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Mini Review

Immunomodulation Effect of Procalcitonin

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Introduction

Sepsis-related mortality is increasing worldwide particularly in immune-compromised patients and the response to therapy has not been substantially improved. We aimed is to provide an overview on the role of Procalcitonin (PCT) in patients with sepsis or malignancies with particular emphasis on its characteristics, genetic, kinetics, production, effects and potential use as a therapeutic target and as an immunomodulator. A detailed electronic literature search to determine the source of materials for this mini-review article was done. To date, no review article summarizes the role and future directions of PCT in patients with systemic inflammation and various types of cancer.

PCT Characteristics and Kinetics

PCT is the precursor for calcitonin hormone that is synthesized in thyroidal C-cells, the pulmonary endocrine cells, and other gastrointestinal neuroendocrine cells [1]. The stored PCT hormone in cytoplasmic granules is release when the stimulus appears at the surface of these cells which is mediated *via* stimulus-specific response elements within the promotor of the *CALC-I* gene. This gene is located on chromosome 11p15.4 and controls the production of PCT protein which is composed of 116-amino acid with 14.5 kDa molecular mass. Unlike the very low concentrations of <0.5 µg/ml found in healthy individuals, PCT hormone level in sepsis reach values of 10-1,000 folds that of normal level in human as well as in several species of animals, such as hamster, rat, pig and baboon [2]. Under basal conditions and in the absence of infection, the low expression of the *CALC-I* gene is confined to neuroendocrine cells found in the thyroid gland and lung [3]. In sepsis, its gene expression in nearly all tissues is a unique phenomenon [4]. The sepsis-related increase of PCT level correlate with the severity of the pathogen-induced disease and remain elevated for the duration of the inflammatory process. Hormokine refers to the cytokine-like behaviour of the PCT during sepsis since PCT is produced within different non-endocrine organs and thus, act as a cytokine. The PCT levels in the exudate of patients whose wounds dehisce are significantly increased compared with patients whose wounds subsequently heal [2].

PCT is a biomarker assisted in diagnosing bacterial sepsis and monitoring the efficacy of antibacterial therapy. The ubiquitous *CALC-1* gene expression indicates the role of PCT as a marker of sepsis survival and prognosis. The highest PCT plasma level was reported in severe bacterial sepsis, SIRS, infection-independent conditions and in the presence of metastasis or carcinoma of neuroendocrine origin. In the presence of sepsis, the released endotoxin (lipopolysaccharide, LPS) from Gram-negative bacteria or Lipoteichoic Acid (LTA) from Gram-positive bacteria and proinflammatory cytokines are the main stimuli for *CALC-1* gene expression [2,5]. The bacterial endotoxin and proinflammatory cytokines (e.g., interleukin-1b, tumour necrosis factor-α, interleukin-6) stimulate the secretion of PCT from parenchymal cells which in turn, reinforce immune cells production of cytokines that augment the high local PCT levels in a feedback manner in patients with systemic or local sepsis. Following administration of a single dose of endotoxin to healthy human volunteers, serum PCT increased within three hours, peaked within 24 hours, persist increased for at least seven days and not normalize until two weeks. The failure of PCT level to decrease by more than 80% over the first 72 hours is associated with an increased mortality rate, independent of other risk scores. These kinetics indicate that PCT is a predictor of mortality and may help in sepsis care when its concentration is serially measured on followed up only [5]. In addition to physical examination, microbiological diagnostic tools and PCT assays support the physicians for monitoring infections, start antibiotic therapy, and limit the number of undue antibiotics prescriptions.

PCT Production and Biological Effects

Ubiquitous PCT-mRNA expression and PCT release from multiple non-endocrine tissues throughout the body, namely liver, lung, kidney, adrenal, brain, pancreas, colon, skin and spleen was described. Several tissues differ in their level of PCT production during bacterial sepsis. The highest PCT concentration was found in liver, kidney, fat, aorta, ovaries, bladder and adrenal gland [6]. Tissues PCT levels are in accordance with the serum PCT levels [2,6]. White blood cells are producers and target of PCT. PCT inhibits the immune response by suppressing the hyperactive T-cells 1 [1].

The biological effect of PCT in host defence is incompletely understood [6]. However, the reported effects include a) increasing the expression of surface markers on human neutrophils and lymphocytes (CD16 and CD14, respectively) which indicate the movement of intracellular secretory vesicles towards the cell surface, b) increasing the concentration of intracellular calcium ions which facilitate the host response, c) decreasing phagocytic activity of neutrophils in a dose dependent manner, d) leading to a dose-dependent increase of pro-inflammatory cytokines, e) increasing malfunction of neutrophils, lymphocytes, and macrophage, f) acting

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as a potent amplifier of the inflammatory cascade, g) increasing body temperature and locomotor activity, h) affecting hypothalamic-pituitary energy homeostasis, i) increasing the vasodilatation and decreases renal function and cardiovascular stability, j) acting as a marker for sepsis in patients with hematological cancers.

PCT improves the risk stratification in community-acquired pneumonia and chronic obstructive pulmonary disease exacerbation and lowers sepsis related morbidity and mortality. The estimated total cost of PCT assay is about $50 USD per test [7]. The highest PCT plasma levels were reported in severe bacterial sepsis, Systemic Inflammatory Response Syndrome (SIRS), infection-independent conditions such as trauma and surgery and in the presence of metastasis or carcinoma of neuroendocrine origin.

PCT in Systemic Inflammation and Malignancy

Serum PCT is a promising biomarker for patients with sepsis and directly affects the disease outcome [4,5]. Cytokines that activate PCT production are IL-1β, IL-6, IL-8, and TNFα while TGFβ and IL-10 are suppressive cytokines [1]. PCT is a reliable biomarker assisted in the diagnosis of bacterial sepsis, monitoring the efficacy of antibacterial therapy and prognosis [2,4]. Microbiological culture results are positive in half cases of clinically-suspected sepsis due to technical problems of the culture and the timing of specimen collection [2]. In severe illnesses, bacteria or their products translocation across the gut, respiratory or urogenital epithelial barriers stimulate the secretion of pro-inflammatory cytokines including PCT. PCT levels are low or slightly elevated in patients with localized infections and in cases where the infection is caused by atypical bacteria. However, PCT value in fungal infections is controversial [5].

PCT is an indicator for neoplastic diseases progression, especially liver metastasis and a reliable marker in the differential diagnosis of cancer patients with bacterial infections. The new biomarkers proadrenomedullin, is better than PCT in identifying undetectable, localized infections in patients with febrile neutropenia secondary to underlying haematological disease. Adrenomedullin (ADM) is a 52-amino acid protein belonging to the calcitonin peptide superfamily produced ubiquitously by endothelial cells in cardiovascular, renal, pulmonary, cerebrovascular and endocrine tissues [11]. Less information is available about the role of PCT assay in the management of patients with infections and haematological malignancy.

PCT as a Therapeutic Target and an Immunomodulator

PCT is an attractive therapeutic target. PCT removal by filtration techniques leads to the restoring of the immune homeostasis in patients with sepsis [4]. Neutralizing antibodies for PCT have been developed and their use markedly decreases the mortality of animals with severe sepsis comparable to that occurring in humans [2]. Further investigations of the potential beneficial therapeutic effect of immunoneutralization of PCT in patients with sepsis or SIRS recommended [8]. The role of circulating miRNA-125b (miR-125b) levels in the diagnosis of sepsis is recognized. The miR-125b is essential for regulating host immune response in septic shock. The miR-125b overexpression in macrophage increases the responsiveness to IFN-γ and functional role of macrophages in immune responses. It is a critical regulator in PCT expression and its function in monocytes after LPS stimulation is mediated through STAT3. The miR-125 and its downstream effectors are the new diagnostic biomarker and potential therapeutic targets for sepsis management in future [12].

Immunomodulation approach is aimed at enhancing the immune cells activity. Natural killer (NK) is an innate lymphoid cell that provides host defence with immunity against microbial infection and tumours. NK cells production of the antibacterial toxins, perforin and granulysin, that has cytolytic activity leads to rupture of the intracellular bacteria in the dying target cells [8]. The delivery of granulysin into infected cells is dependent on perforin, granulysin diffuses through perforin pores and kill pathogenic bacteria [9]. Therapeutic approaches for targeting NK cells in the treatment of cancer is a recent concern [10]. PCT interactions with immune cells in bacterial-induced illnesses are still not fully understood. The molecular mechanism of PCT in modulating NK cells response is not elucidated and its role as an immunomodulator in controlling activation of the NK cell *via* Mitogen-Activated Protein Kinases (MAPK) pathway remains unexplored.

Conclusion

To date, no review article summarizes the role of PCT as an immunomodulator. Proadrenomedullin, is better than PCT in identifying localized infections in patients with febrile neutropenia secondary to haematological disease. Less information is available about the role of PCT assay in the management of patients with infections and haematological malignancies. Further investigations of the therapeutic effect of immunoneutralization of PCT in patients with sepsis or SIRS recommended. The miR-125 and its downstream effectors are the new diagnostic biomarker and potential therapeutic targets for sepsis management in future. PCT interactions with immune cells in sepsis are still not fully understood. The molecular mechanism of PCT in modulating NK cells response is not elucidated and its role as an immunomodulator in controlling activation of the NK cell *via* Mitogen-Activated Protein Kinases (MAPK) pathway remains unexplored. To date, there is no clear understanding of the interaction of Signal Transducer and Activator of Transcription 3 (STAT3) and PCT promotor and why an increase in PCT is associated with increased mortality risk.

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