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Recent advances in cytokine detection by immunosensing

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ABSTRACT

The detection of cytokines in body fluids, cells, tissues and organisms continues to attract considerable attention due to the importance of these key cell signaling molecules in biology and medicine. In this review, we describe recent advances in cytokine detection in the course of ongoing pursuit of new analytical approaches for these trace analytes with specific focus on immunosensing. We discuss recent elegant designs of sensing interface with improved performance with respect to sensitivity, selectivity, stability, simplicity, and the absence of sample matrix effects. Various immunosensing approaches based on multifunctional nanomaterials open novel opportunities for ultrasensitive detection of cytokines in body fluids in vitro and in vivo. Methodologies such as suspension arrays also known as bead assays together with optical fiber-based sensors, on their own or in combination with microfluidic devices will continue to have an important role to address the grand challenge of real-time in vivo multiplex cytokine detection.

Contents

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1. Introduction

Cytokines, low molecular weight (~6–70 kDa) soluble proteins secreted from the immune and non-immune cells are core indicators of the functional status of the body, and strongly associated with the immune system including the modulation of immune reactions such as sensitization (Stenken and Poschenrieder, 2015). Cytokines also play critical roles in chemically-induced tissue damage repair, in cancer development and progression, in the control of cell replication and apoptosis and in many other aspects of physiology. Consequently, monitoring cell functions and cell-to-cell communication by using their cytokine secretions has enormous value in biology and medicine (O'Shea et al., 2011). The effects of cytokines are very potent as they engage various downstream amplification processes. As a result, only a few cytokine molecules may be sufficient to induce a significant cellular response (Xue et al., 2015).

Cytokines are classified into lymphokines (cytokines made by lymphocytes), monokines (cytokines made by monocytes), chemokines (cytokines with chemotactic activities), and interleukins (cytokines made by one leukocyte and acting on other leukocytes) (Nicola, 1994). Based on effects of cytokines in the context of an inflammatory disease, they can also be divided into inflammatory or anti-inflammatory (Wojdasiewicz et al., 2014), and produced both with and without stimuli such as lipopolysaccharide (Zhao et al., 2011). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). Cytokines can also act addictively, synergistically or antagonistically, and induce one another (Whicher and Evans, 1990).

Cytokine detection and measurement is important as elevated concentrations of cytokines may indicate the activation of cytokine signaling pathways associated with inflammation or disease progression. Consequently, these proteins are widely used as biomarkers to characterize the immune function, understand and predict disease, and monitor effects of treatment (Catalfamo et al., 2012). Measurement sensitivity is always an issue for cytokines because they are released into the extracellular milieu resulting in pM concentration range (Schenk et al., 2001). In addition to low concentrations, it is difficult to measure physiological concentrations of cytokines accurately and reproducibly due to some challenges (Fig. 1) such as significant interference from heterophilic antibodies (Bolstad et al., 2013), the rheumatoid factors (Bartels et al., 2011), and specific or non-specific cytokine binding proteins (Whicher and Evans, 1990), and an extremely dynamic, transient cytokine secretion process (Kulbe et al., 2012).

The most common approach for cytokine quantification is based on the idea of an immunoassay. Specific techniques include traditional ELISA assays (Chiswick et al., 2012), enzyme-linked immunosorbent spot (ELIspot) assays (Cox et al., 2006), antibody array assays (Schröder et al., 2010) and bead-based assays (Won et al., 2012). Traditional ELISA assays are reliable, but they are not rapid (6 h) and usually require a relatively large sample volume (100 μL). Generally speaking, all these assays require a long sample preparation time (> 6 h), and multiplexed approaches require a high level of complexity in the sample labeling. Some assay types require specialized flow cytometry infrastructure, and all are unable to monitor the cytokines in real time or in a dynamic manner. These limitations are the driving force for researchers to develop sensitive, selective, and rapid real time cytokine analysis platforms for comprehensive characterization and quantitative analysis of cytokines released in both healthy and pathological conditions.

The purpose of this review is to discuss recent advances in development of analytical approaches especially immunosensors for cytokine detection focusing on designing sensing interfaces to achieve high sensitivity, selectivity, stability, simplicity, and no sample matrix effects. This work is not intended to be a comprehensive review on cytokine detection, as several excellent reviews of analytical methods for measurement of cytokine proteins have been recently published (Chikkaveeraiah et al., 2012; Rusling et al., 2010; Stenken and Poschenrieder, 2015). Rather, we will examine the latest trends in cytokine detection based on immunosensing.

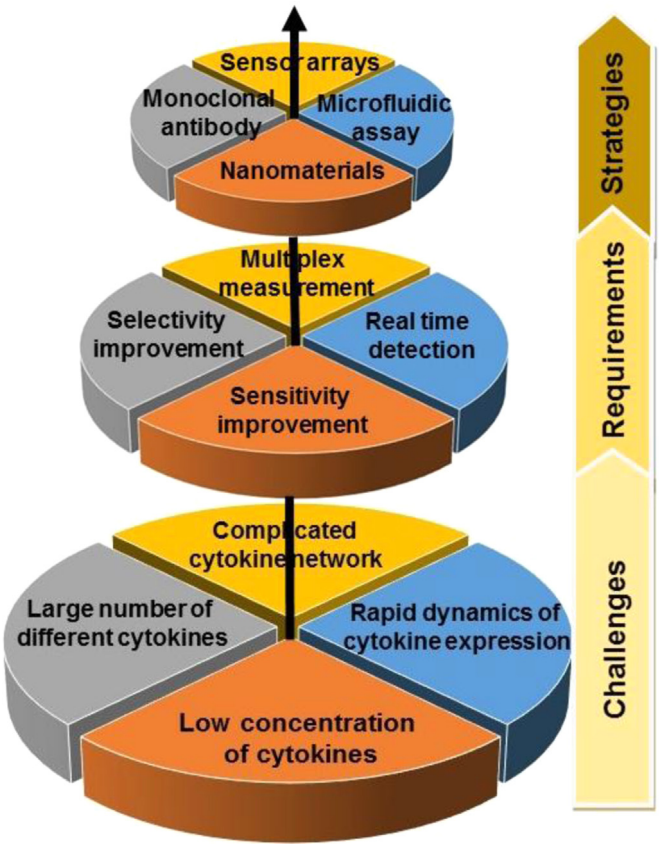

Fig. 1. The scheme showing challenges, requirements and strategies for cytokine detection. The challenges include complicated cytokine network, large number of different cytokines, low concentration of cytokines, and rapid dynamics of cytokine expression. Correspondingly, cytokine detection methods requires multiplex capability, enhancement in selectivity and sensitivity, and real time measurement. The strategies to address these challenges are proposed to be application of sensor arrays, monoclonal antibodies, nanomaterials, multifluidic system, and et al.