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Research review

Intestinal alkaline phosphatase: a summary of its role in clinical disease

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ABSTRACT

Over the past few years, there is increasing evidence implicating a novel role for Intestinal Alkaline Phosphatase (IAP) in mitigating inflammatory mediated disorders. IAP is an endogenous protein expressed by the intestinal epithelium that is believed to play a vital role in maintaining gut homeostasis. Loss of IAP expression or function is associated with increased intestinal inflammation, dysbiosis, bacterial translocation and subsequently systemic inflammation. As these events are a cornerstone of the pathophysiology of many diseases relevant to surgeons, we sought to review recent research in both animal and humans on IAP's physiologic function, mechanisms of action and current research in specific surgical diseases.

1. Introduction

Intestinal alkaline phosphatase (IAP) has an important role in gut mucosal defense. IAP has been shown to be decreased during conditions that commonly affect surgical patients and therefore may contribute to the morbidity experienced by surgical patients. Expression of IAP is known to be affected by prematurity, starvation, and inflammation. Basic research has demonstrated IAP to inactivate bacterial pathogens as well as promote bacterial colonization of the intestine with commensal organisms. Data from several animal and human research trials have demonstrated exogenous IAP may have an effect in mitigating intestinal and systemic inflammation in a variety of diseases commonly treated by surgeons.

Currently, human recombinant for of IAP is undergoing phase 2 clinical trials and therefore in the near future may become adjunct to other treatment options. The purpose of the review was to increase the awareness of IAP for general surgeons and how it may impact their patients. We will review the known mechanisms of action of IAP as well as recent research investigating its role in surgical diseases.

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2. Alkaline phosphatases

IAP is a member of the alkaline phosphatase (AP) family which are ubiquitous enzymes distributed among different tissues throughout the body. In humans, four genes encode AP enzyme isoforms: tissue nonspecific AP (TNAP), intestinal AP (IAP), placental AP, and germ cell AP [1] (Table 1). Each of these enzymes shares significant homology. Germ cell AP is predominately expressed by germ cell neoplasms and otherwise is not normally expressed to a significant degree in normal tissue [2]. As one would expect placental AP is expressed by the placenta and normally not expressed by other tissues except for by seminomas and some germ cell neoplasms for which it is used as a tumor marker [3]. TNAP is mainly expressed in liver, bone, and kidney but is also found in circulating leukocytes and colon and its expression within the intestine is increased during inflammation [4,5]. The function of TNAP is not entirely understood but its genetic absence has been linked to hypophosphatemia and therefore it is believed to play a role in bone matrix mineralization [6]. IAP is predominately expressed by the intestinal epithelium whereas the other three isoforms are not [4,5]. IAP is expressed and secreted by intestinal epithelial cells and remains active within the mucosal membrane as well as the intestinal lumen. IAP is also secreted into the serum, where it remains biologically active. Expression of IAP is found throughout the intestine but is highest in the duodenum, whereas its phosphatase activity is highest in the terminal ileum [7]. The expression of IAP is regulated by developmental stage, nutrition, and inflammation [4,5].

3. Mechanisms of action of IAP and possible role in disease

Of these four isoforms, a large amount of focus has been given to IAP and its role in human disease affecting the intestine. The four major functions of IAP in maintaining intestinal homeostasis can broadly be categorized into regulation of bicarbonate secretion and duodenal surface pH, long chain fatty acid absorption, mitigation of intestinal inflammation through detoxification of pathogen-associated molecular patterns, and regulation of the gut microbiome [4,5] (Fig. 1.). As it's name suggests IAP functions as a phosphatase and its reported substrates include lipopolysaccharide (LPS), flagellin, CpG DNA, and nucleotide diphosphates and triphosphates [8–10]. Although all these functions of IAP are important to maintaining intestinal homeostasis, it is the ability of IAP to inactivate LPS, regulate the microbiome, and affect metabolism of adenosine triphosphate and diphosphate (ATP and ADP, respectively) that warrant specific discussion.

3.1. *Inactivation of LPS*

LPS is a constituent of the cell wall of gram-negative bacteria and is abundant in the gastrointestinal tract. It has been implicated in causing systemic inflammation and septic shock. The toxicity of LPS resides in the Lipid-A moiety, which permits it to bind to toll-like receptor-4 (TLR4). Removal of one of the two phosphate groups on the lipid-A moiety reduces LPS toxicity 100 fold [11] (Fig. 2.). This reduction in the toxicity of LPS inhibits downstream intracellular signaling. LPS acts by binding to TLR4, which acts through two distinct pathways to cause inflammation. These two pathways are either dependent or independent on the adapter molecule, MyD88. The MyD88 dependent pathway acts mainly through NF-kB to cause release of proinflammatory cytokines [12]. By preventing the activation of TLR4, IAP prevents the activation of NF-kB and its subsequent translocation into the nucleus. Ultimately, this prevents the expression of proinflammatory cytokines.

The role of IAP in inactivating LPS and preventing intestinal inflammation was first examined *in vivo* in zebrafish [13]. These studies made two interesting observations. The first observation was that the presence of bacteria is necessary to induce the expression of IAP in the intestine. Using conventionally reared zebrafish, it was determined that IAP expression is significantly increased 5–8 d after fertilization. However, in germ-free zebrafish, IAP expression is significantly diminished indicating that the presence of bacteria is required for IAP expression. Additionally, when germ-free zebrafish was fed bacteria, IAP expression increased to normal levels. Furthermore, feeding LPS alone to germ-free zebrafish was sufficient to induce expression of IAP. The second observation was that IAP could inactive LPS *in vivo* and prevent intestinal inflammation. In comparison to wild-type, IAP knock-down zebrafish had significantly increased neutrophil recruitment to the small intestine with ingestion of

Table 1 – Summary of the alkaline phosphatase isoforms and their known clinical significance.

Isoform	Location	Function
Tissue non-specific (TNAP)	• liver • bone • kidney	• unknown • genetic absence has been linked to hypophosphatemia
Intestinal (IAP)	• intestinal epithelial cells	• detoxification of bacterial endotoxin • dephosphorylation of triphosphorylated and diphosphorylated nucleotides • regulation of the intestinal microbiome • regulation of intestinal lipid absorption
Placental	• placenta	• tumor marker for seminomas and germ cell neoplasms • detoxification of bacterial endotoxin
Germ cell	• germ cell neoplasms	• unknown