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Review

Early diagnosis of disease using microbead array technology: A review

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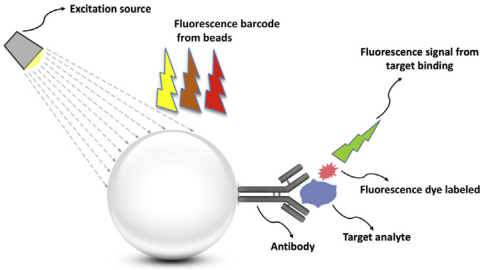
HIGHLIGHTS

- Multiplexed immunoassays are a step forward in early medical diagnosis.
- Up to 100 fluorescent barcodes in the microbeads can be distinguished.
- Both suspension arrays and planar arrays can be used.
- Cancer diagnosis using tumor markers in biosamples such as serum.
- Neurological, inflammatory and infectious diseases are also candidates .

GRAPHICAL ABSTRACT



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ABSTRACT

Early diagnosis of diseases (before they become advanced and incurable) is essential to reduce morbidity and mortality rates. With the advent of novel technologies in clinical laboratory diagnosis, microbead-based arrays have come to be recognized as an efficient approach, that demonstrates useful advantages over traditional assay methods for multiple disease-related biomarkers. Multiplexed microbead assays provide a robust, rapid, specific, and cost-effective approach for high-throughput and simultaneous screening of many different targets. Biomolecular binding interactions occur after applying a biological sample (such as blood plasma, saliva, cerebrospinal fluid etc.) containing the target analyte(s) to a set of microbeads with different ligand-specificities that have been coded in planar or suspension arrays. The ligand-receptor binding activity is tracked by optical signals generated by means of flow cytometry analysis in the case of suspension arrays, or by image processing devices in the case of planar arrays. In this review paper, we discuss diagnosis of cancer, neurological and infectious diseases by using optically-encoded microbead-based arrays (both multiplexed and single-analyte assays) as a reliable tool for detection and quantification of various analytes.

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Contents

1. Introduction

Many life-threatening diseases start out at clinically undetectable levels, and steadily increase in severity with time, until symptoms eventually appear. The sooner that the disease is diagnosed, the more successful therapies will be in curing, treating and reversing the progress of the disease. Early detection of disease has therefore assumed an essential role in modern medical therapy. Surveillance and monitoring of the progression and/or the management of the disease, and individually assessing the response to treatment are becoming the hallmarks of personalized medicine [1,2].

Microbead-based arrays are an emerging technology used for early diagnosis, and in simultaneous detection, quantification and profiling of a range of targets of interest relevant to a particular disease. Preliminary work in this field was carried out as early as 1926 when various particulate materials were used in biological investigations. The first systematic study of the development of well-defined albumin microspheres for diagnostic applications was performed in the late 1960s by Rhodes, Scheffel, Wagner, Zolle and their colleagues [3]. Attempts towards optimizing and developing antibody-based multiplexed assays (and commercial instruments and kits) date back to over 20 years ago [4]. By use of a multiplex detection-based system, scientists can predict the possibility of disease occurrence before the appearance of the first clinical symptoms at the very early stages. Biomarkers may be related to genetic information such as a mutation or change in amino acid positions in a double-stranded DNA or RNA structure, alterations in a complex protein or gene structure, or the appearance of a single specific (or multiple) antigens that correlate with the presence of a disease. This technology also has significant applications in the analysis of protein/gene/DNA profiles, experiments for drug discovery, research, and optimization of clinical laboratory diagnosis [5–9]. Certain particular biomarkers have been shown to be characteristic of many specific disease states, or other physiological disturbances of an organism that can be used as an indicator to diagnosis or predict disease [10–13].

Cancer progression can be broadly divided into two phases (Fig. 1). The first preclinical phase starts at the initial point when enough irreversible mutations in the cells have taken place, until the first noticeable symptoms of disease are detected. The more observable clinical phase comprises the period between symptoms appearing and commencement of therapy. Early detection is defined as taking place in the preclinical stage, and the finding of prognostic or diagnostic biomarkers in this phase may allow effective interventions in order to prevent any symptoms even appearing [3].

Microbeads are defined as spherical polymeric particles in the size range from 0.5 to 500 μm diameter. Reactions take place on the surface of these microbeads that function as a solid-support surface to capture analytes (molecular targets in the sample) of interest.

There are two basic different types of microbead-based technologies: solid-state planar bead arrays, and liquid-state suspension bead arrays, which both have extensive multiplexing capability (Fig. 2). In the microbead planar array format (Fig. 2A), microspheres are attached in place at known locations onto a solid surface by various means (such as creating microholes and micromachined cavities etc.). The solid surfaces can be made of polymers or glass [14–16]. Binding reactions happen in the same way as for suspension arrays, and ultimately there is a two-dimensional array consisting of false or true reacted spots. The identity of each spot is known from its location in the grid [17]. In order to analyze the interactions occurring on the solid support a fluorescent image

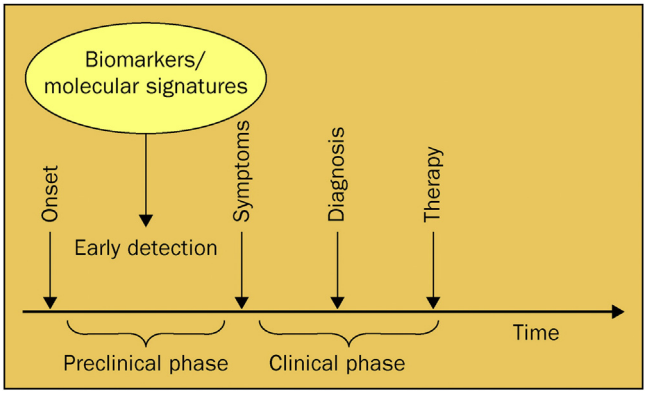

Fig. 1. An epidemiological perspective of cancer progression. Adapted from Ref. [11] With permission.