. The interaction among the microbiome, human cells and immune function must be addressed to try to discover the secrets of small bowel defence against cancer.

Potential Benefits for Cancer Control

Currently, there is nothing to be done to avoid replicative errors in stem cells that might result in cancer.

Exploration of the possible mechanisms that could influence the risk of these errors could pave the way for the prevention of cancer incidence, and consequently, its reduction.

The ongoing development of molecular investigations and advancements in DNA editing confer optimism that in the near future, instead of being “protected by luck”, we can take command of and control these molecular events.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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