Personalized Approaches to Gastrointestinal Cancers

Importance of Integrating Genomic Information to Guide Therapy

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KEYWORDS

• Tumor heterogeneity • Next-generation sequencing • Targeted therapy
• Biomarkers

KEY POINTS

- Cancer is such a heterogeneous disease that combining optimal use of targeted therapies in highly selected patients can achieve the best result.
- Early diagnosis of cancer or precancer lesions can lead to prophylactic surgery and eliminate the risk of certain types of cancer.
- Molecular profiling in cancer has allowed clinicians to correlate cancer genomics data with the cancer phenotype data.
- Fast-growing genomic technology, such as next-generation sequencing, now allow clinicians to obtain genomic profiles for patients with cancer, to guide their targeted chemotherapy, and to predict the response to chemotherapy. This ability will make personalized medical care possible.

If it were not for the great variability among individuals, medicine might as well be a science, not an art.

—Sir William Osler, 1892

INTRODUCTION

Tumor Heterogeneity

A tumor is composed of different subpopulations of cells. Most of those tumor cells are founder cells from which subclones are derived.[1] Each subclone has a distinct

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genotype and phenotype, which then leads to divergent biological behavior. Tumor heterogeneity can explain the differential response to treatment and can be summarized into the following categories (Fig. 1):

- Intratumor heterogeneity,[2] which is defined as heterogeneity among the cells of the primary tumor. Genome-wide sequencing data demonstrate that most somatic mutations are present in all tumor cells and form the trunk of the somatic evolutionary tree. The mutations that cause the intratumor heterogeneity are in the branches. This heterogeneity is the foundation of the intermetastatic heterogeneity.
- Intermetastatic heterogeneity, which is defined as heterogeneity among different metastatic lesions. Patients with advanced cancer often present with multiple metastatic lesions in major organs. The heterogeneity among different metastatic lesions is often extensive, and can pose significant challenges for targeted therapy.
- Intrametastatic heterogeneity, which is defined as heterogeneity among the cells of each metastasis, and develops as the metastases grow.
- Intertumor or interpatient heterogeneity refers to heterogeneity among the tumors of different patients. No two patients with cancer have the same mutations

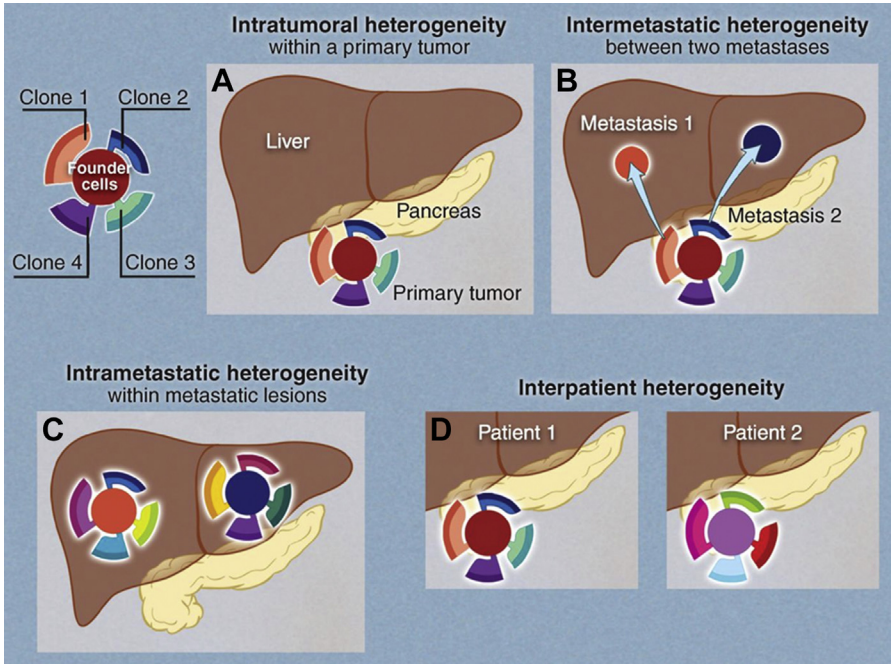

Fig. 1. Tumor heterogeneity. (*A*) Intratumoral: heterogeneity among the cells of the primary tumor. The differently colored regions in the subclones represent stages of evolution within a subclone. (*B*) Intermetastatic: heterogeneity among different metastatic lesions in the same patient. In the case illustrated here, each metastasis was derived from a different subclone. (*C*) Intrametastatic: heterogeneity among the cells of each metastasis develops as the metastases grow. (*D*) Interpatient: heterogeneity among the tumors of different patients. The mutations in the founder cells of the tumors of these 2 patients are almost completely distinct. (*From* Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. Science 2013;339;1552; with permission.)