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Label-free cytokine micro- and nano-biosensing towards personalized medicine of systemic inflammatory disorders

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ABSTRACT

Systemic inflammatory disorders resulting from infection, trauma, surgery, and severe disease conditions pose serious threats to human health leading to organ dysfunction, organ failure, and mortality. The highly complex and dynamic nature of the immune system experiencing acute inflammation makes immunomodulatory therapy blocking pro-inflammatory cytokines very challenging. Successful therapy requires the ability to determine appropriate anti-cytokine drugs to be delivered at a right dose in a timely manner. Label-free micro- and nano-biosensors hold the potential to overcome the current challenges, enabling cytokine-targeted treatments to be tailored according to the immune status of an individual host with their unique cytokine biomarker detection capabilities. This review studies the recent progress in label-free cytokine biosensors, summarizes their performances and potential merits, and discusses future directions for their advancements to meet challenges towards personalized anti-cytokine drug delivery.

Contents

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1. Introduction

1.1. Cytokines: key clinical targets

The immune system provides a critical mechanism for a living organism to protect itself against invasions of external pathogens. Despite the conceptually clear role of the immune system, pathways underlying the defense mechanism are so complex and yet to be fully understood. The complexity of the immune defense system originates from dynamic functional interactions between biomolecules, cells, and organs over time. Among these players, cytokines are key biomolecules acting as mediators and modulators of the complex functional interactions and responses of the immune system [1–3]. They are soluble low-molecular-weight proteins secreted by immune cells and responsible for regulation of host defense, tissue homeostasis, cell-to-cell communication, and inflammatory reaction. The physiologic actions of cytokines are most apparent in the systemic inflammatory response syndrome (SIRS) that results from an excessive production of pro-inflammatory cytokines, such as IL-6 and TNF-α. These highly inflammatory responses cytokines are counteracted by certain anti-inflammatory cytokines, including IL-10, transforming growth factor (TGF-β), and IL-4, which attempt to restore immunological equilibrium. The multifaceted roles of cytokines in maintaining a tightly regulated balance of immunity have attracted enormous clinical interest in quantification of these biomolecules and its application for infectious disease treatment and drug development [4]. Previous studies suggest that quantification of cytokine-based immune fingerprints provides a more accurate way of stratifying and diagnosing bacterial infections than conventional methods based on symptoms, initial clinical observations, and basic laboratory markers [5,6].

There has been an explosion in the use of immunotherapies for treating autoimmune diseases, infection [7], cancer [8], and other immune-related deficiencies [9,10]. Among these therapies, cytokine-targeted methods aiming to establish a normal balance of the cytokine network in the host have shown great promise for some inflammatory diseases, such as rheumatoid arthritis and Crohn's disease [11,12]. Quantifying cytokines secreted by isolated immune cells or by whole blood test allows immune responses to be monitored, providing clinically and immunologically useful information related to infectious diseases, cancer, autoimmune diseases, allergy transplantation, and drug discovery [13]. Multiplexed detection of different cytokines in a single sample has been proven powerful for obtaining a more complete picture of immunity owing to the highly networked nature of their functions [14].

1.2. Current challenges: lack of real-time information on patients' immune status

The conventional "gold standard" methods for cytokine quantification are immunoassay-based techniques including enzyme-linked immusorbent assay (ELISA) and bead-based immunoassay, whose signals are detected either by flow cytometers or plate readers. Involving sample incubation, detector antibody incubation, and labeling reagent incubation processes as well as multiple washing steps, these methods require a minimum assay time (defined as a minimum time between sampling and detection) of 3–8 h in a current centralized clinical laboratory setting. In an ideal scenario, cytokine-targeted immunomodulatory therapy should be tailored to an individual's immune status determined by quantifying a panel of cytokines. However, the setting of acute inflammatory diseases, imposes serious limitations on personalized immunomdulatory therapy, where appropriate cytokine-blockade drugs are to be delivered at a right dose in a timely manner to patients whose immune response may vary from individual to individual. Such immune status variations are exemplified by the dynamic transition of the immune status of sepsis patients from an initial pro-inflammatory phase to an anti-inflammatory phase within a short period of time (several hours to a few days). The pro-inflammatory phase at the early stage of the disease, termed "cytokine storm," contributes to multiple organ dysfunction syndrome (MODS), prolonged chronic immune dysfunction [15], or mortality. The long assay lead time and labor intensiveness of the aforementioned gold standard methods and other similar sensing techniques based on labeled immunoassay inherently fall short of providing the urgently needed cytokine-based immune status information. Thus, this creates a huge technological gap between the clinical demand for rapid, sensitive assays of cytokine levels and the currently available assay techniques. The absence of accurate and rapid diagnostic methods renders the immunomodulation of acute inflammatory states highly empirical with no access to information allowing individualized selection and use of appropriate drugs [16]. Indeed, several review papers suggest that the failure of immunomodulatory therapy could be attributed to the lack of appropriate techniques to monitor inflammatory biomarkers and host defense responses across highly heterogeneous patient cohorts during the course of disease development [17–21]. We anticipate that future intensive care of acute inflammatory diseases will need personalized immunomodulatory drug delivery based on real-time information of cytokine-mediated immune response [21,22]. Such a monitoring mechanism will permit fine-tuned immune control with a system feedback loop during the therapy (Fig. 1).

1.3. Potential of label-free cytokine biosensors

The clinical and immunological relevance of cytokine measurement has promoted recent effort to develop a wide variety of cytokine biosensors [23]. Of particular importance are their rapid, sensitive, sample-efficient bioanalysis capabilities. These biosensors are imperative components for the immune status monitoring system discussed above. For example, immune modulation in sepsis would require sensitivity to detect TNF-α, one of common sepsis biomarker cytokines, with a cut-off concentration value as low as 11.5 pg/mL in some cases [24]. Additional challenges exist in infants and children who need assays that spare clinical samples since their blood volumes are significantly less than those of adults.

Recent advances in nanomaterial synthesis [25,26], nano optics [27–30], nanoelectrochemistry [31], nanomechanics [32,33], and microfluidics [34] have brought together breakthroughs in label-free micro- and nano-biosensing for biomolecular analysis. Nanomaterial-based sensors offer excellent sensitivity in detecting analyte molecules. Integrated in a microfluidic system, these sensors allow for high-

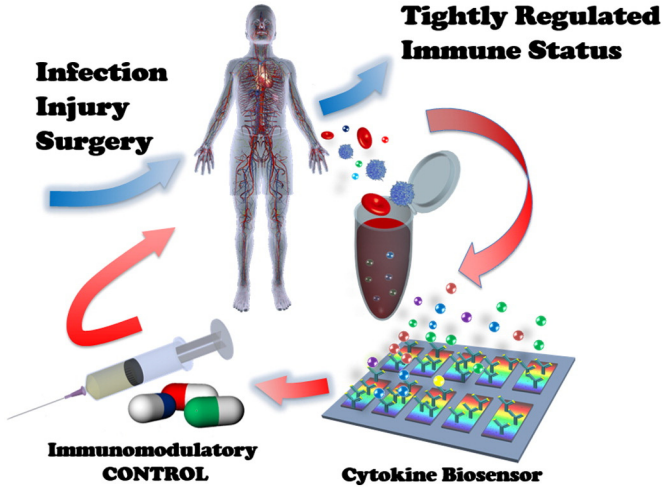

Fig. 1. Concept of personalized immunomodulatory therapy for systemic inflammatory disease enabled by rapid cytokine-based immune status monitoring. This concept is analogous to feedback-loop system control theory used in system engineering that controls the behavior of a dynamical system with an input.

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