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Editorial

Bifidobacterium-Based Therapeutics: is Procalcitonin a Possible Systemic Measurement of Detection?

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Editorial

In the current era of precision oncology therapeutics, impressive developments have been made to increase the efficacy of site-specific drug delivery systems to solid tumors, thereby avoiding the off-target side effects traditionally seen in systemic delivery of cytotoxic chemotherapies. This approach also increases the concentration of drug directly at the site of the tumor. The incorporation of anticancer agents into bacterial or viral vectors, such as *Bifidobacterium*, has been especially promising. *Bifidobacterium* is a diverse genus of non-pathogenic, strictly anaerobic gram-positive bacteria, commonly derived from human intestinal flora. Although these bacteria have often been utilized as probiotic agents, a growing body of preclinical research supports its use in cancer therapeutics as well. A recent 2019 article published by Ngo et al. [1], elucidated these advantages, including the wide array of genes that can be carried by *Bifidobacterium* and its successful delivery of anticancer agents to murine hypoxic tumor sites [1,2]. To treat Wilms tumor, *B.longum* was genetically engineered to express the tumor associated antigen WT1. Mice receiving this novel therapeutic showed a significant decrease in tumor growth and increased survival [3]. Currently, a promising strategy for targeted delivery involves in situ bio-conversion of the inactive pro-drug 5-Fluorocytosine (5-FC) into cytotoxic 5-Flurouracil (5-FU) by Cytosine Deaminase (CD), 5-FC is delivered sequentially afterAPS001F, a recombinant B. longum construct that has been modified to express CD. The first in-human study is now being conducted through a Phase I/II clinical trial (NCT01562626), in which patients with solid tumors receive an intravenous infusion of APS001F, followed by an oral dose of 5-FC, and an injection of 10% maltose. As treatment response to *Bifidobacterium*-based therapies such as APS001F continues to be monitored, Procalcitonin (PCT) could be explored as a potential biomarker candidate.

Procalcitonin as measured by Videos Brahms PCT Assay is an FDA approved test to decide antibiotic use in lower respiratory tract infections. Procalcitonin (PCT) is a peptide precursor of Calcitonin (CT), a hormone involved in calcium homeostasis. The production of PCT occurs in a tissue-specific manner via expression of the CALC-1 gene on chromosome 11 [4]. In response to elevated levels of calcium, glucocorticoid, glucagon, etc, neuroendocrine cells, such as thyroid C cells will stimulate PCT production. Most of the PCT encoded by the CALC-1 gene is then immediately post-translationally converted to mature CT. Thus, blood serum PCT levels are normally low in healthy individuals, at 0.05 ng/ mL or below [5].

Outside the arena of cancer therapeutics, PCT is utilized in a variety of clinical settings as a biomarker for the rapid detection of sepsis, prediction of bacteremia, and management of antibiotics. In the presence of infection and during inflammatory conditions, PCT levels are elevated. Serum PCT levels rise more rapidly compared to traditional inflammatory markers such as C-Reactive Protein (CRP) or White Blood Cell (WBC) count, and consistently elevated PCT has been correlated with poor clinical outcomes in patients with bacterial sepsis. The rapid rise of PCT level has made it a valuable diagnostic marker in detecting sepsis within critical care units. Following an algorithm of serial PCT concentrations to guide antibiotic therapy use, localized infection is interpreted as a PCT concentration between 0.05 ng/mL to 0.49 ng/mL, sepsis at 0.5 ng/mL to 1.9 ng/mL, severe sepsis between 2 ng/mL to 9.9 ng/ML, and septic shock is interpreted at 10 ng/mL and above [5,6]. Some of the highest reported PCT elevations have been observed in acute bacterial Bloodstream Infections (BSI's) and bacterial sepsis, particularly in cases of community-acquired pneumonia.

Recent studies have proposed that several mechanisms may be responsible for triggering the elevation of PCT during inflammation. PCT production may be induced directly by the bacterial endotoxin, LPS, of gram-negative bacteria, or it may be induced by mediators such as IL-6, TNF-α, and IL-1. A recent study by Bai et al. [7], found that NF-κB may be directly involved in the regulation of LPS induced expression of PCT in human hepatocytes. NF-κB is an important master transcription factor that is located in the cytoplasm and is normally bound to inhibitory proteins known as inhibitors of NF-κB (IκBs). Upon stimulation by LPS, the IκB complex is degraded to release NF-κB. NF-κB translocates to the nucleus, where it can then

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attach to specific binding sites on target genes. This specific study proposed that NF-κB enhances the expression of PCT by directly inducing transcription of the PCT gene (CALC-1), or by indirectly inhibiting expression of miR-513b, a single stranded RNA molecule that inhibits the production of PCT [7].

Within clinical studies, high serum PCT levels are more closely associated with infections caused by gram-negative bacteria compared to gram-positive bacteria. The significant differences in BSI's could be explained by different signaling pathways that induce inflammation. LPS is the major membrane component of gram-negative bacteria, and LPS ligation to TLR4 initiates signaling pathways that result in release of pro-inflammatory cytokines. Peptidoglycan (PGN) is the major membrane component of gram-positive bacteria, and a pro-inflammatory response is induced *via*. PGN ligation to TLR2. The mechanistic study by Bai et al. [7] suggests that NF-κB activation is necessary in LPS-induced expression of PCT by gram-negative organisms. While no specific mechanism has been proposed yet to elucidate the expression of PCT by gram-positive organisms, it remains possible that NF-κB could also assume an important regulatory role in inducing PCT expression when triggered by gram-positive organisms such as *Bifidobacterium* [7].

Despite the paucity of clinical data on *Bifidobacterium* outside of probiotic therapies, a few clinical reports have suggested that *Bifidobacterium* is an opportunistic pathogen that could induce bacteremia in immunocompromised patients and potentially present with a sepsis-like picture as well. While only fifteen adult cases of *B. bacteremia* have been reported, these findings may be important to understanding *Bifidobacterium*-based cancer therapeutics [8]. A major obstacle for treating patients enrolled in clinical trials has been assessing the successful colonization and concentration of drug present in the tumor micro environment after the initiation of treatment. In lieu of performing serial tumor biopsies for colony counts or ELISA protein detection, PCT is a potentially promising assay that offers a less invasive alternative to monitoring treatment responses to targeted chemotherapy.

Elevated serum PCT concentrations are generally more challenging to interpret in cancer patients since the values may be influenced by extraneous factors such as the presence of metastasis or increased neuroendocrine tissue activity [9-11]. This would make establishing a baseline level important in cancer patients and may need to be evaluated on an individual basis. In addition, the size of the tumor may have an effect on the level of procalcitonin production either due to the level of colonization compared to the tumor size, or the location of the tumor.

The potential utility of PCT within this specific context remains promising, and would alleviate the need for invasive biopsy procedures that carry significant inherent risk. Continued research into the inflammatory mechanisms behind elevated serum PCT concentrations in gram-positive bloodstream infections, bacteremia, and sepsis is important. Further study of monitoring serum PCT levels in cancer models and patients receiving *Bifidobacterium* based therapy is justified.

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