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Circulating biomarkers to monitor cancer progression and treatment

Suthee Rapisuwon, Eveline E. Vietsch, Anton Wellstein *

Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, 3970 Reservoir Rd, NW, Washington, DC 20007, USA

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ABSTRACT

Tumor heterogeneity is a major challenge and the root cause of resistance to treatment. Still, the standard diagnostic approach relies on the analysis of a single tumor sample from a local or metastatic site that is obtained at a given time point. Due to intratumoral heterogeneity and selection of subpopulations in diverse lesions this will provide only a limited characterization of the makeup of the disease. On the other hand, recent developments of nucleic acid sequence analysis allows to use minimally invasive serial blood samples to assess the mutational status and altered gene expression patterns for real time monitoring in individual patients. Here, we focus on cell-free circulating tumor-specific mutant DNA and RNA (including mRNA and non-coding RNA), as well as current limitations and challenges associated with circulating nucleic acids biomarkers.

Contents

1. Introduction

Tumor heterogeneity that enables malignant progression by evolutionary selection is also the major cause of emergent resistance during

* Corresponding author.
E-mail address: anton.wellstein@georgetown.edu (A. Wellstein).

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cancer treatment. Yet, we rely on few standard diagnostic tumor biopsies for the characterization of a given cancer. These specimens will provide only a partial characterization of the overall makeup of the dynamic systemic disease cancer represents with intratumoral and interlesional heterogeneity as well as emerging host responses [1]. Tumor heterogeneity is generally accepted as following Darwinian evolutionary principles (Fig. 1), where genetic heterogeneity within a cancer cell population translates into a range of phenotypes that includes distinct surface marker expression, metabolism, proliferation, apoptosis, invasion, angiogenesis, drug sensitivity, antigen presentation or organotropism of cell subpopulations present in a given tumor [2,3]. Selective pressure and selection of cancer cell subpopulations are generally thought to drive increasing heterogeneity during tumor growth and metastatic spread (Fig. 2). Additionally, phenotypic plasticity of cancer stem cells in response to changes in the tumor microenvironment contribute to heterogeneity [4].

A striking example that illustrates intratumoral heterogeneity was recently described for kidney cancer specimen that revealed distinct expression of an autoinhibitory domain of the mTOR kinase and multiple tumor-suppressor genes (i.e. *SETD2*, *PTEN* and *KDMSC*). Additionally, this study demonstrated extensive heterogeneous mutational profiles in 26 out of 30 tumor samples from four renal cell carcinoma patients [5]. Another illustrative example of intratumoral/intermetastatic tumor heterogeneity is the extensive whole genome sequencing analysis of a patient with breast cancer and brain metastasis. Four different tissue samples (the primary tumor, blood, brain metastasis and xenografts) showed tumor heterogeneity at a low frequency even at the primary tumor [6]. Therefore, a single tumor biopsy will underestimate the mutational landscape due to intratumoral/interlesional mutational and phenotypic| heterogeneity. These concepts and additional examples were reviewed recently [7].

2. What are circulating biomarkers

Capturing and analysis of circulating biomarkers is an alternative method to gain insight into the molecular makeup of a cancer in a given patient. Historically, circulating biomarkers have been observed and studied since the late 1800s in a form of circulating tumor cells (CTCs) [8]. However, extensive study on CTC did not occur until the mid-20th century when the studies of circulating tumor cells showed that the presence of CTCs in cancer patients was correlated with poorer prognosis or progression-free and overall survival [9–11].

Here we will discuss cell-free circulating tumor-specific mutant DNA and RNA (including mRNA and non-coding RNA; Fig. 3) due to recent improvements in the sensitivity and analysis scope that impacted the potential of these approaches significantly. A review of circulating tumor cells, circulating proteins, and metabolites will not be included here.

3. Circulating tumor DNA (ctDNA)

Circulating, cell-free DNA (cfDNA), i.e. fragments of DNA found in the cell-free blood compartment was first described in 1948 [12], but cell-free DNA fragments that originated from tumor cells (ctDNA) have not been well characterized until the late 1980s [13]. The origin of ctDNA has not been well defined yet, but is thought to result from cell death. The presence of ctDNA has been correlated with overall tumor burden, and disease activities [14,15]. Somatic oncogenic Ras, p53 and other cancer-related gene mutation, promoter hypermethylation of tumor suppressor genes have been detected and measured in several different cancers including, but not limited to, colon, small cell and non-small cell lung cancer, melanoma, kidney and hepatocellular carcinoma [16].

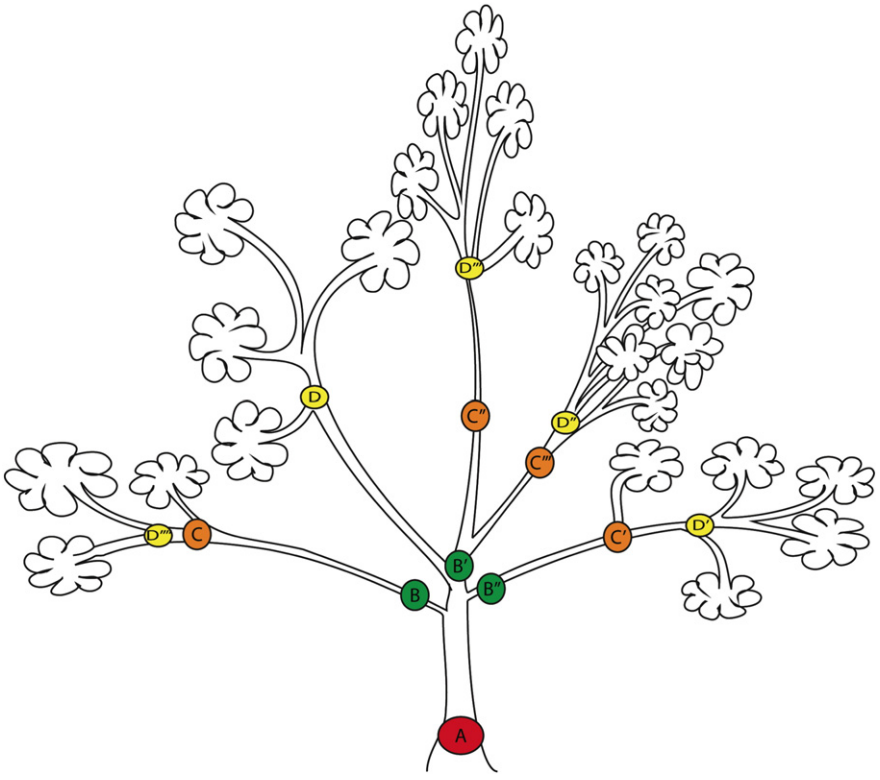

Fig. 1. Branching of a cancer evolutionary tree. This model is similar to animals' phylogeny. A (red) represents a common tumorigenesis event, often characterizes by a common driver mutations. B (green) is the first, C (orange) and D (yellow) are subsequent branch evolutionary events. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)