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Review

State of diagnosing infectious pathogens using colloidal nanomaterials

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ABSTRACT

Infectious diseases are a major global threat that accounts for one of the leading causes of global mortality and morbidity. Prompt diagnosis is a crucial first step in the management of infectious threats, which aims to quarantine infected patients to avoid contacts with healthy individuals and deliver effective treatments prior to further spread of diseases. This review article discusses current advances of diagnostic systems using colloidal nanomaterials (*e.g.*, gold nanoparticles, quantum dots, magnetic nanoparticles) for identifying and differentiating infectious pathogens. The challenges involved in the clinical translation of these emerging nanotechnology based diagnostic devices will also be discussed.

1. Introduction

An infectious disease (ID), also known as a communicable or transmissible disease, is defined as an illness caused by infectious pathogens such as bacteria, virus, fungus, parasite, and prion [1]. There are more than 1400 organisms that cause infection in humans [2–5], and IDs remain as one of the major causes of morbidity and mortality and pose a significant threat to global health and safety [6,7]. In 2009, communicable diseases accounted for 51% of years of life lost (YLL), a measure of premature mortality (Fig. 1) [8]. Interestingly, this number is represented asymmetrically among countries of different income groups. IDs have been reported to be more problematic in low-income countries, where communicable diseases accounted for 68% of YLL compared to only 8% in high-income countries (Fig. 1). However, IDs also cannot be overlooked in the developed world due to the rapid evolution of antimicrobial resistance that render antibiotics less effective against these infections [9,10].

Besides the mortality and YLL, IDs can lead to other consequences such as economic burden due to the loss of worker productivity, and money spent on treatment and replacement of work absences [11,12]. The emergence and re-emergence of IDs will continue to overwhelm the global economy and public health. It has been expected that IDs will remain the most common cause of mortality in the next 25 years, especially in low-income countries [13].

Diagnostics play a crucial role in the management of IDs by providing appropriate information about a patient's disease state, which allows healthcare workers to quarantine infected individuals to prevent further spread of pathogens, and administer appropriate treatments until patients become successfully treated. Nonetheless, the lack of appropriate diagnostics cause poor control over infections in low-income countries, in which undiagnosed or misdiagnosed diseases can spread to other regions of the world with international travels and worsen global morbidity and mortality. Such threats of infectious diseases on a global scale was experienced with Severe Acute Respiratory Syndrome (SARS) pandemic in 2003 [14], H1N1 flu pandemic in 2009 [15], Ebola epidemic in 2014

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[16], and Zika outbreak in 2015 [17].

The advancements in nanotechnology developments are offering innovative solutions to improve current diagnostic strategies in the management of IDs. The National Nanotechnology Initiative of the United States defined nanotechnology as the "understanding and control of matter at dimensions between approximately 1 and 100 nm" [18]. At this scale, nanomaterials have tunable optical, magnetic, electrical, thermal and biological properties, and can be engineered with different shapes, sizes, chemical compositions and surface functionalities [19]. These properties enable them to be exploited for improving the detection of biological molecules or whole pathogens. Additionally, nanomaterials have much greater surface-area-to-volume ratios than macroscopic materials [20], which provides a great capacity to functionalize the surface with many molecules. For example, a cube with 1-cm dimensions can be divided into 10^{21} 1-nm cubes, which will increase the surface area by 10 million times [19]. This enables the surface of nanomaterials to be coated with molecules that can selectively bind to the target molecules or pathogens. The applications of nanotechnology for diagnostics is referred to as "nanodiagnostics".

This review highlights conventional methods for diagnosing IDs and explores their limitations. This article will then examine how nanomaterials are being exploited to overcome some of these limitations. The properties of nanomaterials that are commonly exploited in the development of *in vitro* diagnostics, various nanodiagnostic readout signal modalities, and future direction of nanodiagnostics will be discussed.

2. Conventional diagnostic approaches

Effective diagnosis of IDs is important for the successful control and management of diseases [21–23]. Symptomatic infections may be managed without the need for extensive diagnosis; however, this could also lead to overtreatment due to the administration of inappropriate or unnecessary treatment, and risk of developing antimicrobial resistance. Additionally, a disease can be caused by different pathogens that present similar symptoms. For instance, respiratory tract infection can be caused by influenza virus which produces respiratory syndromes that are clinically similar to those caused by streptococci, mycoplasma, or other viruses [24]. As a result, an accurate and rapid identification of infectious pathogens is desirable before the initiation of a treatment [22,24].

Several diagnostic techniques are currently available to determine the causative agents of infectious diseases, guide healthcare professionals to initiate proper treatments, provide control measures to quarantine the infected individuals, and monitor the disease progression. These techniques include microscopy, culture, enzyme-linked immunosorbent assay (ELISA), lateral flow assay (LFA), and polymerase chain reaction (PCR).

2.1. Microscopy

Numerous microscopic techniques are widely used for the diagnosis of infectious diseases like malaria [25–27], tuberculosis [28,29], and urinary tract infections [30–32]. This involves direct examination of either stained or unstained smears (blood, sputum, urine, *etc.*) at the cellular level using a variety of microscopic techniques (*e.g.* bright field, dark field, and fluorescence microscopy). Such techniques have been reported to achieve high level of diagnostic sensitivity for certain pathogens [26,28]; however, their outcomes can strongly vary depending on the training level of a microscopist, concentration of the pathogen within the clinical specimen, staining methods, and other sample preparation steps [27,31]. Hence, manual microscopy may not be a reliable screening method especially when it is performed by non-experts due to its inherent variability [33]. Microscopes can also be expensive with specialized optical features, which make them mostly unavailable in resource-limited and decentralized regions.

2.2. Culture

Culturing has been extensively used for identification of microorganisms in a laboratory. Some microorganisms can be cultured in artificial media (*e.g.* bacteria, yeast and fungi) while others (*e.g.* viruses) require living host such as mammalian cells or living animals for culturing and isolation. Selective culture media that contains specific inhibitors can be used to allow growth of specific bacterial pathogens while inhibiting growth of other flora. Culturing can provide quantitative results by spreading a specific volume of specimen over the surface of agar media and calculating the number of colony forming units per milliliter (CFU/ml). This is a commonly-used method for the identification of bacterial

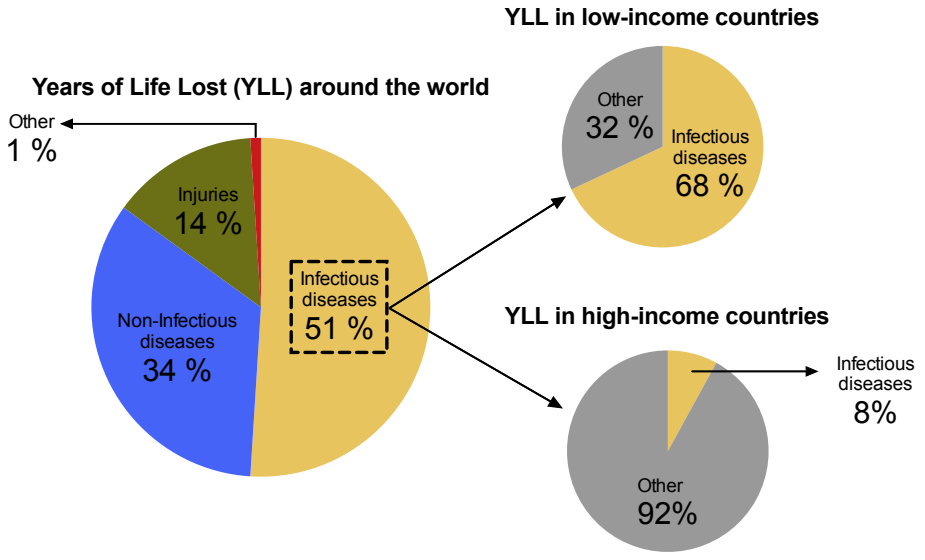

Fig. 1. YLL caused by infectious diseases around the world, in low-income countries and in high-income countries [8].