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MassARRAY determination of somatic oncogenic mutations in solid tumors: Moving forward to personalized medicine

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ABSTRACT

This article will review the impact of the recently developed MassARRAY technology on our understanding of cancer biology and treatment. Analysis of somatic mutations is a useful tool in selecting personalized therapy, and for predicting the outcome of many solid tumors. Here, we review the literature on the application of MassARRAY technology (Sequenom Hamburg, Germany) to determine the mutation profile of solid tumors from patients. We summarize the use of commercially available panels of mutations – such as OncoCarta™ or other combinations – and their concordance with results obtained by using other technologies, such as next generation sequencing.

Introduction

Over the last decade, significant advances have been made in identifying oncology biomarkers, which have yielded greater insight into the molecular and cellular mechanisms that drive the initiation, maintenance and progression of tumors. Therapeutic approaches have also shifted substantially during this period, as new sequencing technologies have increased our understanding of the molecular and genetic make-up of cancers. As a result, classic chemotherapy treatments are being gradually displaced by targeted drug therapies, which interfere with specific molecules and thereby block cancer cell growth. This new approach has improved the overall survival of cancer patients, as seen with use of trastuzumab for the treatment of breast cancers that overexpresses *HER2*, or vemurafenib as a targeted therapy for melanomas in which the *BRAF* gene is mutated [1,2]. In other words, the analysis of key cancer-driving mutations has become enormously useful in selecting personalized medicine.

The current gold standard technique for identifying somatic mutations is next-generation sequencing (NGS); however, other technologies, such as mass spectrometry, may also be used for this purpose [3]. The mass spectrometry technique, based on matrix-assisted laser desorption/ionization-time of flight, detects known genetic variations with target therapies available and is widely used to assess point mutations across different solid tumors to treat patients with known response or to identify resistant clones. The Sequenom MassARRAY technology (Sequenom, San Diego, CA) is a mass spectrometry technique that when is used in combination with the commercial kit OncoCarta™ v1.0 (http://agenabio.com/oncocarta-panel), screens for up to 238 somatic mutations across 19 oncogenes in 24 multiplexed assays. Further versions, v2.0 and v3.0, include additional oncogenes and tumor suppressor gene mutations. Custom assays, such us the ColoCarta™, GyneCarta™, LungCarta™ and MelaCarta™ panels have also been incorporated in the overall design to permit detection of specific target genes as needed by different research groups.

Mass spectrometry is cost-effective, but its usefulness in clinical care is still being debated [3–5]. This review provides a systematic overview of all available data from studies that have used this technology to determine the mutational profile of tumors. We also highlight the clinical value of this methodology, in the context of the experience of research groups that have applied this technology across different panels and across a wide range of tumors.

Methods

Search strategy and study identification

Articles were selected from the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed), with use of key search terms, or aliases, for: "OncoCarta", "OncoCarta Sequenom", "Somatic mutation analysis Sequenom", "ColoCarta", "GyneCarta", "LungCarta", "MelaCarta", "Ultraseek" and "OncoMap". Publication library available at Agena Bioscience website was also explored for the same key

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search terms (http://agenabio.com/oncology; http://agenabio.com/resources/publication-library). In order to increase the sensibility of the search results, reference lists of the retrieved articles were manually screened and necessary citations were included into the review.

Literature search results

The initial database search included 160 articles, 28 of them in both searches. Among the remaining 132 publications, the eligibility criteria included studies in patients with clinical and histological diagnosis of solid tumors that were molecularly characterized by the Sequenom technology as the principal tool. Forty one articles were excluded because of different reasons: (a) Sequenom technology was used for the genotyping of specific polymorphisms (9 reports) or used as a validation technique (5 papers); (b) lack of specific data analysis (2 reports); (c) studies not focused on solid tumors (9 reports); (d) studies performed on cell lines or mice models (3 reports); (e) studies involving pediatric populations (6 report) and (f) not mutation profile determined in the study (4 reports). Finally, 3 manuscripts were not a research article and were excluded (Fig. 1).

Somatic mutation analysis using MassARRAY technology

Ninety one articles, published between January 2009 and April 2016, described the use of the Sequenom MassARRAY technology in order to detect somatic mutations among different tumor types and were included in this review. Among them, 45 works were performed using the OncoCarta™ panel v1.0 for mutation profiling, whereas the other 46 studies used a customized-panel (See Tables 1 and 2, respectively).

Regarding tumor types, 20 studies (22.0%) were conducted in patients with lung cancer, 11 (12.1%) in cervix and other gynecologic tumors, 10 (11.0%) in individuals with breast cancer, 8 (8.8%) in colorectal cancer patients (CRC), 8 (8.8%) in several solid tumors, 8 (8.8%) in melanoma tumors, 4 (4.4%) in head and neck tumors, 3 (3.3%) in sarcomas and 19 (20.9%) in other tumor types including adenoid cystic, adrenal, cholangiocarcinoma, central nervous system, urothelial, germ cells, gastrointestinal stromal tumor (GIST), thyroid, kidney, esophageal, gastric skin, myofibroblastic, salivary gland and penile carcinomas (See Fig. 2) [1,3–93].

Positive results were reported in fresh tissue, cell lines and plasma samples; however, most of the studies were done in formalin-fixed paraffin-embedded (FFPE) tissues. Results of 52 studies (57.1%) were validated with the use of different techniques, including NGS, Sanger sequencing, pyrosequencing, real-time PCR (RT-PCR), Droplet Digital PCR (dd-PCR) or Affymetrix (Santa Clara, CA). Concordance rate was 100.0% in 31 (59.6%) articles whereas concordances higher than 85.0% were reported in 15 (28.8%) papers (Tables 1 and 2).

OncoCarta panels to determine the mutation profile in solid tumors

The forty five studies that accomplished the molecular characterization of solid tumors using the OncoCarta™ panel v1.0, used FFPE, frozen or blood tissues. Additionally, three of the works used the OncoCarta panels v2.0 or v3.0. Moreover, 23 of them used an extra panel or technology to validate their results. Samples sizes varied from 2 to more than 2200 individuals. Among the 45 studies, 10 (22.2%) were conducted in patients with lung cancer, 6 (13.3%) in those with varied solid tumors, 5 (11.1%) in those with breast cancer, 3 (6.7%) in those with CRC, 4 (8.9%) in those with melanoma, 3 (6.7%) in those with endometrium cancer, and 14 (31.1%) in those with other tumor types including ovary, cholangiocarcinoma, sarcoma, oral cavity, GIST, myofibroblastic, nasopharyngeal, adenoid cystic, thyroid, penile, salivary gland and adrenal carcinomas. Furthermore, for all studies, the accuracy between any sequencing result and the OncoCarta™ panel v1.0 output was high, with independence of the type of sample analyzed (FFPE, fresh tissue, cell lines or blood).

Visualizing the mass spectra and determining the frequency of mutant and wild type alleles is done by the MassARRAY software called Typer Viewer. A wide range of thresholds have been used for considering alleles "mutated" or "non-mutated". Information regarding the cut-off used is available in 10 studies and the cutoffs varies from 1.0% (in 3 studies) [8,22,52] to 10.0% (in 5 studies) [5,7,16,17,49,51,56].

Beadling and colleagues published one of the most comprehensive studies in 2011, in which they molecularly characterized 820 different FFPE solid tumors, using Sequenom OncoCarta™ Panels

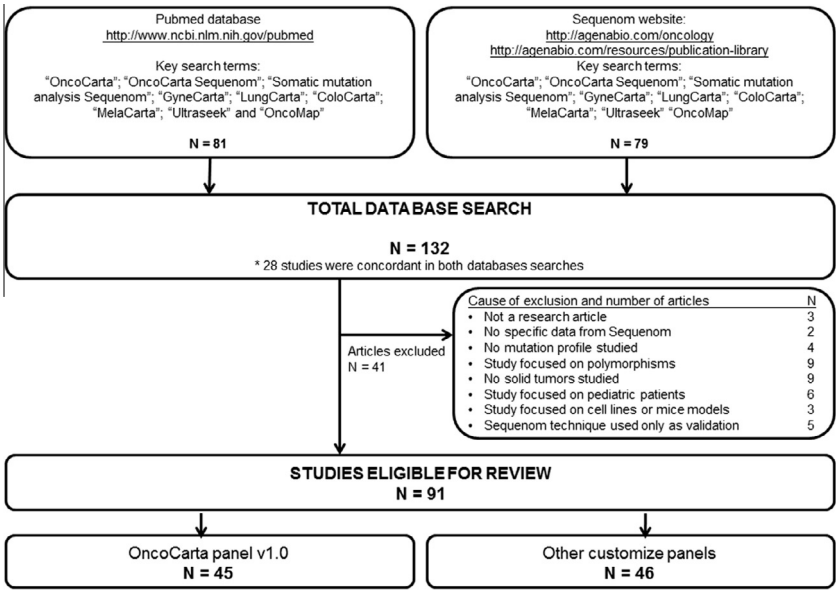

Fig. 1. Flowchart of the eligible studies focused on the somatic mutation analysis using MassARRAY technology.