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Biological Activities and Clinical Applications of Alkaline Phosphatase: A Minireview

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ABSTRACT

Deficiency of alkaline phosphatase is characterized by bone hypomineralization. Alkaline phosphatase is considered an indicator of bone mineralization. Alkaline phosphatase has also been considered a marker of differentiation of osteoblasts. In 1990, Dr. Hui began to study the possible bioactivity of alkaline phosphatase. The initial hypothesis of the study proposed that the expression of alkaline phosphatase on the cell surface is not only a marker of cell maturation and differentiation but also promotes these processes. This hypothesis was substantiated by Dr. Hui's gene transfer method, which demonstrated that cell surface-expressed alkaline phosphatase could cease cell proliferation and augment cell volume. Further investigation into the expression of recombinant alkaline phosphatase on the surface of different cell types revealed its role in promoting pathological calcification. In 1997, Dr. Poelstra et al. found that alkaline phosphatase can dephosphorylate and inactivate endotoxin, suggesting that alkaline phosphatase can be used to treat acute kidney injury, resulted from endotoxin-related sepsis. AM-Pharma has promoted an injectable recombinant human alkaline phosphatase to complete three clinical studies. Recent studies conducted by Dr. Gao and Hui indicated that regardless of the presence of endotoxin, alkaline phosphatase inhibits the migration and functions of neutrophils. Therefore, alkaline phosphatase is expected to be used to treat inflammatory diseases unrelated to endotoxin. The study also showed that alkaline phosphatase also dephosphorylates extracellular ATP, ADP, and AMP to adenosine which binds to its receptors on the surface of inflammatory cells, therefore generating anti-inflammation action. The ATP is also hydrolyzed to ADP, AMP, and adenosine by ectonucleotidases CD39 and CD73. In summary, the alkaline phosphatase and the ectonucleotidases CD39 and CD73 together play important roles in treatment of inflammatory diseases.

Keywords: Alkaline Phosphatase; Injection; Biological Activity; Cell Proliferation; Cell Maturation; Inflammatory Diseases; Neutrophils; Phagocytosis; Apoptosis; ROS; CD39; CD73; ATP; ADP; AMP; Adenosine; Endotoxin; Sepsis

Alkaline Phosphatase and Deficiency of Alkaline Phosphatase

Alkaline phosphatase (AP), a plasma membrane-associated glycoprotein, hydrolyzes several monophosphate esters to produce inorganic phosphate. Alkaline conditions most effectively promote this reaction [1]. Alkaline phosphatase, mainly expressed on the surface of functional mature osteoblasts, has always been considered a marker of differentiation of osteoblasts [2]. Deficiency of alkaline phosphatase is a rare, and sometimes fatal, inherited [3] metabolic bone disease. It is also called hypophosphatasia (phosphoethanolaminuria [4]/Rathbun's syndrome [5], named after Dr. John Campbell Rathbun in 1948). The clinical features are diverse, from the perinatal variety that induces intense bone hypomineralization, respiratory impairment or seizures that respond to vitamin B6 [4] and commonly cause mortality, to a milder, gradual osteomalacia later in life. Therefore, alkaline phosphatase is considered an indicator of ossification; its deficiency impairs bone mineralization, leading to rickets or osteomalacia [3].

A Preliminary Study on the Bioactivity of Alkaline Phosphatase

In 1990, the corresponding author of this article, Dr. Hui, began to study the possible bioactivity of alkaline phosphatase at the University of Toronto [6]. The initial hypothesis of the study proposed that the expression of alkaline phosphatase on the cell surface is not only a marker of cell maturation and differentiation but also promotes these processes; this is manifested in halted cell proliferation and increased cell volume [6]. This hypothesis was substantiated by Dr. Hui's gene transfer method, which demonstrated that cell surface-expressed alkaline phosphatase could cease cell proliferation and augment cell volume [7,8]. Further investigation into the expression of alkaline phosphatase on the surface of different cell types revealed its role in promoting calcification. Hence, the expression of alkaline phosphatase on the surface of vascular cells may be implicated in both cellular morphology change and pathological calcification [9,10].

Clinical Application of Alkaline Phosphatase

In 1997, Dr. Poelstra et al. found that alkaline phosphatase can dephosphorylate and inactivate endotoxin, suggesting that alkaline phosphatase can be used to treat acute kidney injury, resulted from endotoxin-related sepsis [11-14]. A multicenter clinical study by Dr. Peters showed that a Human Recombinant AP (recAP) was safe and effective in patients with sepsis-associated acute kidney injury [15] In conclusion, recAP is one of the limited pharmaceutical treatment options for sepsis-associated acute kidney injury undergoing clinical trial testing [16]. AM-Pharma (a Dutch pharmaceutical company) has promoted an injectable recombinant human alkaline phosphatase to complete three clinical studies (http://www.am-pharma.com) [17]. Oral alkaline phosphatase supplementation may improve gut metabolic homeostasis, according to a clinical research article in the Journal of Internal Medicine[18].

Anti-inflammatory Function of Alkaline Phosphatase

The anti-inflammatory function of alkaline phosphatase can be assessed by the behavior of inflammatory cells and the secretion of inflammatory factors at the cellular level. In this paper, cytological level studies have shown that alkaline phosphatase effectively inhibits the phagocytosis, and release of oxidized groups by human neutrophils [19]. Alkaline phosphatase is suggested to effectively treat inflammatory diseases by inhibiting neutrophils. Other cytological studies have also found that alkaline phosphatase can inhibit the biological activity of immune T cells [20-26]. Interestingly, regardless of the presence of endotoxin, alkaline phosphatase inhibits the migration and function of neutrophils [19]. Therefore, alkaline phosphatase is expected to be used to treat inflammation unrelated to endotoxin. Most studies have shown that endotoxin reduces neutrophil apoptosis [27] and prolongs neutrophil life span and inflammatory processes [28]. Moreover, AP counteracts the endotoxin-induced prolongation of neutrophil lifespan and inflammation [19,28], as confirmed by the cytological results of this paper [19,28].

Mechanism of Alkaline Phosphatase

Mechanisms of alkaline phosphatase include endotoxin dephosphorylation to reduce its toxicity [29]. By hydrolysis, alkaline phosphatase transforms the diphosphoryl lipid A moiety of LPS from toxic to non-toxic monophosphoryl lipid A [30]. The study also showed that alkaline phosphatase not only inactivates endotoxin but also dephosphorylates ATP, ADP, and AMP to adenosine [31]. To initiate inflammation, extracellular purines (adenosine, ADP, and ATP) and pyrimidines (UDP and UTP) stimulate purinergic receptors via autocrine and paracrine signaling. The aforementioned purines and pyrimidines are released from host cells, including nerve termini, immune cells, injured or dead cells, and the gut luminal commensal bacteria [32]. Once released, extracellular ATP (eATP) is rapidly hydrolyzed to ADP, AMP, and adenosine by alkaline phosphatase, which has been confirmed by our study [33]. The ectonucleotidases CD39 and CD73 pathway plays an important role in the conversion of ADP/ATP to AMP and AMP to adenosine, respectively [34]. Anti-inflammation is mediated by the binding of adenosine to its receptors [31,35-37] on the surface of inflammatory cells [28,38,39]. The ectonucleotidases CD39 and CD73 pathway, represented by nucleoside enzymes, such as CD39 / CD73, has received increasing attention [20-26]. The ectonucleotidases CD39 and CD73 pathway is important for the immunosuppressive function of T cells [40]. In summary, this review highlights the clinical potential, molecular function, and mechanisms of alkaline phosphatase as a candidate of anti-inflammatory drug. Further, the alkaline phosphatase and the ectonucleotidases CD39 and CD73 together play important roles in treatment of inflammatory diseases.

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