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Highlight

Maltohexaose-based probes for bacteria-specific imaging: Great sensitivity, specificity and translational potential

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ABSTRACT

Infectious diseases have always been a major cause of mobility and mortality, early and accurate diagnosis is important for their management. However, current clinical diagnosis for bacterial infection still remains troublesome. Recently, many attempts on molecular imaging have been made for prompt bacteria detection, especially for early and precise disease diagnosis. Among them, maltohexaose-based probes serve as a superb candidate due to the bacteria-specific maltodextrin transport pathway. These probes can visualize bacterial foci with unparalleled sensitivity and specificity. Such metabolism-based targeting strategy offers a powerful delivery platform for imaging and theranostic agents, providing good translational potential for developing antibacterial agents.

Infectious disease is one of the highest causes of morbidity and mortality in human history. Current golden standard for diagnosing infection relies on conventional means, such as tissue biopsies, microbiological culture, urine and blood test [1]. However, these methods are only valid when patients are at late-stage of infection. It is imperative to develop new powerful tools for sensitive and specific bacterial detection [2]. Molecular imaging has been widely researched to precisely diagnose diseases [3,4]. It shows pathological progress in cellular or even molecular level, by providing unparalleled sensitivity for early diagnosis, and therefore serves as a promising tool for early-stage infection diagnosis [5,6].

^{67}Ga-citrate, ^{18}F-fluorodeoxyglucose (^{18}FDG) and radiolabeled leukocytes have been approved as clinic tracers for bacterial infection imaging, and provide good sensitivity for early-stage diagnosis [7]. Unfortunately, these clinic tracers are not able to specifically recognize bacteria [8]. In order to improve this, many attempts were made to develop new targets for bacterial infections, including antibiotics, antibacterial peptide, antibodies, metabolizable compounds and ligands, and others [9–12]. Among these targeting strategies, bacteria-specific metabolism pathway attracted great interests. Unlike mammalian cells, bacteria have their own specific pathway for nutrients metabolism, such as sugar metabolism based on maltodextrin transporter system [13]. This system is also found to be implicated in the virulence mechanisms of some of these pathogens and prove to be absent in mammalian cell, making it promising for bacteria targeting [14].

The maltodextrin transporter belongs to adenosine triphosphate (ATP)–binding cassette (ABC) family of transporters, it has been shown to be present in many bacterial species, both gram-positive and gram-negative [15]. For bacteria, maltodextrin transporters in the surface can recognize non-reducing end of maltohexaose, and internalize imaging agents conjugated to maltohexaose [16]. These probes can selectively enter pathogenic bacteria cells through maltodextrin transporter induced internalization, and provide unambiguous imaging signal for diagnostic purpose, moreover, glucose oligomers in maltohexaose structure allow these compounds bypass the lumen of intestinal tissues and the skin outer layers, resulting in little accumulation of normal flora, so that imaging sensitivity is guaranteed [17]. All these traits make it potential to translating maltohexaose-based probes into clinical use.

Maltodextrin-based imaging probes (MDPs) were first reported in 2011, for *in vitro* and *in vivo* bacteria detection. In this work, alkyne-functionalized fluorescent dyes perylene and IR786 were clicked onto an azide-functionalized maltohexaose at the modification-tolerable reducing end [18]. It is verified that MDPs can specifically and selectively accumulate in bacterial infection site,

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rather than mammalian cells or lipopolysaccharide (LPS) induced infection. The experiment results also confirmed the targeting mechanism as active maltodextrin-transporter pathway, which is consistent with former hypothesis. Besides the capacity of detecting bacterial biofilm and discriminating bacterial lesion from sterile inflammation, MDPs are also capable of imaging *Escherichia coli* (*E. coli*) microflora as few as 10^5 colony-forming units (CFU) *in vivo*, whose sensitivity is two orders of magnitude higher compared with many peer probes. This work efficiently settled the interference we former talked about, and gives a precisely diagnostic result.

Unfortunately, as fluorescent probes, MDPs still suffers from some short-comings of fluorescent imaging, particularly the poor tissue penetration of light. To address this issue, ^{18}F-labeled maltohexaose (MH^{18}F) was introduced as a positron emission tomography (PET) tracer for acute diagnosis of bacterial infection [19]. MH^{18}F was compared with ^{18}FDG for *E. coli* imaging in rats, and generated 30-fold signal to noise ratio between infected *versus* healthy tissue, while ^{18}FDG only achieved 1.5-fold. Besides the excellent targeting ability, MH^{18}F has promising potential in identifying bacterial drug resistance. Maltodextrin transports are ATP-binding cassette (ABC) transporters, in other words, the process of maltohexaose substrates internalization, like MH^{18}F, has close connection with cellular metabolism and bacterial viability, and the results showed that MH^{18}F could identify drug resistance of bacteria and measure the efficacy of antibiotic therapy. This striking result indicates that MH^{18}F might be a good candidate for guiding the antibiotics selection.

It is lucky that we may find a way to precisely detect bacterial infection, but the cure still remains intractable, especially when facing the multi-drug resistant strains. We need treatments that immediately and directly attack bacteria with little chance to induce drug resistance, fortunately nano-theranostics offers a feasible solution to this [20]. By combination of diagnostic imaging with anti-bacterial therapy, the nano-formula purpurin 18-loaded nanoliposome (MLP18) has potent efficacy in labelling and fighting methicillin-resistant *Staphylococcus aureus* (MRSA) [21]. The purpurin 18 payload in MLP18 is an excellent fluorescence imaging/photoacoustic imaging (FLI/PAI) probe, as well as excellent sono-sensitizer. This makes MLP18 able to accomplish precise bacteria detection following by instant sono-dynamic therapy (SDT). Unlike nucler tracers hampered by their short life and radiation risk, MLP18 can be used to monitor infection progress with longer period and for multiple times, while its signal of near-infrared FL and PA can overcome tissue absorption and scattering [22]. With multi-model imaging guidance, bacterial foci can be well located so that ultrasound irradiation can be applied at the infection site to activate purpurin 18 and generate singlet oxygen. After SDT treatment, the integrity of bacterial membrane was disrupted, and the cell walls were wrinkle and lysed with intracellular content leakage. This lethal effect was broad-spectrum and has no concern of drug-resistance.

In the age of post-antibiotics era, early diagnosis is an effective mean to alleviate the burden caused by drug resistance in public health [23,24]. Maltohexaose-based probe was well proven to be specific and sensitive for targeting bacterial infection, while its implication with bacterial virulence adds to the use for differentiating drug-resistant strains. This strategy holds good promise for developing new contrast agent to diagnose bacterial infection. However, looking back to those already approved drugs, there is still a long way to go before maltohexaose-based probes can enter clinic. At the same time, lots of different targeting mechanisms and probes are undergoing preclinical research for early and accurate diagnosis, such as siderophores and bacterial antibody, it is hopeful that human can win the battle against drug resistance by combination of effective prevention, precise diagnosis and prompt treatment.

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