Perspectives

Traps and trumps from adjacent-to-tumor samples in gastric cancer research

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Abstract

The search for cancer biomarkers is frequently based on comparisons between tumors and adjacent-to-tumor samples. However, even after histological confirmation of been free of cancer cells, these adjacent-to-tumor samples might harbor molecular alterations which are not sufficient to cause them to look like cancer, but can differentiate these cells from normal cells. When comparing them, potential biomarkers are missed, and mainly the opportunity of finding initial aberrations presents in both tumors and adjacent samples, but not in true normal samples from non-cancer patients, resulting in misinterpretations about the carcinogenic process. Nevertheless, collecting adjacent-to-tumor samples brings trumps to be explored. The addition of samples from non-cancer patients opens an opportunity to increase the finds of the molecular cascade of events in the carcinogenic process. Differences between normal samples and adjacent samples might represent the first steps of the carcinogenic process. Adding samples of non-cancer patients to the analysis of molecular alterations relevant to the carcinogenic process opens a new window of opportunities to the discovery of cancer biomarkers and molecular targets.

Keywords: Adjacent-to-tumor; trumps; traps

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Background

The search for cancer biomarkers is frequently based on comparisons between cancer and non-cancer samples (1-4).

Due to practical issues, including easy access and avoidance of inter-individuals differences, the "normal" tissue is usually collected from an area nearby the tumor, and macroscopically free of cancer cells (5-7).

Even after histological confirmation of being free of cancer cells, these adjacent-to-tumor samples might harbor molecular alterations which are not sufficient to cause them to look like cancer, but can differentiate these cells from normal cells (8).

Most of the findings related to gastric carcinogenesis, including the search for new biomarkers, were performed from the comparison of tumor samples and adjacent-to-tumor samples (9-12), and many advances have come from this type of analysis, such as the foundation of the multi-institutional consortia, the Cancer Genome Atlas (TCGA). Currently, strategies for molecular research in cancer, including gastric cancer, have been based on these multi-institutional consortia, favoring extensive investigations

with relevant sample numbers and patients from different backgrounds, and ensuring more robust and potentially applicable conclusions worldwide (13-17). However, there is a bias arising from the potential occurrence of molecular alterations in the tissue adjacent to the tumor, leading to suboptimal analysis with eventual loss of opportunities for the discovery of biomarkers, since they are expressed in both tissues. On the other hand, there is also an opportunity to explore these undervalued changes favoring knowledge of the initial steps of carcinogenesis.

Cancer field

Slaughter *et al*. (18), aiming to explain the occurrence of multiple cancers among head and neck tumors, proposed the theory of "field effect", also known as cancerization field or cancer field. Accordingly, exposure to a carcinogenic insult promotes alterations not restricted to the cancer site, but also in the surrounded exposed areas. These alterations in the adjacent-to-tumor cells might evolve, or not, to additional aberrations, and even cancer.

Due to the broad access to high throughput molecular investigations, this field effect theory was re-accessed, deeply evaluated and confirmed (19-21).

Currently, the field effect is widely accepted for many cancer types, and genetic and epigenetic alterations have been strongly demonstrated nearby tumors (22-25).

Additionally, the cancer field might be present with or without morphological alterations, and seems to interact with the surrounding microenvironment, resulting in significant functional modifications, or not (17,26,27).

Carcinogenic process and cancer diagnosis

From the first driver mutation to the onset of an invasive cancer, a long period of time is necessary. For the majority of tumors, the carcinogenic process takes over 20 years (28).

Such a long time might enable researchers and physicians to discover cancer, or even stop the process at the initial phases. Nevertheless, the current clinical practice is mainly based on the presence of symptoms and signs of cancer to launch a cancer investigation. In other words, with the exception of few cancer types that are screened, a diagnosis of cancer waits for occurrence of alarm signs such as weight loss, anemia, dysphagia, vomiting, hemorrhage, palpable mass and others to be performed (29-31).

Evidently, in such cases, the diagnosis will be made in very advanced stages, and the treatment outcomes will be invariantly poor (32-34).

Field effect and carcinogenic process

The field of cancerization encompasses cells exposed to a carcinogenic insult, which is able to provoke diverse molecular alterations (35). Although the majority of such molecular aberrations are neutral, or passenger alterations, without relevance to the carcinogenic process, driver mutations can also emerge (36,37).

Even in the case of occurrence of driver mutations, this will rarely evolve to an additional cancer (second primary tumor), since the completeness carcinogenic cascade must be reached (28).

Although not harboring every element of the carcinogenic process, the adjacent-to-tumor samples may present the earliest event of the carcinogenic process, and by this way, should be deeply explored by a different approach from the usual consideration of being a normal control to be compared to cancer samples (15,17).

Adjacent-to-tumor sample trap

The conventional practice of using adjacent-to-tumor samples as normal controls, to be compared to cancer samples, aiming to find cancer biomarkers, might be a trap (15).

Molecular alterations presenting in both tumor and adjacent samples will not be identified as "abnormal" (15).

Missing potential biomarkers and mainly the opportunity of finding initial aberrations presenting in both tumors and adjacent samples, but not in true normal samples from non-cancer patients, should be a dramatic loss, resulting in misinterpretations about the carcinogenic process (15).

Adjacent-to-tumor sample trumps

Nevertheless, collecting adjacent-to-tumor samples brings trumps to be explored.

The addition of samples from non-cancer patients opens an opportunity to increase the finds of the molecular cascade of events in the carcinogenic process. Differences between normal samples and adjacent samples might represent the first steps of the carcinogenic process.

It should be noted that patients undergoing endoscopy for non-neoplastic causes are usually submitted to multiple gastric biopsies, and although the molecular evaluation of an additional biopsy does not represent an assured benefit to the patient, this biopsy is practically free of additional risks.

Additionally, searching for known driver mutations, presented in both adjacent and cancer samples, could also shed light to the understanding of this pathway, and

provide opportunities to find biomarkers and potential targets to stop the process.

Triple trumps

Adding samples from non-cancer patients to the analysis of molecular alterations relevant to the carcinogenic process opens a new window of opportunities to the discovery of cancer biomarkers and molecular targets.

Making comparisons among these three sources of cells might allow elucidation of hidden molecular steps of the carcinogenic process, as is the case of transitions from normal status to the cancer field, and from the cancer field to cancer.

The analysis of alterations presented in both adjacent and cancer cells (and absent in non-cancer patients) instead of being neglected should be addressed, because it might represent initial driver alterations, and potential biomarkers, or also targets for innovative approaches to interfere in the cancer process.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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